ORIGINAL ARTICLE

Development and characterization of oral fast-dissolving strip incorporated with olmesartan medoxomil nanocrystals for solubility enhancement: Multilevel categoric optimization using DOE

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Abstract

Aim: Olmesartan medoxomil (OLM) is an antihypertensive drug available as an oral solid dosage form (tablet) with a restricted bioavailability of 28.6%. This might be attributed due to the low solubility and low permeability of the drug. The primary goal of this study was to enhance the solubility of OLM by formulating OLM nanocrystals (NC) and incorporating them into Oral Fast-Dissolving Strips (OFDSs) that will be made available for geriatric patients. **Materials and Methods:** Initially, nanosuspension (solvent-anti-solvent addition) was prepared using different concentrations of stabilizers and characterized for particle size (PS), polydispersity index (PDI), and zeta potential. Further, the nanosuspension was freeze-dried to obtain NC and it was characterized for crystallinity and surface morphology. In addition, the OLM NCs were incorporated into OFDS (solvent evaporation technique) and optimized by Multilevel Categoric design ($2^4 \times 2^2$) using Design Expert® software. The OFDS was evaluated for weight variation, thickness, tensile strength, drug content, disintegration time, and dissolution. **Results and Discussion:** F_{30} shows PS, PDI, and zeta potential of 764.6 nm, 0.310, and −28.7 mV, respectively. The DSC thermograms showed that the reduction in crystallinity of OLM NC compared to pure OLM and the SEM images reveal rod-shaped crystals. The weight variation, thickness, surface pH, and drug content of OLM loaded OFDS obtained satisfactory results. The disintegration time, folding endurance, and tensile strength of the optimized formulation were found to be 20 ± 0.41 s, 125 ± 0.47 times, and 1328.8 ± 0.82 N/m, respectively. The drug release from the formulation was found to be 85.28% at the end of 5 min; the drug release kinetics indicated that it follows non-fickian diffusion and stability studies (25°C/60% RH) reveal that the formulation was stable. **Conclusion:** The results conclude that NCs approach is a promising techniques to improve solubility of poorly soluble drug.

Key words: Design of experiment, nanocrystals, olmesartan medoxomil, oral fast-dissolving strip, solvent evaporation, solvent-antisolvent addition

INTRODUCTION

In the pharmaceutical industry, around 40% of market approved drugs and nearly 90% of the molecules in the discovery pipeline are water-insoluble.[1,2] The new challenge in the formulation of poorly soluble drugs for the oral route is to enhance the solubility and bioavailability of active pharmaceutical ingredients.[3] To overcome this impediment in the drug development process, nanotechnology will be a more acceptable and promising technique.

Olmesartan medoxomil (OLM) is a selective angiotensin II receptor blocker (ARB) used to treat hypertension.[4] In comparison to other ARB drugs like Losartan, Candesartan, the therapy of OLM provides increased anti-hypertensive activity.[5] Depending on a dose, lowering of blood pressure occurs.[6] As OLM is a BCS class II drug, significant drawback is its low aqueous solubility (28.6%) and bioavailability.[7] Consequently, the therapeutic efficacy

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of OLM oral dosage form remains unabsorbed in GIT which causes side effects such as abdominal pain, gastroenteritis, nausea, and dyspepsia.[8]

To overcome the problem, researchers employed nanonization approach which may result in improved solubility and enhanced oral bioavailability of OLM. The oral fast-dissolving strip (OFDS) was developed for the geriatric and bedridden patients who have difficulty in swallowing and to acquire faster onset of action.

Nanocrystals (NCs) are pure solid drug particles with a mean diameter below 1000 nm.[9] NCs have several advantages such as increased saturation solubility, dissolution rate, stability, and dose reduction.[10] The drug particle is surrounded by stabilizing polymer or surfactant layers on the surface which forms a steric or an electrostatic layer.[11] From this, the solubility of the poorly soluble drug can be increased through increase wetability and lower contact angle. The NCs can be prepared in several ways, which include bottom-up, top-down, and combination techniques.[2] Nanosuspension was prepared by solvent-antisolvent addition.[12] To mitigate agglomeration, nanosuspension can be converted into lyophilized powder. Cryoprotectant was added to improve physical stability of the nanosuspension, and freeze-drying was accomplished to generate NC.[13]

The OFDS is a thin, flexible, and non-friable polymeric film containing one or more dispersed APIs.[14] The oral strip delivery is a better alternative for the conventional oral delivery, because it enhances solubility and bioavailability. The absorption of the drug by oral mucosa is an effective strategy since it is found to be vascularized and highly permeable into the systemic circulation. The oral strip technology is formulated for a bedridden and geriatric patient who has difficulty in swallowing.[15] The solvent-casting method was used for preparing an OFDS by the direct casting of OLM NC into a polymeric solution. This oral strips help in improving the bioavailability of OLM.[16]

In this work, the formulation of OFDS was optimized by Multi-level Categoric design ($2^4 \times 2^2$) using Design Expert® Software. The utilization of DOE software helps to optimize the best formulation, detect the interaction of formulation variables, reduces time, and wastage.

MATERIALS AND METHODS

Materials

OLM was obtained as a gift sample. Polyvinyl alcohol (PVA), Hydroxy Propyl Methyl Cellulose (HPMC) E5 LV Premium, Menthol crystals, and Methanol (analytical grade) were procured from Loba Chemie Pvt Ltd. Polyethylene glycol (PEG) was acquired from Sigma Aldrich. Poly Vinyl Pyrrolidine K30 (PVP) was purchased from Aero Chemical Pvt Ltd, Mumbai. Citric acid and Mannitol were procured from Rankem Chemical Laboratory. Saccharin sodium was obtained from S.D. fine chemicals, Mumbai. All reagents and solvents used were of analytical grade.

