RESEARCH ARTICLE

Optimization and Characterization of Meloxicam Orodispersible Tablets using Mixed Hydrotropy for Enhanced Water Solubility

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Abstract

Introduction: In order to attain rapid discharge in saliva and enhanced absorption, drug was incorporated in a fast-dissolving dosage form (ODTs) as a solid dispersion.

Objective: In this work, ODTs of Meloxicam were prepared by sublimation techniques where different subliming agents were used with super disintegrant.

Materials and Methods: Hydrotropic solid dispersions were prepared using different ratios (1:2, 1:4 and 1:6) of drug and hydrotropic blends (Niacinamide, Anhy. Sodium citrate, Sodium Salicylate and Sodium benzoate). Best hydrotropic solid dispersion was selected to prepare ODTs comprising croscarmellose sodium and camphor in different concentrations and other pharmaceutical excipients. T3 was selected for optimization experimental designs from the primary trial batches due to lowest disintegration time and highest in vitro drug release. Secondary batches (F1-F9) were prepared by using 32 full factorial designs with different concentrations of croscarmellose sodium (12, 14 and 16 mg) and camphor (8, 10 and 12 mg) as two independent variables while disintegration time and percent friability were considered as two dependent response variables. These formulations were subjected to study of various post-compression evaluation

Results and discussion: parameters like hardness, thickness, friability, weight variation, disintegration time (25-117 sec) and in-vitro drug release (99.09%). Equilibrium solubility studies were reported that by utilizing hydrotropy, the solubility of meloxicam got enhanced from 20.5 to 140.96 times as compared to its aqueous solubility. The desirability fraction was used to optimize the response variables for specific targets, i.e., minimum disintegration time and maximum dissolution, and the responses obtained were consistent for experimental values.

Keywords: Factorial design; Meloxicam; Mixed hydrotropic solid dispersion; Orodispersible tablet; Solubility; Sublimation

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INTRODUCTION

Swallowing difficulty is a commonly associated problem for the age groups especially geriatric and pediatric patients, other groups include mentally ill patients and those with developmental disabilities. In some instances, such as dizziness, travel sickness, unexpected outbreaks of allergic reactions or vomiting and lack of drinking water, it is difficult to swallow conventional tablets.[1] In novel Drug Delivery systems (NADDS) recent developments are available, known as Orodispersible Tablets (ODTs) to overcome this issue. Advantages of these solid dosage formulations include water-free administration, dosage consistency, simple and easy portability, increased patient compliance and rapid onset of action.[2] ODTs may be dissolved or suspended in the mouth (Saliva) for rapid swallowing, typically disintegrating within 60 seconds or less, and the drug is absorbed by local oral mucosal tissue or gastrointestinal tract.[3]

Meloxicam is well known as a non-steroidal anti-inflammatory (NASAID) drug of the oxicam class used to treat rheumatoid arthritis, osteoarthritis, primary dysmenorrhea, and acute postoperative pain management.[4] It is stated to be critical inhibitor of COX-2 (Cyclooxygenase 2) enzyme. This enzyme is accountable for transforming arachidonic acid to prostaglandin H_2, which are known as inflammatory mediators.[2]

Meloxicam is BCS (biopharmaceutical classification system) class II drug.[5] Although it has excellent bioavailability (89%), its poor aqueous solubility reduces the rate of absorption and dissolution. The current therapeutic scenario calls for a strong need for a delivery strategy to improve meloxicam's therapeutic efficacy by means to increase its solubility.[6]

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Solubility is, therefore a very significant property for the design of pharmaceutical products because it influences the effectiveness of the drug, its potential production and also influences pharmacokinetic parameters such as release, transport and the degree of absorption in the organism.[7] But most of the time it gets difficult to formulate poor-water soluble drugs as the dissolution is rate-limiting step for its absorption in the gastrointestinal tract. Different methodologies can be studied comprehensively to boost water solubility and dissolution rate of poor water-soluble drugs such as micronization, self-emulsification, pH-changing solubilization, salt formation, co-solvent, solid dispersion and hydrotropy application etc. This analysis summarizes the use of hydrotropy first coined by the Scientist Carl A. Neuberg, which is one of the promising methods for improving solubility in several folds by adding a large quantity of a hydrophilic solute to improve the aqueous solubility of the poor water soluble solute without any chemical alteration of the drug compound.

