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Box-Behnken Design for Development of Meloxicam Fast Disintegrating Sublingual Tablets with Enhanced Solubility and Dissolution by Dispersion Technique in the Management of Acute Pain

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Short Title: Fast Disintegrating Sublingual tablets of Meloxicam

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KEYWORDS
Box- Behnken Design; Fast disintegrating; Meloxicam; Sublimation; Sublingual tablets.

ABSTRACT:

Meloxicam (MOC) is selected as the model drug with poor aqueous solubility and bitter taste to maximize its potential over sublingual absorption. Fast disintegrating sublingual tablets (FDSTs) of MOC are fabricated to eliminate first-pass hepatic metabolism deliberating faster onset of action. Three-level and three-factor Box-Behnken Design (BBD) of experimentation was employed to develop FDSTs employing dispersion technology. The combined influence of three independent variables, namely, the concentration of super disintegrant (X1), the concentration of subliming agent (X2), and the ratio of drug: β-CD (X3), were estimated on dependent responses such as percent dissolution efficiency (% DE) (Y1), *in vitro* disintegration time (Y2) and force of adhesion (Y3). The results of the relevant responses are within the following ranges, 70.71- 95.75 % of DE, 30.3-132.8 sec of *in vitro* disintegration time, and 0.009-0.018 N of mucoadhesive force. Pre-compression and post-compression parameters also showed promising results, and the model was cross-validated by calculating the percent prediction error. The promising results of biopharmaceutical characterization of the developed FDSTs make this formulation an ideal sublingual drug delivery system for MOC with reduced GIT drug-related adverse reactions and faster onset of action in managing mild-to-medium-level acute pain.

Introduction

Meloxicam (MOC) is non-steroidal anti-inflammatory drug (NSAID) regarded as a prostaglandin-specific COX-II inhibitor [1,2]. Chemically speaking, it is 4-Hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1, 2-benzothiazine-3-carboxamide 1, 1-dioxide, which is a member of the oxicam derivatives enolic acid group [3,4]. The extended half-life of the oxicam medication family allows for once-daily administration, which is one of its main benefits. MOC is a BCS Class-II drug having poor solubility (around 4.4 µg/mL in water), limited dissolution, and high permeability [5,6]. It is used as an analgesic, particularly in cases where there is an inflammatory component, and for the symptomatic treatment of fever, sciatica, primary dysmenorrhea, renal colic, arthritis, and ankylosing spondylitis[7]. MOC is associated with adverse events related to GIT drugs and has limited solubility in acidic aqueous solutions. When taken orally, it experiences significant hepatic biotransformation that postpones the start of effect. Moreover, the acute aching or its related injuries may lessen the motility and production of stomach fluids, which would negatively impact the solubility, oral absorption, and breakdown of MOC[8].

In order to effectively address acute pain and inflammatory diseases, a sublingual medication delivery

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method for MOC was developed with the goal of improving absorption and quick beginning of action. Pharmaceutical dispersion technology was used in the current work to prepare the MOC solid inclusion complexes to increase their solubility and dissolution rate.[9–12]. Hydrophilic polymers were combined with β-cyclodextrin (β-CD) to produce an inclusion complex for preparation of MOC solid dispersions (SDs) [13,14]. Numerous patents, research publications, and SD-based products authorized by the U.S. FDA attest to the rising recognition of the significance of hydrophilic, polymer-based solid inclusion complexes using β-CD as a complex building agent [15-22]. To increase the solubility of poorly soluble medications, Water soluble cellulose ethers such as (Hydroxypropyl methyl cellulose, Hydroxy propyl cellulose, and Hydroxy ethyl cellulose), Polyvinyl pyrrolidine, Polyethylene glycol, and particular polysaccharides have been extensively used. [23–31].

In the current study, MOC solid dispersions (MOC-SDs) were made utilizing hydrophilic polymers and the kneading process at various ratios of drug: β-CD (1:0, 1:1, and 1:2)[32]. Phase solubility experiments were first carried out by creating inclusion complexes of MOC with several polymers, including HPMC K15, PEG 4000, and PVP K-30, and at varied β-CD concentrations ranging from 0 to 15 mM. When the dosage form comes into touch with saliva, solid inclusion complex development enables it to solubilize or dissolve more quickly in the sublingual region of the oral cavity. It also aids in hiding the drug's unpleasant taste. Sublimation was used to include the produced MOC-SDs into the formulation of MOC fast disintegrating sublingual tablets (FDSTs), which dissolve in the sublingual cavity in less than a minute. Using Design of Expert software (DOE Version 11.1.2), BBD of experimentation three factors at three levels using 17 runs was created using to study the impact of formulation factors on the delivery of MOC from FDSTs [33–35]. Combining the technologies of sublimation and dispersion might improve the drug's absorption via the sublingual mucosa and increase its dissolving efficiency, which would help relieve acute discomfort. Other tablet excipients are combined with inert solid components that volatilize easily, such as menthol, camphor, urea, naphthalene, ammonium carbonate, ammonium bicarbonate, etc., and their combination is then compacted into tablets. The tablets were then made to have porous architectures by sublimating the volatile ingredients out.