Methods

Selection of drug – stabilizer concentration

For the preparation of OLM nanosuspensions, various stabilizers such as Poloxamer 188, Poloxamer 407, PVA, polyvinyl pyrrolidone, Tween 80, and sodium lauryl sulfate were used in concentrations of 0.5%, 1%, and 1.5%.

Preparation and lyophilization of OLM nanosuspension

The OLM nanosuspension was prepared by solvent – antisolvent addition technique. Initially, 50 mg of OLM dissolved in 2.5 ml methanol. The antisolvent phase was prepared by dissolving 375 mg of PVA as stabilizer (1.5% w/v) in 25 ml of distilled water. The drug solution was injected drop-wise into stabilizer solution with continuous stirring at a speed of 800 rpm for 1 h at room temperature.[17] The organic solvent was evaporated and further subjected to ultrasonication for 15 min at 27°C. The nanosuspension was characterized for particle size (PS), polydispersity index (PDI), and zeta potential [Table 1]. From these, the stabilizer with least concentration was selected and subjected to further optimization with reduced drug concentration of 20 mg. The same procedure was carried out for optimized drug concentration.

The formulation with least PS and ideal zeta potential was selected for freeze-drying to obtain OLM NC. Mannitol (1% w/v) was added to the prepared nanosuspension as a cryoprotectant and stored in a deep-freezer under −18°C for 24 h before lyophilization. Finally, the nanosuspension was dried in the vacuum freeze-drying chamber for 32 h to obtain OLM NC.

Selection of film former and plasticizer concentration[18]

Blank film was prepared with various concentrations of film-forming polymer (HPMC) such as 0.5%, 1%, 1.5%, and 2%. The plasticizer (PEG and PG) concentrations of 1 ml and 2 ml were chosen. The prepared blank film was further studied and selected based on the physical appearance, folding endurance, and disintegration time.

Optimization of OFDS

The Multilevel Categoric designs ($2^4 \times 2^2$) were used to optimize the OFDS using Design Expert® Software. In this factorial design, the two factors are film former at 4-level and plasticizer concentration at 2-level was taken into consideration. The disintegration time, folding endurance, and tensile strength

Table 1: Particle size and PDI of OLM nanosuspension

Code	Stabilizer	Drug (mg)	Stabilizer (%)	Particle size (nm)	PDI	Zeta potential
F_1	Poloxamer188	50	0.5	2246	0.885	−13.5
F_2		50	1	839.5	0.490	−3.6
F_3		50	1.5	1732	0.984	−8.96
F_4	Poloxamer 407	50	0.5	1245	0.520	−14.8
F_5		50	1	931.5	0.035	−5.8
F_6		50	1.5	1862	1.000	−5.42
F_7	PVA	50	0.5	779	0.752	−12.6
F_8		50	1	4048	0.978	−19.4
F_9		50	1.5	1075	0.654	−5.47
F_{10}	PVP	50	0.5	1296	0.916	−12.8
F_{11}		50	1	1567	0.865	−14.6
F_{12}		50	1.5	1478	0.589	−9.13
F_{13}	SLS	50	0.5	5489	0.127	−26.7
F_{14}		50	1	1923	0.325	−16.7
F_{15}		50	0.5	1758	0.456	−6.45
F_{16}	PVA: PVP	50	0.5	5526	0.903	−1.65
F_{17}		50	1	2901	0.765	−5.42
F_{18}		50	1.5	3439	0.779	−17.9
F_{19}	Tween 80,	50	0.5	1657	0.885	−12.6
F_{20}	Poloxamer188,	50	1	1539	0.886	−1.9
F_{21}	Poloxamer 407	50	1.5	1923	0.779	−19.5
F_{22}	Poloxamer188	20	0.5	2489	0.891	−3.7
F_{23}		20	1	3740	0.986	−2.6
F_{24}		20	1.5	1648	0.683	−21.9
F_{25}	Poloxamer 407	20	0.5	1346	0.476	−18.2
F_{26}		20	1	1345	0.341	−14.7
F_{27}		20	1.5	2365	0.429	−2.11
F_{28}	PVA	20	0.5	1331	0.264	−18.2
F_{29}		20	1	1975	0.480	−2.11
F_{30}		**20**	**1.5**	**764.6**	**0.310**	**−28.7**
F_{31}	PVP	20	0.5	1235	0.651	−3.4
F_{32}		20	1	1568	0.448	−19.4
F_{33}		20	1.5	3456.5	0.510	−13.3

The formulation F30 contains 20mg drug with stabilizer PVA of 1.5% shows satisfactory results for particle size, PDI and zeta potential

Table 2: Variable utilized in multilevel categoric design ($2^4 \times 2^2$) for oral fast-dissolving Strip

Factors (independent variable)	Level			
Concentration of film former (%)	0.5	1.0	1.5	2.0
Concentration of plasticizer (ml)	1		2	
Response (dependent variable)	**Constraints**			
Disintegration time (s)	Minimum			
Folding endurance	Maximum			
Tensile strength (N/m)	Maximum			

were taken as responses. A total of 8 runs were generated in this software and the variable utilized in Multilevel Categoric design ($2^4 \times 2^2$) is shown in Tables 2 and 3.