The agents that cause the solubility enhancement are called hydrotopes or hydrotropic agent. This enhancement in solubility can be as high as 100–500 folds is a result of the creation of organized micellar assemblies of hydrotropes at critical micelle concentration (CMC) and its usually considered to be an exponential function of hydrotropic agents concentration. Commonly use hydrotopes include citric acid, urea, nicotinamide, sodium lauryl sulphates, sodium acetate, sodium citrate, and sodium salicylate etc.[8] This study's main objective was to improve meloxicam's water solubility by using combinations of various hydrotropic agents so that oral bioavailability can be increased and the side effect of individual hydrotropes used in large amounts should be minimized.[9]

MATERIALS AND METHODS

Chemicals

Meloxicam (Akums drugs and Pharmaceutical Ltd. Haridwar) was used as a model drug niacinamide, anhydrous sodium citrate (Crest life science, Baddi) and sodium benzoate, sodium salicylate (Alina Healthcare, Baddi) were selected as a hydrotropic agents, camphor, menthol and thymol (Alina Healthcare, Baddi) as subliming agents were added to promote porosity of tablets. Croscarmellose sodium (CDH Pvt Ltd. Mumbai) was used as a superdisintegrants to reduce tablets disintegration time. A small amount of saccharin sodium (CDH Pvt Ltd. Mumbai) was used as artificial sweetener. Magnesium sterate and mannitol (IIMT College of Pharmacy, Greater Noida) were used as glident and bulking agent respectively. All used solvents were of analytical grade.

Experimental

Solubility analysis (UV Spectrophotometric method)

Meloxicam is freely soluble in methanol. Thus, using the UV method, methanol has been used as a solvent to build the meloxicam calibration curve. To prepare stock solution of concentration (1000 µg/mL), 100 mg of meloxicam was dissolved in 100 mL of methanol. Accurately weighed meloxicam transferred in 100 mL volumetric flask and then added 80 mL of methanol in it. The drug was allowed to mix for 20 minutes. The remaining quantity of methanol was added to complete the volume and ensure complete mixing by manually shaking the mixture. After that serial dilution were prepared from this stock solution (0.05, 0.10, 0.15, 0.20 and 0.25 mL of this stock solution was pipette out in 10 mL volumetric flask and make up the volume to the mark with methanol) and absorbance of each concentration was reported at 364 nm using UV spectrophotometer. The standard calibration curve was attained by plotting absorbance vs. concentration in graph. Over the range of 5 to 25 µg/mL, calibration curve for meloxicam was linear (R2=0.999). Overlain spectra describing the reproducibility of λ_{max} that confirmed and validated the process shown in Figure 1.

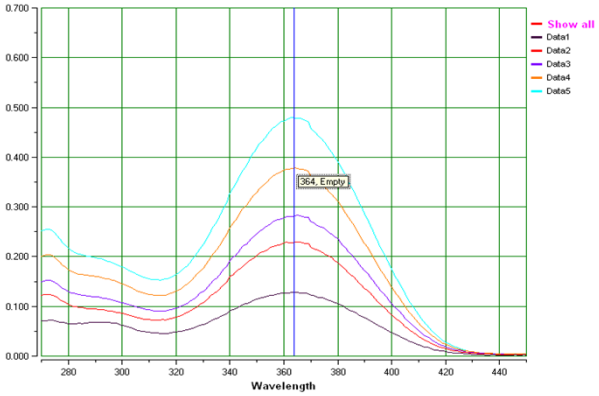

Figure 1: Overlain spectra of meloxicam

Comparative solubility determination analysis with various hydrotropic agents at room temperature

Primarily, meloxicam solubility was calculated individually in hydrotopes solutions i.e., Sodium Salicylate (SS), Sodium Benzoate (SB), Anhyd. Sodium citrate (SC), Niacinamide (N) at 40% solution concentration using distilled water as solvent system (Table 1). For determining solubility, a surplus amount of meloxicam has been applied to a 10 mL volumetric flask containing various aqueous system like distilled water and 40% hydrotropic agets solutions. Through an orbital shaker, the volumetric flask was shaken mechanically at 28oC ±1 °C for 12 hours. For next 24 hrs this solution was allowed to equilibrate and then centrifuged for 5 min at 2000 rpm. Supernatant layer of volumetric flask was filtered over Whatman filter paper grade 41. Aliquot has been properly diluted with water and spectrophotometrically analyzed using UV spectrophotometer at 364 nm.

From the results of the above studies, it has been concluded that meloxicam solubility increased with the use of various hydrotropic agents. For example, solubility in 40% solution of Sodium salicylate, Sodium benzoate, Anhyd. Sodium citrate, Niacinamide was found to be 20.5, 26.25,

29.7 and 64.54 respectively. After that all these 4 hydrotropic agents were used in combination to determine solubility enhancement. The blend of (SS+SB+SC+ N) in total

Table 1: Meloxicam solubility in various Hydrotropes

Hydrotropic agents	Total concentration (%w/v)	Solubility (%w/v)	Solubility enhancement ratio
Sodium Salicylate	40	0.246	20.5
Sodium benzoate	40	0.315	26.25
Anhyd. Sodium citrate	40	0.356	29.70
Niacinamide	40	0.774	64.54
Niacinamide + Anhyd. Sodium citrate + Sodium benzoate + Sodium Salicylate	40	1.688	140.96

* Meloxicam solubility in distilled water = 0.012 mg/mL

Table 2: Composition of hydrotropic solid dispersion using blend of hydrotropic Carrier

Drug: Hydro tropes blend	Individual quantity of hydrotropic agent in blend taken (gm)				
	Melox icam	Niacina mide	Anhydrous Sodium citrate	Sodium benzoate	Sodium Salicylate
1:2	1.00	0.75	0.55	0.45	0.25
1:4	1.00	1.45	1.05	0.85	0.65
1:6	1.00	2.00	1.75	1.25	1.00

concentration of 40% shows highest solubility enhancement ratio (140.96) therefore, this optimized blend of hydrotropic agents was chosen for solid dispersion preparation.