1. Materials And Methods

2.1 Materials

Yarrow Chemicals Mumbai kindly donated meloxicam, HPMC 5cps, Crospovidone, camphor, beta cyclodextrin, PVP K30, and PEG 4000, in that order. Finnar Chemicals provided the mannitol and talc. We purchased magnesium stearate from Molychem in Mumbai. Analytical-grade chemical agents and solvents were employed in this investigation.

2.2 Phase solubility studies

Phase solubility studies were carried out according to the protocol described by Higuchi and Conners. Fifty milligrams of excess MOC were combined with twenty milliliters of double-distilled water with different β-CD concentrations (0-14 mM). It was agitated with a rotary flask shaker for 48 hours at room temperature (28±0.5 °C) after being stoppered in a succession of 50 mL conical flasks. After agitating the mixture for 48 hours to reach equilibrium, two milliliter portions were taken out every hour and immediately passed through a 0.45 µ nylon disc filter. After the samples were appropriately diluted, they were evaluated for MOC at 363 nm using a UV-visible spectrophotometer, and the results were compared to prepared blanks. Three rounds of shaking were conducted until the estimations were stable.[36, 37]. Phase solubility tests were conducted for each of the three hydrophilic polymers—PVP K30, PEG 4000, and HPMC15cps—with and without adding them to the drug and β-CD solution at a concentration of 0.5%w/v, as indicated in Table 1. The studies were conducted twice, and the findings were presented as the mean ± standard deviation.

Table l: Experiment range and level of variables

Independent variables	Levels	Low	Medium	High
X_1 = Concentration SD (%)		3.0	6.0	9.0

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X2 = Concentration of SA (mg)		7.5	15.0	22.5
X3= D: β-CD ratio		1:0	1:1	1: 2
Dependent variables	**Code**	**X1 (%)**	**X2 (mg)**	**X3 (ratio)**
Y1 = *In vitro* disintegration (sec) Y2 = Dissolution efficiency (%) Y3 = Force of adhesion (N)	**F1**	6	22.5	1:2
	F2	3	15.0	1:2
	F3	6	22.5	1:0
	F4	6	7.5	1:0
	F5	9	22.5	1:1
	F6	6	15.0	1:1
	F7	6	15.0	1:1
	F8	3	7.5	1:1
	F9	6	15.0	1:1
	F10	3	22.5	1:1
	F11	6	7.5	1:2
	F12	9	15.0	1:2
	F13	3	15.0	1:0
	F14	6	15.0	1:1
	F15	9	15.0	1:0
	F16	9	7.5	1:1
	F17	6	15.0	1:1

2.3 Preparation of solid inclusion complex by kneading method

A homogenous mixture was created by combining precisely weighed quantities of medication and β-CD in equimolar ratios of 1:1 and 1:2 to prepare the ternary inclusion complex. Slowly, while kneading continuously, about 1.5 times the water to the physical mixture's entire weight was added. A hydrophilic polymer, HPMC 15cps, was added to the mixture at a concentration of 10%w/w of the total weight of the solid dispersion (SD) and worked into the mixture. After kneading the mixture for approximately 45 minutes, it was dried for 24 hours at 40 °C. A sieve with an 80 mesh opening was used to ensure that the powder's particle size distribution was homogeneous.

2.4 Design of experimentation

Design expert software was utilized to improve MOCFDSTs. The concentration of the super disintegrant (cross povidone) (X1), the concentration of the sublimating agent (camphor) (X2), and the rate of D:ß-CD (X3) in solid dispersions were chosen as the three most important independent process variables (factors), as shown in Table 1. We examined the effects of changing the independent factors on the dependent parameters, which included force of adhesion (Y3), percentage dissolving efficiency (Y2) and *in vitro* disintegration (Y1).

2.5 Preparation of MOC-FDSTs by direct compression method

Drug: β-CD (1:0/1:1/1:2) complex was mixed with super disintegrant at a concentration of 4 %, 5 %, and 6 %. Depending on the total weight of the tablet required, quantities of the diluent mannitol and later subliming agent, camphor (5 %, 10 %, and 15 %), were adjusted. The blend was finally mixed with lubricant and glidant and punched with the 6 mm dies to get the tablets (150 mg) with good mechanical strength.