Formulation of OFDS loaded with OLM NC

The formulation of OFDS loaded with OLM NC are listed in Table 4. Solvent casting method was used for the preparation of the OLM NC loaded OFDS. Film former HPMC E5 was used in different concentrations, such as 0.5, 1, and 1.5, 2% w/v of the total solution. 1 ml and 2 ml of PEG was used as a plasticizer. Citric acid (saliva stimulating agent), PVP K30 (surfactant and disintegrant), saccharine (sweetener), and menthol (flavoring agent to give mouth pleasing effect) were used. Concentrations of citric acid, saccharin, and menthol were kept constant.[16] The polymer solution consisting of HPMC E5, PVP K30, citric acid, and saccharin were dissolved in 20 ml of distilled water. 80 mg of OLM NCs were dissolved in water and transfer into a polymeric solution. Simultaneously, the menthol crystal was dissolved in plasticizer. The solution of plasticizer was added to the polymeric dispersion containing the drug. It was stirred on the magnetic stirrer at 400 rpm for 1 h to form a homogeneous dispersion. The resultant solution was transferred to a petri dish (78.50 cm^2) and kept at room temperature for drying. The dried film was removed cut into a size of 4.90 cm^2. The physicochemical parameter of the formulated OFDS was evaluated.

Table 3: Optimization of oral fast-dissolving strip in multilevel categoric design ($2^4 \times 2^2$)

Batch code	Film former concentration (%)	Plasticizer concentration (ml)	Disintegration time (s)	Folding endurance times	Tensile strength (N/m)
F1	0.5	1	23±1.63	70±2.16	93±0.75
F2	1	1	21±1.69	87±1.69	114.5±2.67
F3	1.5	1	35±2.44	98±3.29	850.9±1.46
F4	**2**	**1**	**20±0.41**	**125±0.47**	**1328.8±0.82**
F5	0.5	2	27±1.14	83±1.24	15±0.12
F6	1	2	38±3.50	91±2.62	18.4±0.47
F7	1.5	2	45±1.22	103±3.68	188.608±1.42
F8	2	2	58±1.54	122±3.39	356.1±2.13

From the optimization, it was evident that batch code F4 shows good desirability with desired disintegration time, folding endurance and tensile strength.

Table 4: Formulation of oral fast-dissolving strip loaded with OLM nanocrystals

Ingredient		F1	F2	F3	F4	F5	F6	F7	F8
OLM nanocrystals	(mg)	80	80	80	80	80	80	80	80
HPMC E5	(mg)	200	400	600	800	200	400	600	800
PEG	(ml)	1	1	1	1	2	2	2	2
PVP K30	(mg)	10	20	30	40	10	20	30	40
Citric acid	(mg)	20	20	20	20	20	20	20	20
Na saccharin	(mg)	30	30	30	30	30	30	30	30
Menthol	(mg)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Distilled water	(ml)	40	40	40	40	40	40	40	40

Characterization

Characterization of OLM nanosuspension

PS, zeta potential, and PDI

The Malvern Zetasizer (Nano ZS90, Malvern instruments) utilized Dynamic Light Scattering technique to quantify the average diameter, electrophoretic mobility (charge) between the particles, and homogeneous distribution of size in the sample.[19] The sample was diluted with de-ionized water and placed at a temperature of 25°C in a disposable polystyrene cuvette at 90° dispersion angle. Similarly, zeta potential was analyzed in a disposable cuvette with a zeta dip cell.[6] The average PS, zeta potential, and PDI measurements were reported.

Entrapment efficiency

The entrapment efficiency of OLM nanosuspension was determined by centrifugation technique.[18] 1 ml of nanosuspension was centrifuged at 12,000 rpm for 10 min at 4°C. The supernatant solution was filtered and analyzed using UV-visible spectrophotometer at 257 nm. The percentage entrapment efficiency was calculated using the below formula

$$\%EE = \frac{\text{Total amount of drug present} - \text{Amount of free drug in the supernatant}}{\text{Total amount of drug present}} \times 100$$

The average values are noted as triplicates.

Saturation solubility

5 ml of pure OLM, OLM nanosuspension, and OLM NC sample were kept in centrifuge tubes for 24 h to ensure saturation. After 24 h, the samples were centrifuged at 5,000 pm, for 5 min (Eppendorf, 5415 R, Germany). The resultant supernatants were analyzed by UV-visible spectrophotometer at 257 nm.[6]

In vitro drug diffusion studies

A dialysis sac method was used to carry out *in vitro* drug diffusion studies. The dialysis sac is approximately 4–5 cm long. To remove any clog in the sac, it was previously immersed in distilled water for 24 h. The dialysis sac was filled with 2 ml of OLM nanosuspension. The sac was suspended in a 100 ml phosphate buffer solution with a pH of 6.8. 5 ml of the sample which was taken at intervals of 30 min, 1, 2, 3, 4, 5, 6, 7, and 8 h. To maintain the sink condition, 5 ml of buffer was replaced. The same procedure was repeated with pure OLM solution. The samples were examined spectrophotometrically at 257 nm. To determine the diffusion rate, the OLM nanosuspension was compared with pure OLM solution. The amount of drug diffused was calculated and recorded.[6]

Characterization of OLM NC

Differential scanning calorimetry (DSC)

Thermal changes that occurred in pure OLM and OLM NC were analyzed using Differential Scanning Calorimeter

(Mettler Toledo, Germany). 5 mg of sample was weighed and sealed in an aluminium crucible at a temperature range of 30–300°C and heat flow was maintained at a rate of 10°C/min. At a specific pressure, dry nitrogen gas was passed through the sample.[20] DSC calculates the loss of crystallinity and determines the enthalpy changes that occur in the system.