Preparation of hydrotropic solid dispersion (HSD)

This process is similar to common solvent evaporation method except distilled water was used in place of organic solvent like ethanol and methanol. To prepare HSD, meloxicam and hydrotropic carriers (Niacinamide +Anhydrous Sodium Citrate + Sodium Benzoate + Sodium Salicylate) were precisely weight in different ratios (1:2, 1:4, and 1:6) and allowed to dissolve in sufficient quantity of distilled water by continuous stirring with magnetic stir and solvent was allowed to evaporate by applying heat at 40°C (Table 2). As a result, semisolid mass was formed.

To make this semisolid mass pulverized, it will spread in thin layers on watch glasses and kept it in oven for complete drying till a constant weight obtained with no further loss of weight. After that this dried mass was triturated with the help of glass pestle mortar and allowed to pass via sieve #100 and kept for six days in desiccator. Finally, this dried HSD powder stored in air tight glass bottle for formulation development [10].

Evaluation of hydrotropic solid dispersion for tablet formulation

Determination of drug content

Powdered hydrotropic solid dispersion containing 1-gm equivalent meloxicam were precisely weighed and taken into a 500 mL volumetric flask. Approximately 450 mL of distilled water was added in the flask and shaken to fully dissolve the solid dispersion mass. After that volume was made to complete with distilled water and the absorbance of this solution was calculated at the respective wavelengths against concerned reagent blank at 364 nm. The drug content was determined using regression equation.[11]

In-vitro dissolution Rate Study

In dissolution rate tests, bulk drug samples and hydrotropic Solid Dispersions equal to 1-gm of the meloxicam were used. USP paddle apparatus is used to carry out dissolution study for 1 hour. The stirrer was calibrated for rotation at a rate of 50 rpm. All of the tests preserved a temperature of 37 ± 0.5°C using 900 mL distilled water. 5 mL sample of the dissolution medium were collected at specific time intervals and replaced after each withdrawal by the same volume of distilled water. The samples were tested for drug content by calculating the absorbance of sufficiently diluted sample solutions with distilled water against the appropriate reagent blank at respective wavelength of 364 nm.[11]

Drug- carriers' compatibility analysis

Fourier transformed infrared (FTIR) spectroscopy

Pure drug, hydrotropes and individual polymers were subjected to FTIR spectrophotometer (Shimadzu, Affinity-1) to obtained spectra for compatibility analysis. About 10 mg of sample was directly mixed with equal weight of dried KBr (potassium bromide) and compressed into a disc in a hydraulic press at a pressure of 75 Kg/cm2. These samples were scanned from 400 to 4000 cm^{-1}.[12]

Chromatographic determination (Thin layer chromatography)

For the compatibility analysis of drug and hydrotopes,

Table 3: Formulation composition for meloxicam ODTs (preliminary trial batches)

Ingredients used	Formulation codes (quantité in mg)								
	T1	T2	T3	T4	T5	T6	T7	T8	T9
HSD	50	50	50	50	50	50	50	50	50
CCS	10	12	14	6	7	8	8	7	6
Camphor	8	9	10	-	-	-	-	-	-
Thymol	-	-	-	-	-	-	8	10	12
Menthol	-	-	-	8	9	10	-	-	-
Magnesium Stearate	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Sodium Saccharine	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mannitol up to	130	130	130	130	130	130	130	130	130
TOTAL	200	200	200	200	200	200	200	200	200

*HSD equivalent to equivalent to 7.5 mg of the drug

Table 4: Formulation composition for meloxicam ODTs (factorial batches)

Ingredients used	Formulation codes (quantité in mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
HSD	50	50	50	50	50	50	50	50	50
CCS	12	12	12	14	14	14	16	16	16
Camphor	8	10	12	8	10	12	8	10	12
Thymol	3	3	3	3	3	3	3	3	3
Menthol	3	3	3	3	3	3	3	3	3
Magnesim Stearate	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Sodium Saccharine	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Mannitol up to	121.7	119.7	117.7	119.7	117.7	115.7	117.7	115.7	113.7
TOTAL	200	200	200	200	200	200	200	200	200

*HSD equivalent to equivalent to 7.5 mg of the drug

experiments were performed on silica gel coated TLC plates against Methanol: Dichloromethane: Ammonia in a proportion of (2:8:0.1). Samples were applied on 10 mm base band on plates and then it was placed into previously mobile phase saturated TLC chamber for 20 minutes. Well defined separation and clear peaks were developed after a short period of time. Separated spot densiometric calculation was performed in the range from 200-400 nm [13].