2.6 Characterization of MOC-FDSTs

Drug-excipient compatibility study

For pure drug (MOC), β-CD, HPMC K15, physical drug mixture: β-CD (1:0.5), and optimized formulation, compatibility studies of drug excipients were carried out using FT-IR spectroscopy.

Pre-compression evaluation parameters

The flow characteristics of the formulation to be compressed, including the tapped density, bulk density, angle of repose, Carr's index, % porosity, and Hausner's ratio were assessed in the powder mix.

Post-compression evaluation parameters

The post-compression characteristics of the compressed FDSTs of MOC were assessed for weight variation,

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hardness, friability, thickness, diameter, surface pH, wetting time, disintegration time, water absorption ratio, and homogeneity of drug concentration [38-40].

In vitro visual disintegration test

In order to facilitate an easier characterization, a visual disintegration experiment was carried out by taking pictures of the disintegration process. Briefly, FDSTs were placed into glass crucibles and submerged in 1 mL of phosphate buffer solution (pH 6.8) that had been previously warmed to 37 ± 0.5 °C.

In vitro dissolution test

The dissolution investigation was performed in a USP type II apparatus using 300 mL of imulate salivary fluid (SSF) of pH 6.8 as the medium, which was spun at 50 rpm and kept at 37±0.5°C. At intervals of 1, 3, 5, 7, 10, 15, 20, 25, 30, 45, 60, 75, 90, and 105 minutes, 5 mL samples were taken out and replaced with 5 mL of new dissolving media. Using a double-beam UV-visible spectrophotometer, the materials were diluted appropriately and measured spectrophotometrically at 363 nm.

Mucoadhesion force and time

The *ex vivo* mucoadhesion strength and time were measured using a modified physical balancing technique. The sublingual tissue of a recently removed goat was extracted. The tissue was removed and then stored in SSF pH 6.8 at 4°C for further utilization. Using surgical method, the epithelium (slice thickness range: 1-2 mm) was removed from the underlying connective tissue while maintaining the presence of the basal membrane. The membrane was then given an hour to reacclimate to its newfound flexibility in receptor fluid. The *ex vivo* bio adhesive strength and bio adhesion strength were measured using the modified physical balancing method. Goat sublingual mucosa was cut into pieces around 2 cm in size and kept on a stainless-steel plate. Double-sided tape was used to secure the tablet to the top probe. Using a pipette, 30 µL of buffer was injected into the mucosa to provide uniform hydration following attachment. Over the course of 30 seconds, the FDSTs were applied with a force of around 0.5 N to the mucosa. Preload was taken out of the clamp and water was gradually supplied to the beaker from the burette. Mucoadhesive strength was defined as the weight of water needed to separate the tablet from the mucosa. Fresh mucosa was used to duplicate the experiment in exactly the same way (Figure 1)

Figure 1: Measurement of mucoadhesion strength using modified physical balance

A-Scale, B-Watch glass, C-Sublingual tissue, D-Sublingual tablet, E-Weight

Ex vivo permeation study

To assess MOC penetration via the procaine oral cavity epithelial layer, a vertical-type Franz diffusion cell (a two-compartment open model) was employed. To get rid of all the biological material that may have interfered with the drug analysis, the epithelium was allowed to acclimate in the isotonic solution for a whole night at room temperature. As seen in Figure 2, appropriate mucosa pieces were placed flanked by the Franz diffusion cell donor and acceptor compartments. After that, phosphate buffer solution (pH 6.8) was added, and it was allowed to equilibrate for 15 minutes at 37 ± 0.5 °C. A 0.5 mL sample aliquot was removed from the acceptor compartment and replaced with blank phosphate buffer at predefined intervals to maintain a constant sink condition.

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Figure 2: *Ex vivo* permiation study

A) Donor compartment B) Clip C) Oral tissue D) Receptor compartment E) Magnetic bead F) Water bath G) Magnetic stirrer

3. Results

3.1 Drug-excipient compatibility studies

FTIR data showed no shift in the pure drug (MOC) characteristic peak, suggesting no significant interaction between the MOC and the excipients in this study (Figure 3).