FT-IR spectrophotometric studies

FT-IR of pure OLM, physical mixture, and OLM NC were determined by the KBr pellet technique using Fourier Transform Infrared Spectrophotometer (FT-IR 8400 Shimadzu 240V, Shimadzu Corporation). In this method, KBr pellets were crushed in a press mode M 15 with samples and compressed at a pressure of 6 ton/nm^2. The wavelength of IR was selected in the range of 400–4000 cm^{-1}.[21]

Scanning electron microscopy (SEM)

SEM analysis was used to determine the surface morphology of OLM NCs (Carl ZEISS EVO 18, Germany). Before analysis, samples were placed in aluminum stubs containing double side carbon tapes coated with gold-palladium under high pressure of 10–400 Pa.[22] Then samples were examined at various magnifications using an accelerated voltage of 0.2–30 kV.

Characterization of OLM NC loaded OFDS

Weight variation and thickness

The weight variation of the strip was determined in an electric weighing balance[23] and thickness was precisely determined by a screw gauge by cutting the strip into 4.90 cm^2.[24] The mean value was calculated and noted as ± SD.

Folding endurance

Folding endurance was measured by folding the strip in the same direction until it breaks. The folding endurance is calculated as the number of folds it needs to break the strip.[18] The average values are noted as triplicates.

Surface pH

The surface pH was determined using a pH meter. The electrode was placed on the surface of the strip after it had been wet with distilled water.[18] The average values were reported.

Tensile strength and elongation

The mechanical properties of OFDS were determined using a Texture Analyzer (TA.XT PLUS Stable Microsystem, UK). The tensile strength and elongation was measured by placing the strip between the two clamps and closing tightly.[25] The average values were noted and reported.

In vitro disintegration time

The Petri dish method was used to determine the disintegration time of the strip.[26] Each strip was placed in the petri dish with 10 ml of phosphate buffer of pH 6.8 and record the time required for the strip to disintegrate. The average values were noted and reported.

Percentage drug content

The strips of 4.90 cm^2 containing 5 mg of oral strip were dissolved in 10 ml of distilled water. The strips were completely dissolved in the solution, which was then filtered and analyzed at 257 nm.[27] The percentage drug content in the strip was calculated.

In vitro drug dissolution studies

The *in vitro* dissolutions studies for OFDS loaded with OLM NC and plain OLM strip was carried out using USP II dissolution apparatus. 5 mg of the strip was placed in the dissolution medium containing 900 ml of phosphate buffer of pH 6.8. The medium was maintained at 37°C and rotated at 50 rpm. 5 ml of the aliquots were withdrawn and replaced with fresh buffer to maintain the sink condition. The samples were taken at the interval of 30 s, 1, 2, 3, 4, and 5 min[16] and examined by a UV-visible spectrophotometer at 257 nm. The absorbance was noted to determine the percentage drug release at the end of 5 min.

Kinetic modeling

The kinetic modeling is based on a model-dependent approach to determine the order of release. The release kinetics of OFDS loaded with OLM NC were fitted into various kinetic models such as zero-order, first-order, Higuchi, Korsmeyer-Peppas, and Hixson-Crowell to determine the release pattern of the strip using DD solver.[28]

Stability studies

Stability studies of the optimized formulation were performed over 60 days at a temperature of 25°C and relative humidity of 60%. The strip was enclosed in aluminium foil and kept in the stability chamber. At regular intervals, the strips were examined for visual appearance, surface pH, disintegration time, and folding endurance.[28]

RESULTS AND DISCUSSION

Characterization of OLM Nanosuspension

PS, zeta potential, and PDI

PS and PDI influences the drug solubility, dissolution rate, and uniformity of the NC. The OLM NCs were prepared with different types of stabilizers to study the influence of stabilizer type and concentration on PS [Table 1]. Among all the stabilizers, the formulation containing 1.5% PVA (F_{30}) shows the least PS of 764.6 nm and PDI of 0.310 [Figure 1a]. The decreased PDI indicates homogenous PS distribution. Increase in PVA concentration along with decreased drug concentration shows predominant reduction in the PS. Besides, the nanosizing of OLM NC was influenced by stirring speed and sonication time. The increase in stirring speed and drug concentration induces particle aggregation which is evident from the larger PS.

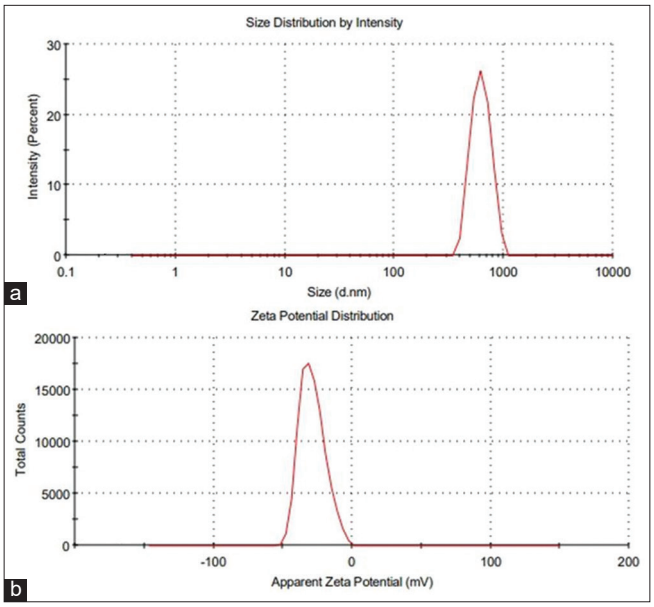

Figure 1: (a) Particle size and (b) Zeta potential of formulation F_{30} OLM nanosuspension

The zeta potential confirms the surface charge and stability of the NC. The formulation stabilized by 1.5% PVA F_{30} exhibits the zeta potential of −28.7 mV and found to be highly stable [Figure 1]. This may be due to the steric stabilization provided by the PVA between the surfaces of the particle.