Formulation of Meloxicam Orodispersible tablets (ODTs)

Sublimation method was used for the preparation of meloxicam ODTs trial batches namely T1-T9 (Table 3). Accurately weight quantity of hydrotropic solid dispersion (quantity equivalent to 7.5 mg of the drug), super disintegrant such as croscarmellose sodium and variety of subliming agents such as camphor, thymol and menthol were used in different concentration for final tablet formulation. Other pharmaceutical excipients like magnesium sterate, sodium saccharine and mannitol were used as lubricant, sweetener and diluents respectively [14].

Before use, every single one of the material was passed through sieve No. 60 and precisely weighed quantities of ingredients were systematically mixed and compressed into tablets using 8 mm flat Punch and Die set of single punching machine. Meloxicam ODTs were then put in an oven at 40 0C until we obtained a constant weight.

Formulation of meloxicam ODTS using experimental design (Factorial batches)

Statistical analysis

Effect of formulation variables on the response variables was assessed statically by the implementation of ANOVA at 0.05 levels with commercial software "State ease, USA ® 6.05 design of experiment". The concept was estimated using a quadratic model. The polynominal equation for the response was built using regression coefficient of the factor.

In experimental design factorial design is a methodology that allows evaluation of the factor involved and its relative significance in formulation of dosage forms. 32 full factorial designs consist of 2 factors assessed at 3 levels (low, mid and high) and experimental trials were allowed to perform at all possible potential combinations [15].

From the preliminary trials batch (T1-T9), T3 showed highest drug release of 96.14% and 98.91% in phosphate buffer and simulated salivary fluid both at pH 6.8 respectively and disintegration time of 35sec which is within acceptable limits so that it was selected for optimization design. In optimization designing of T3 batch, two independent formulation variables - Factor A (% of super disintegrant-croscarmellose sodium) at three levels (X1) (12, 14 16mg)

and Factor B (%of subliming agent-camphor) at three levels (X2) (8,10,12 mg) were evaluated. 9 experiments in total were conducted with all potential combination to get three replicates centre point. The composition of factorial batches (F1-F9) shown in Table 4.

Response surface designs

Response surface designs are useful for modelling continuous factors to a curved quadratic surface. If within the factor region there is a minimum or maximum response, it can be defined by a surface response model. For a quadratic function, three distinct values are required for each component, so that the typical two-level designs cannot match curved surfaces. Central composite design is the most common response surface design. It combines two-level fractional factor and two other kinds of points

Center points- factor values are at mid-range (Zero) Axial points-one factor is set at mid-range (Zero) and other one factor is set at axial value [16].

Characterization parameters of prepared Meloxicam ODTs

Weight uniformity test

Weight variation of solid dosage form was done by weighing 10 tablets independently, and mean weight was determined. Each individual tablet weight was compared with mean weight to evaluate weight uniformity of tablets [17.]

Thickness and Hardness uniformity

Mean break strength of 10 individual tablets were calculated by Monsanto tablet hardness tester. Vernier calliper was used for the measurement of thickness of 10 individual tablets at three different positions. Results were recorded as three-measurement mean (±SD) [17].

Friability test

In Roche Friabilator, 10 pre-weighed tablets were subjected to place in plastic drum of friabilator chamber that rotates at 25 rpm for a period of 5 minutes. The tablets were reweighed and percentage weight loss was reported as a friability factor [18].

In -vitro disintegration time (D.T)

In- vitro dissolution analysis was executed by means of USP paddle apparatus (Type II) at 50 rpm using phosphate buffer and simulated salivary fluid as dissolution media (pH 6.8) managed at 37°± 0.5°C. Part of dissolution media were removed at specifically different time period intervals and replaced with fresh media and filtered. Dissolved quantity of drug was calculated by U.V. Spectrophotometric study at364 nm of collected samples against reagent blank. The tests were carried out in triplicate [17].

Accelerated stability analysis at 40o± 2o C/75 % ± 5 % RH

The optimized formulations were stored at 40 °C and 75 % RH in a stability chamber for duration of 90 days. The samples were tested each month for their drug content.

RESULTS AND DISCUSSION

Evaluation of hydrotropic solid dispersion

Estimation of drug content in meloxicam hydrotropic solid dispersion

Hydrotropic solid dispersion of meloxicam and mixed hydrotopes in weight ratio (1:6) showed maximum drug content that is 98.72%. The drug content grew constantly as the hydrotropic carrier ratio increased (shown in Table 5).