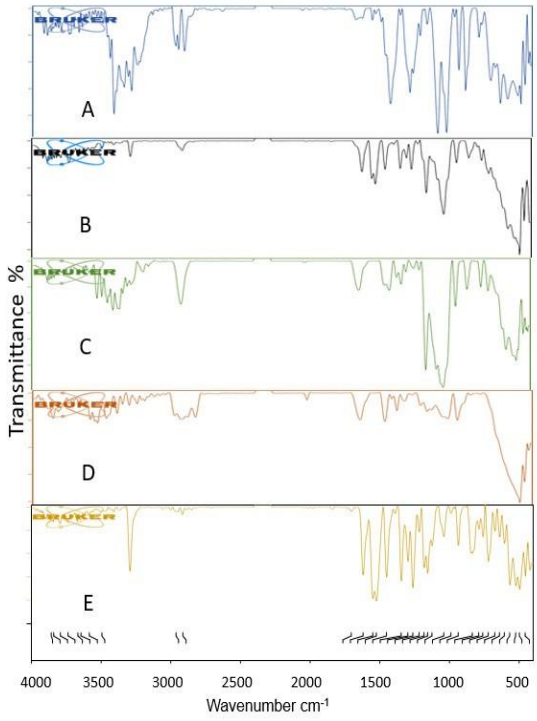

Figure 3: FTIR spectra of a) Meloxicam, b) β-CD, c) MOC: β-CD (1:0.5) d) HPMC 15 cps and e) FDST$_{OPT}$

3.2 Phase solubility studies

The phase solubility studies of MOC were conducted to know the solubility behaviour of the drug by forming inclusion complexes with β-CD at varying concentrations of 1-14mm. Three hydrophilic polymers viz., PVP K-30, PEG4000 and HPMC K-15 were included in the drug: β-CD complexes to assess the enhancement in the drug solubility. The order of increase in solubility of MOC was in the following manner D: β-CD: HPMC K15> D: β-CD: PEG 4000> D: β-CD: K30> D: β-CD> D (pure drug). Hence, the MOC solid inclusion complex prepared with β-CD as complex forming agent and HPMC K15 as hydrophilic polymer exhibiting highest solubility of 95.8 mM was chosen for further studies (Table 2).

Table 2: Phase solubility studies

Hydrophilic carrier	Slope (S_o)	Stability constant (K_s) (M^{-1})	Gibbs free energy (ΔG^o) (KJ.mol^{-1})	r^2
PVP K30	0.0072	2.86	-7.16	0.9336
PEG 4000	0.0127	5.02	-12.56	0.9688
HPMC K15	0.0148	5.83	-14.60	0.9527

3.4 Evaluation of pre-compression and post-compression parameters

The prepared powdered mixes showed good flow properties, with their angle of repose falling between 27° ± 0.4 and 33.6° ± 0.3. The manufactured powder blends were found to have good compressibility, with the compressibility index and percent porosity falling within the range of 7.7% ±0.1 to 16.0 ± 0.7 and 8.3% ± 0.3 to 20.0% ± 0.0, respectively. A Hausner's ratio of less than 1.25 indicated favourable flow property.

According to the Indian Pharmacopeia (I.P) specifications, the allowable percent deviation of weight

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variation for a tablet weighing from 130 to 324 mg should be NMT 7.5 % and it was found to be an average of 2.7 % ± 1.37. Adequate tablet hardness (3.5 to 4.0 kg/cm^2) and percent friability (<1 %) was found to be within limits for all the batches of formulations ensuring the tablets were mechanically stable. The thickness of the tablets was found to be in the range of 0.5 to 0.6 mm with less than 0.01 % RSD. The diameter of the tablet was found to be around 6mm less than 0.07 % RSD. The percent drug content was found to be NLT 89.1 % and 111.4 %, which was found to be with in the official acceptable of MOC NLT 85 % and NMT 115 % I.P.

The surface pH of the pure drug was 5.3, and the surface pH of the tablet was in the range of 6.1 to 6.6. The mucoadhesion force and time were found to be 0.009 to 0.018 N and 25 to 50 seconds, respectively. The water absorption ratio and wetting time were found to be 25 to 50 and 46 to 182 seconds, respectively. Hence, the batch of prepared FDSTs passed the post compression evaluation parameters as given in Table 3.

Table 3: Post compression parameters evaluated for prepared FDSTs

Formulation	SurfacepH	#Disintegration #(sec)	Muco-adhesion force #(N)	Muco-adhesion time #(sec)	Wetting time #(sec)	Water absorption ratio #
FDST1	6.3 ±0.1	132.8 ±1.9	0.011 ±0.001	25.5± 2.5	182.5±1.5	25.0±0.7
FDST2	6.5 ±0.0	111.8 ±1.7	0.009 ±0.001	33.0± 2.0	176.0±2.0	27.2±0.2
FDST3	6.2 ±0.2	30.3 ±0.9	0.010 ±0.001	38.5± 1.5	46.5±1.5	44.5±0.5
FDST4	6.1 ±0.3	30.5 ±1.7	0.015 ±0.001	47.0± 5.0	52.0±1.0	50.6±0.4
FDST5	6.4 ±0.1	94.1 ±1.0	0.016 ±0.005	50.0± 5.0	108.5±1.5	33.5±0.5
FDST6	6.6 ±0.3	69.1 ±1.5	0.012 ±0.006	41.5± 1.5	112.5±1.5	36.5±0.4
FDST7	6.6 ±0.0	69.1 ±1.5	0.012 ±0.006	41.5± 1.5	112.5±1.5	36.5±0.4
FDST8	6.2 ±0.2	54.8 ±0.9	0.011 ±0.000	38.5± 2.5	132.5±1.5	40.7±0.3
FDST9	6.6 ±0.01	69.1 ±1.5	0.012 ±0.006	41.5± 1.5	112.5±1.5	36.5±0.4
FDST10	6.3 ±0.3	80.0 ±2.7	0.015 ±0.001	40.0± 1.0	128.5±0.5	35.7±0.2
FDST11	6.5 ±0.2	105.5 ±1.8	0.018 ±0.002	35.0± 7.0	212.5±2.5	29.5±0.4