Entrapment efficiency

The entrapment efficiency was determined by centrifugation method. The concentration of drug and stabilizer has a major impact on the entrapment efficiency. The formulation F_{30} shows highest entrapment efficiency of 89.80 ± 2.40%. This is attributed to the higher concentration of PVA which results in increased viscosity. It retards the diffusion of drug into the aqueous medium which results in maximum entrapment.[18]

Saturation solubility

The saturation solubility of pure OLM, OLM nanosuspension, and OLM NC (F_{30}) was found to be 0.0764 ± 0.12, 0.373 ± 0.26, and 0.735 ± 0.12. There is an 8.2-fold increase in saturation solubility when compared to pure OLM. The reason for solubility improvement is a reduction in PS, which leads to increased surface area and increased dissolution.

In vitro drug diffusion studies

The *in vitro* drug release studies of OLM loaded NC were carried out by dialysis sac method. The data of percentage drug diffusion of plain OLM and OLM nanosuspension are shown in Figure 2. At the end of 8 h, the percentage drug release of plain OLM and OLM nanosuspension was found to be 29.47% and 85.45%, respectively. This indicates a nearly 3-fold times increase in drug diffusion. The increase in the diffusion rate of nanosuspension is primarily due to increased saturation solubility and dissolution rate.[6]

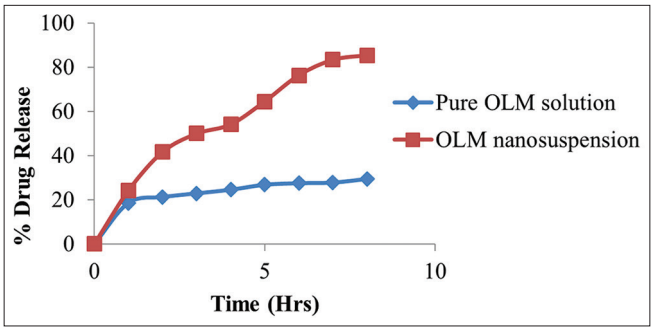

Figure 2: *In vitro* drug diffusion of Plain OLM and OLM nanosuspension

Characterization of OLM NCs

DSC

DSC study predicts the crystallinity of the drug from the melting point and enthalpy changes that occur in the formulation. According to Figure 3, the pure OLM exhibits a sharp melting endotherm peak at 186.90°C. However, the thermogram of OLM NCs showed a sharp peak in the range of 166.60°C. It demonstrates the reduction in crystallinity of OLM NCs when compared to pure OLM. This indicates that weaken crystalline lattice bond which leads to increased solubilization. The small peak in the temperature range of 166.43°C in OLM NCs indicates the evaporation of water bound to PVA.[29]

FT-IR spectrophotometric studies

Figure 4 depicts FT-IR spectra of pure OLM, physical mixture, and OLM NC. The pure OLM exhibits a sharp absorption peak at 2970 cm^{-1}, indicating C-H stretching of the aromatic ring. The peak at 1707 cm^{-1} observes C=O stretching of ester and region,[21] whereas the peak at 1681 cm^{-1} observes C=N stretching. The absorption peak of aromatic ether is positioned at 1136–1168 cm^{-1}. C-N stretching is indicated by the band at 1476 cm^{-1}.The small peaks at 764 cm^{-1} show small N-H molecules. The band in the physical mixture and OLM NC has a comparable peak region, suggesting that there is no interaction between the drug and the formulation.

SEM

The SEM image in Figure 5 illustrates that the OLM NC shows rod-shaped crystals with slightly rough and porous surfaces. The surface roughness may be due to the process involved in the lyophilization. Besides, the stabilizer PVA induces small crack on the surface of the NCs with mild aggregation.[30]

Characterization of OLM NCs Loaded OFDS

Optimization of OLM NCs loaded OFDS

The concentration of film former and plasticizer (HPMC and PEG) was optimized using Multi-level categoric design

to obtain the best film properties. A total of 8 runs were generated in this design. The disintegration time, folding endurance, and tensile strength were found to be in the range of 20–58 s, 70–125 times, and 15-1325.8 N/m^2. Various models, including linear, quadratic, 2FI, and cubic, were used to interpret the results. Based on regression analysis, the quadratic model was chosen as the best-fitting model for folding endurance (R^2 = 0.9901) and tensile strength (R^2 = 0.9620). Concurrently, cubic model was identified as the best-fitting model for disintegration time (R^2 = 0.9393).

Effects of variables on disintegration time

F-value (64.48) and *P*-value (0.0001) generated from the statistical data of cubic model suggest that the model were significant. The ANOVA result [Table 5] states that concentration of film former has a synergistic effect. The concentration of the plasticizer does not have a significant effect on disintegration time. From the contour and 3D-surface plot [Figure 6], it is shown that disintegration time decreases, when the film former concentrations varied at 1.61455–1.86847%.