Estimation of in vitro dissolution studies of meloxicam hydrotropic solid dispersion

Meloxicam HSD in weigh ratio of 1:2, 1:4 and 1:6 showed percent drug release of 71.19%, 75.12% and 86.19% respectively (showed in Table 6). Due to highest drug release in meloxicam HSD weigh ratio 1:6 (86.19%), it was selected for formulation of ODTs trial batches.

Table 5: Drug content of meloxicam hydrotropic solid dispersion

Hydrotropic blend	Drug : Hydrotrope	Percent Drug Content(HSD)
Niacinamide+Anhyd. Sodium citrate+Sodium benzoate +Sodium Salicylate	1:2	96.93%
	1:4	97.84%
	1:6	98.72%

Table 6: In-Vitro Dissolution Rate Studies of HSD containing drug and hydrotropic blends in distilled water

SL. No.	Time in seconds	% drug release		
		1:2	1:4	1:6
1.	0	0	0	0
2.	5	44.38	52.11	62.14
3.	10	56.01	59.08	68.01
4.	15	61.93	64.18	72.78
5.	20	65.58	68.01	77.19
6.	25	68.71	70.93	81.08
7.	30	71.19	75.12	86.19

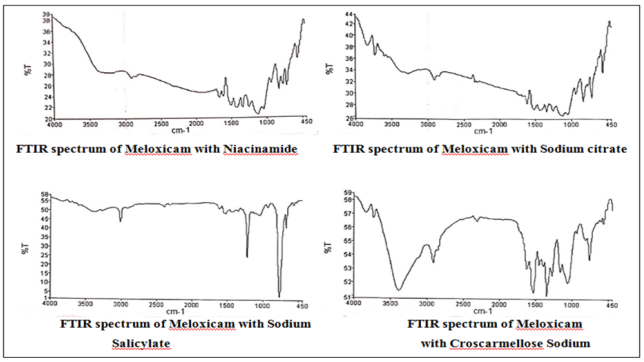

Figure 2: FTIR spectrum of meloxicam with hydrotopes Niacinamide, Sodium citrate, Sodium salicylate and Croscarmellose sodiumDrug-carriers' compatibility analyses

Fourier transformed infrared (FTIR) spectroscopy analysis

IR absorption spectrum of pure drug showed characteristic sharp peaks –NH stretching at 3286 cm-1, C=O amide at 1607 cm-1, C=C aromatic ring at 1452 cm-1, S=O stretching vibration for two sulphonyl groups at 1335 cm-1 and 1157 cm-1. Similarly, IR spectrum of excipients i.e., Niacinamide, Anhydrous sodium citrate, Croscarmellose sodium, Sodium salicylate and Sodium benzoate were obtained [19]. FTIR spectra of pure drug and its physical mixture with excipients demonstrate the identical characteristic drug bands at the same ranges, suggesting there was no interaction between the drug and the excipients used in the formulation shown in Figure.2.

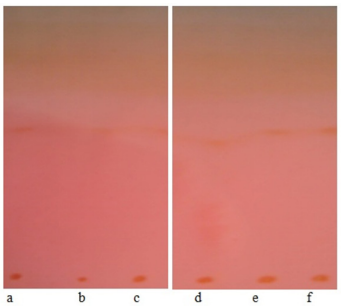

Figure 3: Photographic illustration of TLC with different combination of drug and carriers

Table 7: RF values data for pure drug and different combination of drug and carriers

Spot No.	Pure drug and carriers	Rf value
a.	M	0.38
b.	M +SS	0.38
c.	M+N	0.39
d.	M+SC	0.37
e.	M+SB	0.38
f.	M+CCS	0.37

*M (meloxicam), SS (sodium Salicylate), N (Niacinamide), SC (anhyd. Sodium citrate), SB (sodium benzoate), CCS (croscarmellose sodium)

Thin layer chromatography (TLC) analysis

The Rf values of pure drug and with combination of different excipients was found almost similar with the pure drug thus demonstrated compatibility between drug and different excipients used in the formulation shown in Table 7 and Figure.3.

Evaluation of meloxicam ODTs prepared by using experimental design (factorial batches)

Nine factorial batches (F1-F9) prepared by selected trial batch T3 were allowed to evaluate for pre and post compression parameter. Formulated tablets were of uniform in weight variation which passes the criteria as per IP specification because material was free flowing (Carr's index<15 and angle of repose <30) [20]. Hardness was reported to be 2.09-3.7 Kg/ cm2. Friability less than 1 per cent showed good tablet mechanical resistance. Formulation F9 were considered to be effective and showed in vitro disintegration time of 25 sec, which promotes their faster dispersion in the mouth as compared to others factorial batches shown in Table 8.Photographic representation of in-vitro release of factorial batches in phosphate buffer and simulated salivary fluid both at pH 6.8 shown in Figure. 4.