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FDST12	6.6 ±0.2	123.0 ±1.6	0.012 ±0.004	36.5± 1.5	192.5±1.5	26.0±0.1
FDST13	6.1 ±0.3	30.3 ±1.1	0.013 ±0.004	28.0± 3.0	60.0±1.0	48.8±0.3
FDST14	6.6 ±0.1	69.1 ±1.5	0.012 ±0.006	41.5± 1.5	112.5±1.5	36.5±0.4
FDST15	6.2 ±0.3	31.0 ±1.6	0.012 ±0.006	32.5± 9.5	48.0±1.0	46.3±0.1
FDST16	6.3 ±0.2	65.1 ±1.4	0.018 ±0.002	37.5± 7.5	119.0±7.0	39.6±0.3
FDST17	6.6 ±0.0	69.1 ±1.5	0.012 ±0.006	41.5± 1.5	112.5±1.5	36.5±0.4

n=2, Mean ± S.D.

3.5 In vitro disintegration visual test

It was challenging to provide a specific time point (in seconds) to each of the suggested images to more accurately depict the MOC FDSTs rapid disintegration. The *in vitro* visual disintegration test sequence of the FDST photos in 55 seconds, broken down by time points A through F, is displayed in Figure 4. For the manufactured batch of 17 formulations, the *in vitro* disintegration time varied between 30.3 ± 1.1 and 132.8 ± 1.9 seconds (Table 3).

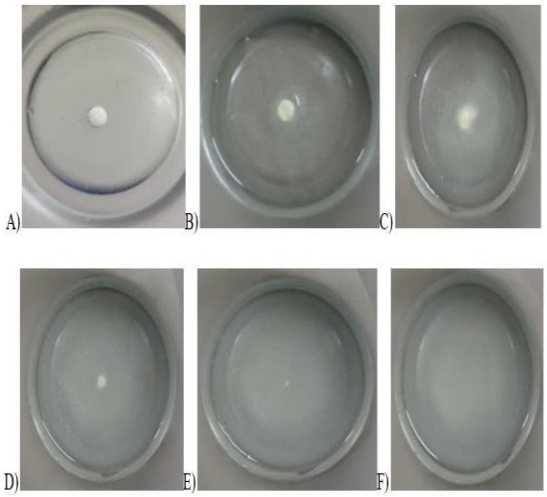

Figure 4: *In vitro* visual disintegration test a) to f) sequence of photographs at different time points

3.5 In vitro dissolution studies

The formulations FDST3, FDST4, FDST13, and FDST15 containing pure drug MOC without complex forming agent β-CD and hydrophilic carrier (HPMC) were found to release around 93.7 %, 88.1 %, 89.5 %, and 95.5 % of the drug, respectively, within 90 minutes. The formulation FDST5, FDST6, FDST7, FDST8, FDST9, FDST14, FDST16, and FDST17 containing pure drug meloxicam, complex forming agent β-CD in 1:1 ratio, and hydrophilic carrier (HPMC) were found to release around 92.6 %, 89.06 %, 89.06 %, 87.6 %, 89.06 %, 88.1 %, 89.06 %, 89.1 % and 89.06 % of drug respectively, within 90 minutes. The formulation FDST1, FDST2, FDST11, and FDST12 containing pure drug MOC and complex forming agent β-CD in 1:2 ratio and hydrophilic carrier (HPMC) were found to release around 86.3 %, 83.8 %, 84.6 % and 86.7 %, of drug respectively within 90 minutes. The *in vitro* release profiles of MOC from FDST1-17 are represented in Figure 5.