Effects of variables on folding endurance

The ANOVA result indicates that the quadratic model was significant with an F-value of 675.98 and *P* = 0.0001. From Table 5, it was evident that concentration of film former and plasticizer has a greater impact on folding endurance. However, folding endurance primarily depends on plasticizer concentration. It is evident from the decrease in folding endurance when there is a increase in plasticizer

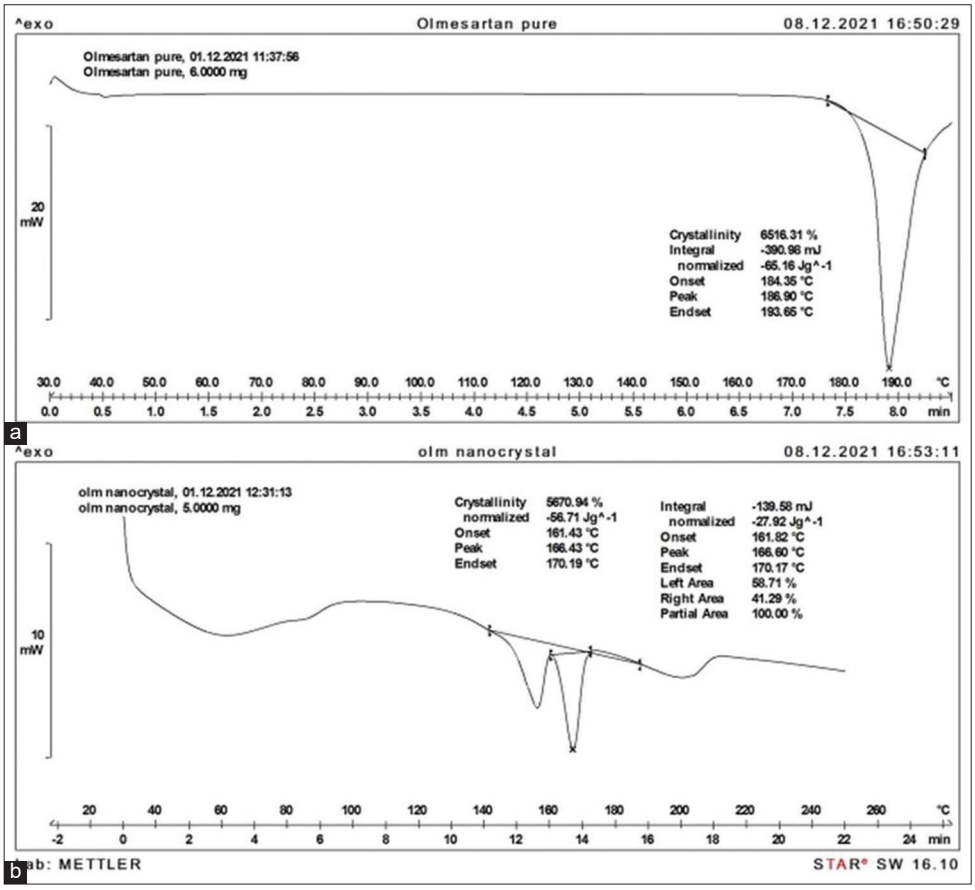

Figure 3: DSC thermograms of (a) Pure OLM and (b) OLM nanocrystals

Table 5: Report of regression analysis data for oral fast-dissolving strip with three responses

Response	Model	R^2	Adjusted R^2	Predicted R^2	SD	Regression analysis
Disintegration time	Cubic	0.9393	0.9247	0.9053	3.48	+35.09+16.84A+6.28B+7.12AB-3.09A^2+4.22A^{2}B
Folding endurance	Quadratic	0.9901	0.9886	0.9873	1.92	94.09+22.88A+2.38B-3.53AB+5.91A^2
Tensile strength	Quadratic	0.9620	0.9564	0.9503	93.94	+273.80+422.12A-225.76B-243.10AB+173.67A^2

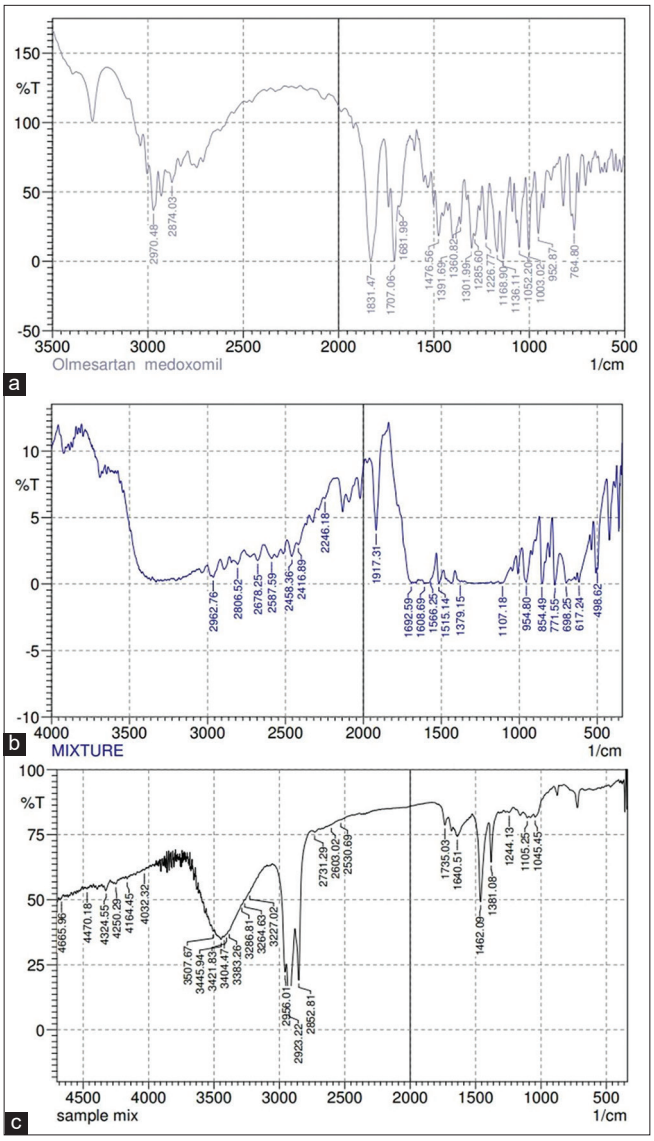

Figure 4: FT-IR studies of (a) Pure OLM, (b) Physical mixture containing drug and Excipient, and (c) OLM nanocrystals