Table 8: Post- compression data for meloxicam ODTs factorial batches (F1-F9)

Evaluation parameters					
Formulations Code	Thickness (mm)	Hardness (kg/cm2)	Weight variation	Friability (%)	D.T(sec)
F1	2.56	3.70	passes	0.238	117
F2	2.61	3.70	passes	0.241	68
F3	2.62	3.60	passes	0.346	80
F4	2.49	3.10	passes	0.322	106
F5	2.64	3.00	passes	0.312	68
F6	2.54	2.90	passes	0.387	54
F7	2.59	2.70	passes	0.419	44
F8	2.60	2.50	passes	0.404	30
F9	2.89	2.09	passes	0.351	25

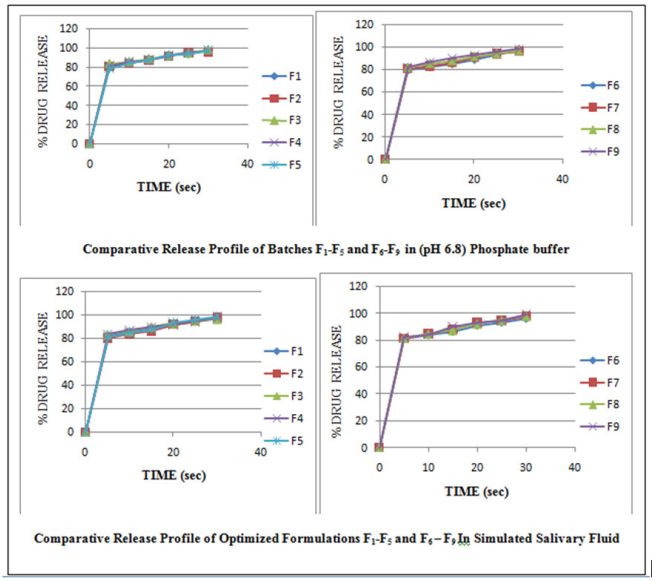

Figure 4: Photographic illustration of release profile of factorial batches F1-F9 in phosphate buffer and simulated salivary fluid both at pH (6.8)

Optimized formulation using 32Full factorial design

The present research used 32 full factorial designs for the optimization of different variables to obtained desired responses for the formulation development. In the present factorial design Croscarmellose Sodium (superdisintegrant), and camphor (subliming agent) were elected as independent variables, both were at three different levels while percentage friability and disintegration time were elected as dependent variables. Layout of 32 full factorial is shown in Table 9.

Table 9: 32 full factorial design layout for optimized batch

Factorial batches codes	Levels of variables in coded forms		D.T.(sec)	Friability %
	X1 (mg)	X2 (mg)		
F1	-1	-1	117	0.238
F2	-1	0	68	0.241
F3	-1	1	80	0.346
F4	0	-1	106	0.322
F5	0	0	68	0.312
F6	0	1	54	0.387
F7	1	-1	44	0.419
F8	1	0	30	0.404
F9	1	1	25	0.351

Coded values	Actual value	
	X1(mg)	X2 (mg)
-1	12	8
0	14	10
1	16	12

Table 10: Calculation data for testing model

For D.T (sec)							
Source	SS	df	MS	f value	p value		R2
Model-Quadratic	751 0.3	5	150 2.03	9.02	0.04 99	Significant	0.9367
For friability (%)							
Model-Quadratic	0.03 31	5	0.0 066	28.86	0.00 97	Significant	0.9796

*(SS), Sum of squares ; (df), degree of freedom ; (MS), mean of square ; (R2), regression coefficient.

Table 11: Predicted data of optimized formulation

Factor A	Factor B	Disinte gration time (sec)	Friability %	Desira bility	Remarks
12.34	10.15	67.7	0.344	1.000	Selected

Through implementing one-way ANOVA design was evaluated using quadratic model with the forms of equation. Calculation involves in testing of model shown in (Table 10) and polynominal equation for the response was built using the regression coefficient of the factors. The desirability fraction was used to optimize the response variables for specific targets, i.e. minimum disintegration time and maximum dissolution, and the responses obtained were consistent for experimental values. A desired batch (optimized formulation) was formulated at X1= 12.34 (mg) and X2= 10.15 (mg) to confirm the predicted responses of disintegration time and percentage friability shown in Table [11].

In vitro evaluation of optimized formulation

In vitro dissolution study reveals that release of meloxicam from the prepared ODTs was very fast. Formulation shows 98.76% in phosphate buffer (pH 6.8) and 99.65% in simulated salivary fluid shown in Table 12 and Figure 5. Initial rapid swelling has been induced by super disintegrant like croscarmellose sodium which is consistent with tablet disruption. Hydrotropic blended tablets demonstrate rapid dissolution of the drug so that optimized formulation absorption and bioavailability has been enhanced.