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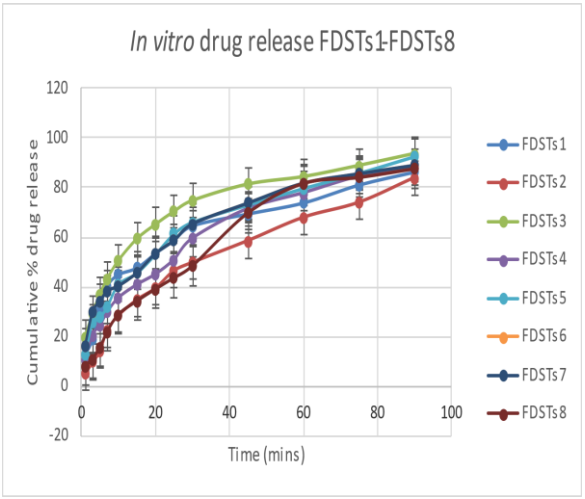
a .



b.

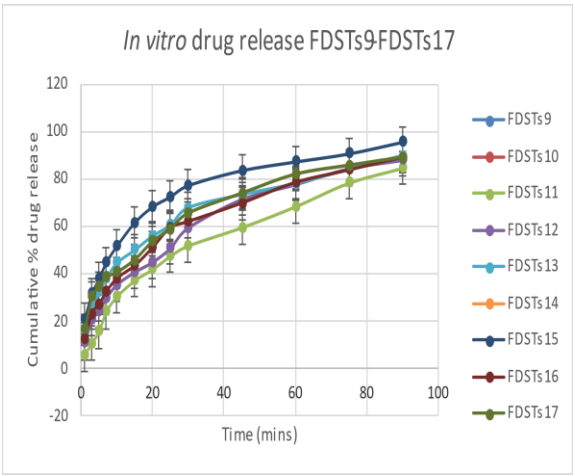


Figure 5: *In vitro* drug release profiles of a) FDST1-FDST8 and b) FDST9-FDST17

For each constructed FDSTs, the correlation coefficient (r) values for the first and zero-order kinetics were found. With strong correlation coefficient values (r) ranging from 0.995 to 0.973, it was shown that the manufactured FDSTs of MOC obeyed first-order kinetics, i.e., the drug release is reliant on its starting drug concentration.

The dissolution data were fitted to the Hixon Crowell, Korsmeyer-Peppas and Higuchi for finding the drug release mechanism. The Higuchi diffusion process was followed by all generated FDSTs, with correlation coefficient (r) values ranging from 0.921 to 0.992. The Korsmeyer Peppas plots, with the exception of the FDST 2, FDST8, FDST11, and FDST12 formulations, which follow a non-Fickian diffusion mechanism, were shown to be linear with Peppa's value (n) larger than 1, suggesting a super case 2 transport mechanism.

3.6 Box-Bhenken design of experimentation

The outcomes of the model cross-validation, improved formulation prediction, and statistical assessment of dependent variables were analyzed below[41, 42]. By using one-way analysis of variance at a 5% level of significance, the intended response parameters were statistically analyzed, and the model's significance was determined. Using the F-test, each parameter was assessed separately. The independent and dependent variables showed a strong association, as evidenced by the R^2 values of Y1, Y2, and Y3, which were determined to be 0.6426, 0.9746, and 0.9933, respectively. Multiple linear regression analysis was used to establish a mathematical link among the components (independent variables) and outcomes (dependent variables) in order to ascertain the factor levels that result in the best dissolving responses. Following is the second-order polynomial regression equation (1) that fixed to the data:

$$Y=P_0+P_1X_1+P_1X_2+P_3X_3+P_{12}X_1X_2+P_{13}X_1X_3+P_{11}X_{12}+P_{22}X_{22}+P_{33}X_{32} \quad - (1)$$

where P1, P2, P11, P12, and P22 are the coefficients measured from the determined observational values of Y; X1, X2, and X3 indicate the primary effects; and P0 is the intercept, which is the arithmetical mean of the results from 17 runs. The BBD model's factor effects and corresponding p-values are displayed for the responses Y1, Y2, and Y3. If effects differ substantially from zero and p-values are less than 0.05, then a factor impacts the response. The model coefficients of the three responses and their equations are specified as follows:

$$Y_1 = 74.17-4.08X_3 \quad (2)$$

$$Y_2 = 72.63 + 4.54X_1 + 10.62X_2 + 43.88X_3 \quad (3)$$

$$Y_3 = 0.12 – 0.0125X_2 – 0.015X_2 – 0.005X_1X_2 – 0.01X_{32} \quad (4)$$

The quantitative impact of the variables (X1 and X2) on the replies (Y1, Y2, and Y3) is represented by equations (2), (3), and (4). Both graphical and numerical

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optimization methods were used to carry out the optimization. The Y1 (minimum), Y2 (maximum), and Y3 (maximum) constraints were used in the optimization process to find the ideal configurations for the independent variables in the new formulation. The desirability function was determined to be 0.942, which is effective for the optimized formula demonstrating the acceptability of the formulation. The desirability and overlay plots are displayed in Figure 6 A) and B), respectively.