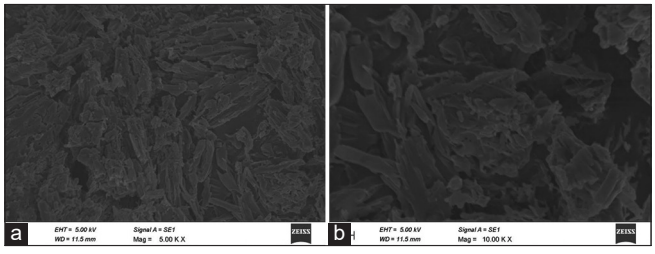

Figure 5: Scanning electron microscopy of OLM nanocrystals with (a) 5000 magnification (b) 10,000 magnifications

concentration. This may be due to the absorption of moisture in the oral strip. The 3D-surface plot and contour plot for folding endurance are depicted in Figure 6, which shows that there is an increase folding endurance at varying plasticizer concentration (1–1.2 ml) and fixed film former concentration (1.7%).

Effects of variables on tensile strength

The analysis of variance for tensile strength proved that quadratic model was significant with F-value of 171.11 and $P < 0.0001$. The tensile strength indicates the rigidity and resistance to break. The regression analysis of tensile strength is shown in Table 5. The 3D-surface and contour plot [Figure 6] indicate that concentration of plasticizer has a substantial impact on tensile strength. The maximum tensile strength was obtained at the plasticizer concentration of 1.01–1.10 ml. The film former concentration in the range of 1.97–1.99% has a slight impact on tensile strength. When the film former concentration is kept constant and the plasticizer concentration is increased, there is a reduction in the tensile strength.

Weight variation and thickness

The average weight of all the oral strips (4.90 cm^2) was evaluated. The formulations, F4 was found to have minimum weight variation of 166.44 ± 0.80 mg. The thickness of the oral strip must not be too thick or too thin as it may damage the strip and increase the disintegration time respectively. It was found that formulation F4 had an optimum thickness of 0.31 ± 0.01 mm.

Folding endurance

The oral strips were assessed for folding endurance and the results are shown in Table 3. The formulation F4 exhibits maximum of 125 ± 0.47 folds and did not show any sign of cracks. This demonstrates that the oral strip has good strength and flexibility which is attributed to the concentration of film former and plasticizer.

Surface pH

The pH of oral film strip should be neutral or close to 6.4–6.7 to avoid irritation and to feel at ease in the oral cavity. Surface pH of all the oral strips was found to be in the acceptable range.

Tensile strength

The optimized formulation F4 exhibits the tensile strength and % elongation of 1328.8 ± 0.82 N/m [Table 3] and 49.36 ± 0.02%. This indicates that the strip is more resistant to stress and possessed more stretchability or expandability than the other formulations. At optimum plasticizer concentration, tensile strength increases. As the concentration of plasticizer increases, it absorbs moisture and reduces the strength of oral strip.

In vitro disintegration time

Disintegration time is a major consideration in the development of OFDS which should disintegrates rapidly within a second. The optimized formulation F4 showed a low disintegration time of 20 ± 0.41 **s** [Table 3]. The faster