Table 12: Dissolution data of Optimized Formulations in (pH- 6.8) Phosphate buffer and Simulated Salivary Fluid (SSF)

S. No.	Time in seconds	%Drug release (pH- 6.8) Phosphate buffer	Simulated salivary fluid (SSF)
1	0	0	0
2	5	85.26	86.02
3	15	86.17	88.23
4	30	90.86	92.34
5	45	92.03	93.74
6	60	96.57	98.19
7	70	98.76	99.65

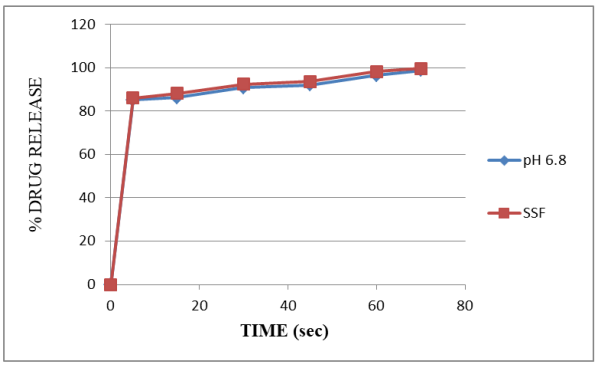

Figure 5: graphical representation of release profile of optimized formulations in (pH- 6.8) phosphate buffer and in simulate salivary fluid

Elucidation of Response Surface Graph

Contour graph

In the contour graph, disintegration time and Percent friability increases from blue to red region and the prediction points were determined shown in Figures 6 and 7.

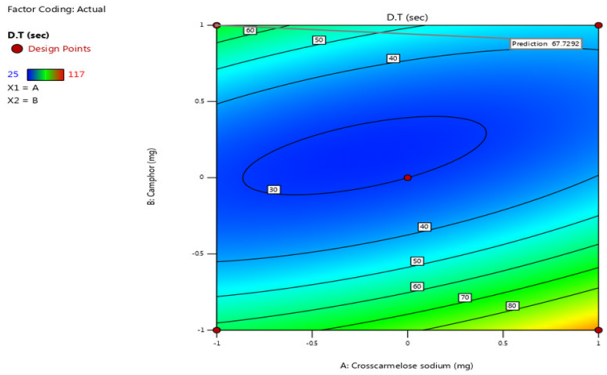

Figure 6: Contour plot demonstrating the impact of Croscarmellose sodium and camphor on disintegration time

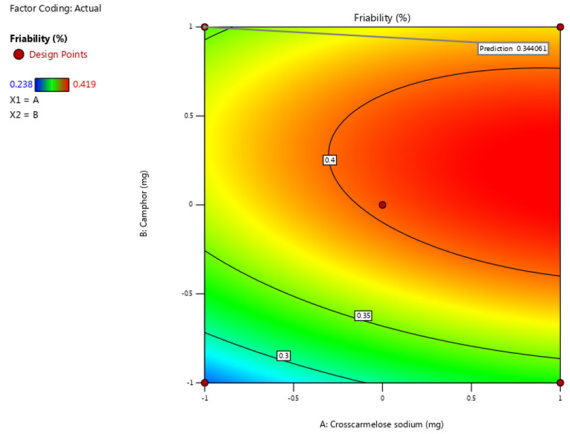

Figure 7: Contour plot demonstrating the impact of Croscarmellose sodium and camphor on friability

Response surface plot

Friability and disintegration were influenced via the Percent of camphor and Croscarmellose sodium in the response surface graph shown in Figures 8 and 9.

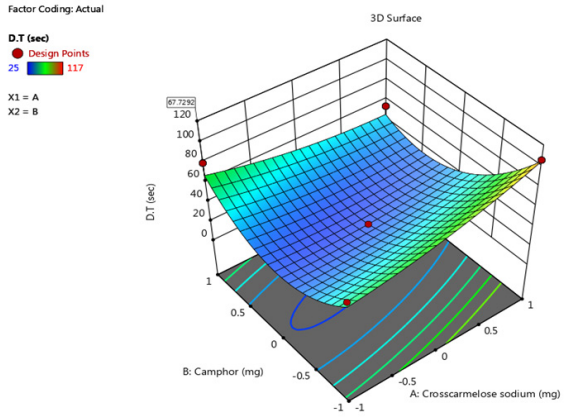

Figure 8: Response surface demonstrating the impact of Croscarmellose sodium and camphor on disintegration time

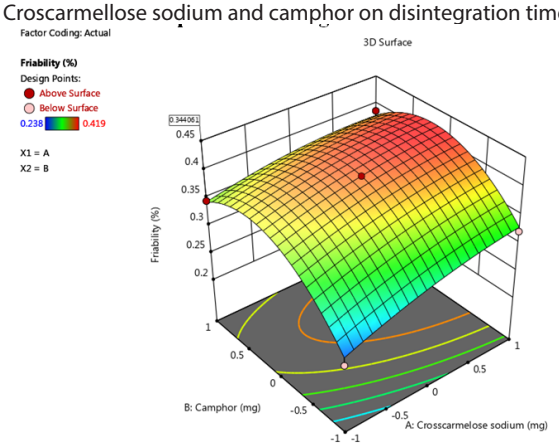

Figure 9: Response surface plot demonstrating the impact of Croscarmellose sodium and camphor on friability

Accelerated stability analysis of optimized formulation (F)

The stability analysis was conducted on optimized meloxicam ODTs in accordance with ICH guidelines under an accelerated atmosphere (40o ± 2oC/75% ±5% RH), which reported that formulations had no physic-chemical changes and there was no significant reduction in drug content shown in Table 13.