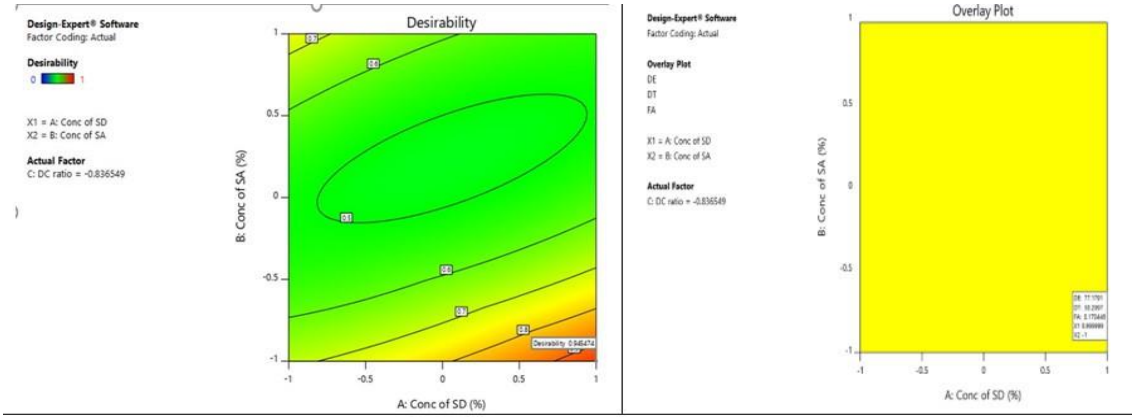

Figure 6: a) Desirability Plot and b) Overlay plot for FDST$_{OPT}$

3.7 Preparation and characterization of optimized FDST (FDST$_{OPT}$) of MOC

The independent variables X_1 (concentration of SD), X_2 (concentration of SA), and X_3 (D: β-CD ratio) were found to be 9.0 mg, 7.5 mg, and 1:1, respectively for optimum formulation included with the drug inclusion complex of 21.225 mg per a 150 mg tablet weight adjusted accordingly with the diluent (mannitol). Optimized formulations were prepared with the optimal level's values (X_1, X_2, and X_3) and evaluated for pre and post-compression evaluation parameters. All the pre and post-compression parameters for the prepared FDST$_{OPT}$ were within the limits of IP specifications with a less % RSD as given in Table 4. *Ex vivo* permeation study was performed and the drug release from the receptor compartment was found to be 3 mg of drug release in 2 hours. The flux value was 0.007 ± 0.00194 mg/cm^{2}h^{-1}, and the drug efficiency was 0.4 ± 0.011 mg/cm^2 (Figure 7).

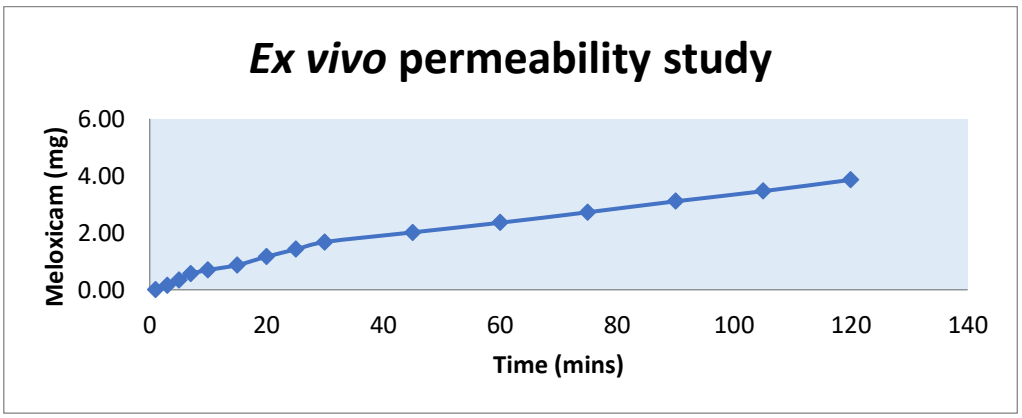

Figure 7: *Ex vivo* permeability plot of optimized formulation

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Table 4: Precompression and post compression evaluation parameters of optimized formulation

Precompression evaluation parameters #					
Bulk density (g/cc)	**Tapped density (g/cc)**	**Hausner's ratio**	**% Compressibility index**	**% Porosity**	**Angle of repose (º)**
0.4±0.004	0.52±0.002	1.16±0.005	15.6±0.300	19.04±0.000	26.5±0.400
Post compression evaluation parameters #					
% Weight variation	**% Friability**	**Thickness (mm)**	**Diameter (mm)**	**Hardness (kg/cm^2)**	**% Drug content**
2.7±0.88	0.645	0.6±0.000	6.0±0.170	4.0±0.050	108.3±1.300
Surface pH	**Disintegration time (sec)**	**Mucoadhesion force (N)**	**Mucoadhesion time (Sec)**	**Wetting time (Sec)**	**Water absorption ratio**
6.7±0.0	55.5±1.5	0.016±0.0	46.5±2.5	55.5±1.5	44.6±0.3

n=2, Mean ± S.D.