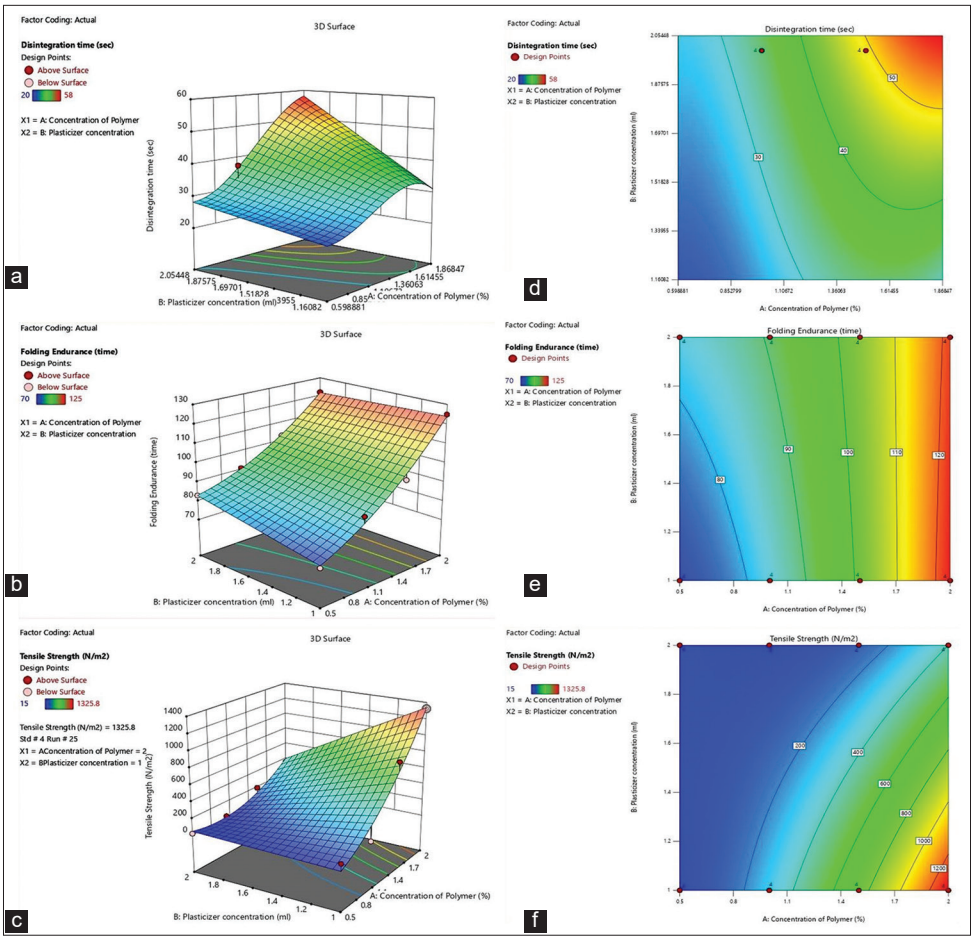

Figure 6: 3D-Plot of (a) Disintegration time, (b) Folding endurance, (c) Tensile strength and Contour plot of, (d) Disintegration time, (e) Folding endurance, and (f) Tensile strength

disintegration time of the optimized oral strip was due to an increase in the concentration of disintegrant which aids in the easy penetration of water in to the oral strip which subsequently leads to faster disintegration.

Percentage drug content

For formulations F1–F8, the percentage drug content ranged from 70.70% to 92.38%. The drug content of the formulation F4 was found to be **92.38%**, which lies within the limit of 90–110%.

In vitro dissolution studies

In vitro dissolution studies were conducted to estimate the percentage drug release. In this study, the dissolution behavior of OLM NC loaded OFDS was compared to plain OLM strip. All formulations from F1 to F8 showed an improved dissolution rate than plain OLM film. The percentage drug release at the end of 5 min from the plain OLM film and optimized formulation F4 was found to be 30.78% and 85.28%, respectively [Figure 7]. Formulation F4 showed 2-fold increase in dissolution rate than the plain OLM strip. This is due to the increased concentration of film former which has a greater effect on the drug release. However, an increase in plasticizer concentration does not have a significant effect on the drug release.

Kinetic modeling

Based on the physical characteristics and drug release studies, formulation F4 was chosen as best and it was subjected to kinetic modeling. Table 6 displays the kinetic release data and the results revealed that the release rate of the investigated formulations was best fitted with the Korsemeyer-peppas model with a higher R^2 value of 0.9336. The diffusion exponent "n" value in Korsmeyer-Peppas is >0.5, indicating that the model employs a non-fickian diffusion mechanism.[31]

Stability studies

The stability studies were conducted at 25°C/60% RH for the period of 60 days and the results are shown in Table 7. During the stability period, there is no discernible difference in the physical appearance of the oral strip. There are no significant changes in the disintegration time, folding endurance, and surface pH, which indicate that the formulation is stable.

Table 6: Kinetic modeling of optimized F4 oral fast-dissolving strip

Formulation	% Drug release at 5 min	Release kinetics of OLM strip					
		Zero-order	First-order	Higuchi's	Hixson Crowell	Korsmeyer Peppas	Diffusion exponent (n)
Optimized F4 strip	85.28%	0.8241	0.8802	0.9300	0.8690	0.9336	0.562

Table 7: Stability Studies of the oral fast-dissolving strip at 25°C at 60% RH for Formulation F4

Parameter	0 Days	30 days	60 days
Disintegration time (sec)	20.5±0.41	25±0.28	26.2±0.46
Folding endurance (Times)	124±1.69	121±0.47	116±0.47
Surface pH	6.46±0.021	6.38±1.39	6.31±0.008

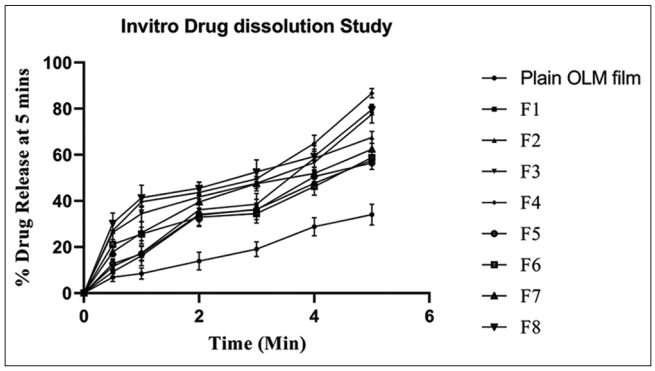

Figure 7: *In vitro* drug dissolution studies of Plain OLM film and OLM nanocrystals loaded into OFDS (F1-F8)

CONCLUSION

In comparison to the conventional method, the novel techniques such as nanonization provide better solubility for poorly soluble drugs. The optimized OLM NCs showed least PS. The saturation solubility of OLM NCs increased to 8.2-fold in comparison to pure OLM. In this work, the OLM NCs were successively incorporated into an OFDS. The OLM OFDS was optimized using multilevel categoric design. The dissolution profile of OLM loaded oral OFDS shows a 2-fold increase than plain OLM strip. The results conclude that low solubility of the drug can be resolved by the NC method. Hence, the OFDS loaded OLM NCs may serve as a viable alternative to conventional oral dosage form which helps in overcoming the poor patient compliance and first-pass metabolism.

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