3.8 Cross-validation of model

Cross-validation of $FDST_{OPT}$ was performed, and the experimental values, predicted values, and relative percentage error of optimized formulation responses (*in vitro* disintegration time, % dissolution efficiency, and mucoadhesion strength) were represented in Table 5. A reasonable agreement was observed between predicted and experimental values, as indicated by low values (<5 %) of prediction error. This proved the model's validity and ascertained the effect on drug release and mucoadhesion strength.

Table 5: Percent prediction error of responses

Responses	**Predicted value**	**Experimental value**	**% Prediction error**
% Dissolution Efficiency	77.10	80.50	-4.44
In vitro disintegration time	30.30	55.50	-83.16
Mucoadhesion strength (g)	0.17	0.16	5.88

4. Discussion

In order to optimize its potential over sublingual absorption, meloxicam (MOC), a bitter medicine with limited water solubility, is chosen as the model medication. The objective of this research was to prepare FDSTs that comprise of MOC solid dispersions (MOC-SDs) combined with β-cyclodextrin and a hydrophilic polymer. This permits the formulation to dissolve or disintegrate in the sublingual region of the oral cavity in a matter of minutes upon contact with saliva, thereby alleviating acute pain and concealing the unpleasant taste of the medication[43, 44]. Phase solubility tests of MOC were carried out at different concentrations of 1-14 mm to form inclusion complexes with β-CD in order to determine the drug's solubility behavior. Powder flow is the first important factor to take into account when deciding if the powder is suitable for a specific process route since continuous processing necessitates the powder's movement from one piece of equipment to another. The second most crucial element to take into account is compressibility, or the powder's capacity to permanently deform under pressure and form a hard compact. FDSTs of MOC-SDS were prepared using the continuous blending and direct compression method since the medicinal product blend had good powder flow as well as good compressibility. The effect of changing

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any of the three independent factors—namely, concentration of super disintegrant (cross povidone) (X1), concentration of sublimating agent (camphor) (X2), and rate of D: ß-CD (X3) in solid dispersions on the dependent parameters, such as *in* v*itro* disintegration (Y1), % dissolution efficiency (Y2), and force of adhesion (Y3), were analysed. The response surface analysis's p-values made it clear that there may be an interaction among the three independent variables at the relevant factor levels, suggesting that every independent variable may tend to change the outcome of the others on the MOC dissolution lag time.

Because MOC is a weakly acidic medication whose solubility depends on pH due to various ionization states, it dissolves poorly in the upper gastrointestinal system when taken orally. The sublingual mucosa becomes irritated by the pure MOC medication, which has a surface pH of 5.7. The surface pH of the FDSTs of MOC-SDs was 6.7±0.2, preventing pH change-induced mucosal irritation. The MOC-FDSTs that were generated demonstrated a rapid disintegration time of 42.6±2.6 seconds and dissolved 99.2±0.1% of the total drug content in 2 hours after the formulation was improved. Examining the drug *ex vivo* permeation, the optimized MOC-FDSTs released 3.86±0.1 mg, 1.76±0.1 mg, and 0.48±0.1 mg of MOC in the acceptor solution, donor solution, and sublingual tissue after two hours. The *ex vivo* assessment of MOC-SDs loaded FDSTs yielded the biopharmaceutical metrics drug flux (Js), constant of permeability (Kp), t_{lag} in mins, drug taken up per unit area of the sublingual tissue (De), and accumulation (Ac). In the treatment of mild-to-medium-level acute pain, FDSTs of MOC produced using dispersion technology not only offered greater water solubility to permit a speedier start of action but also enhanced dissolving rate for better oral absorption.

5. Conclusion

Sublingual administration offers a scalable, economical, and industrially applicable method for improving drugs with low solubility and low bioavailability caused by pre-systemic first-pass metabolism. The purpose of FDSTs is to facilitate this. These consist of a hydrophilic polymer that, upon coming into contact with saliva, dissolves or disintegrates the dosage form in the sublingual region of the mouth in less than a minute, eliminating the need for chewing or drinking. The chemical modification of the bitter functionality also aided in the taste improvement. The formulation was ideally suited for straightforward scale-up because of the fewer steps in the process. It is possible to finish it with standard equipment from the pharmaceutical sector. These findings suggest that elderly patients or those with swallowing difficulties may benefit from the use of MOC-FDSTs to treat acute pain.

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Conflict of interest

None.

Source of support

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