Table 13: Stability analysis data under extended conditions (40o± 2oC T and 75% ±5% RH)

Study parameters	Time Duration in days			
	0	30	60	90
Appearance	Unchanged	Unchanged	Unchanged	Unchanged
Hardness (Kg/cm2)	3.1	3.1	3.0	2.9
Disintegration time (seconds)	40	40	43	47
Percent friability	0.2535	0.2548	0.2586	0.2601

CONCLUSION

The main goal of mixed hydrotropic solubilization technique is to enhance the solubility of poorly water-soluble drug. Equilibrium solubility studies were performed and its results concluded that by exploiting hydrotropic, the solubility of meloxicam got enhanced from 20.5 to 140.96 times as compared to its aqueous solubility. Drug release levels of the orodispersible tablets were significantly superior to those of the traditional tablets. The result suggested that the presence of croscarmellose sodium and camphor not only improves the rate of or dispersion but also increases the drug release rate. Thus, sufficient ODTs of meloxicam for the large-scale formulation is achievable.

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REFERENCES

1. Jaafar, I.S., Sabar, M.H. and Mahmood, S.Z., Formulation and In-vitro Evaluation of Fast Dissolving Tablets of Meloxicam Solid Dispersion.
2. Swamy, P.V., Areefulla, S.H., Shirs, S.B., Smitha, G. and Prashanth, B., 2007. Orodispersible tablets of meloxicam using disintegrant blends for improved efficacy. *Indian Journal Of Pharmaceutical Sciences, 69*(6), p.836.
3. Samprasit, W., Akkaramongkolporn, P., Ngawhirunpat, T., Rojanarata, T. and Opanasopit, P., 2015. Formulation and evaluation of meloxicam oral disintegrating tablet with dissolution enhanced by combination of cyclodextrin and ion exchange resins. *Drug Development and Industrial Pharmacy*, *41*(6), pp.1006-1016.
4. Kulkarni, U., Karkar, V., Bhavik, P. and Ahmad, Q.J., 2010. Formulation and Optimization of Fast Dissolving Meloxicam Tablets by Vacuum Drying Technique. *International Journal of Pharmaceutical Sciences and Research*, *1*, pp.8-133.
5. Noor, R., Hasan, S.M., Hassan, F. and Rehman, A., 2017. Formulation and Dissolution enhancement of Meloxicam tablets using Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer and Povidone in combination. *Pakistan Journal of Pharmaceutical Sciences*, *30*(2).
6. Sapra, K. and Singh, S., 2013. Formulation development and optimization of self emulsifying drug delivery system (sedds) of meloxicam. *Int J Pharm Pharm Sci*, *5*(2), pp.524-30.
7. Sharma, S., Chauhan, V. and Neha, M., 2015. Formulation optimization of mouth dissolving tablets of meloxicam

using mixed hydrotropic solublization. *Journal of Scientific and Innovative Research*, *4*(2), pp.76-82.

8. Vivek Chauhan at el., Formulation Optimization of Immediate Release Tablets of Ofloxacin Using Mixed Hydroptropic Solublization Technique. Indo American Journal of Pharm, ISSN NO:2231-6876, Research.2015:5(02).
9. Lionberger, R.A., Lee, S.L., Lee, L., Raw, A. and Lawrence, X.Y., 2008. Quality by design: concepts for ANDAs. *The AAPS journal*, *10*(2), pp.268-276.
10. Maheshwari, R.K. and Jagwani, Y., 2011. Mixed hydrotropy: Novel science of solubility enhancement. *Indian Journal of Pharmaceutical Sciences*, *73*(2), p.179.
11. Malviya, T., Shah, S. and Tyagi, C.K., 2021. Formulation Evaluation and Characterization of fast Dissolving Tablets of Meloxicam. Research Journal of Pharmaceutical Dosage Forms and Technology, 13(2), pp.113-117.
12. Vippagunta, S.R., Maul, K.A., Tallavajhala, S. and Grant, D.J., 2002. Solid-state characterization of nifedipine solid dispersions. International Journal of Pharmaceutics, 236(1-2), pp.111-123.
13. Starek, M. and Krzek, J., 2012. TLC determination of meloxicam in tablets and after acidic and alkaline hydrolysis. *Acta Poloniae Pharmaceutica. Drug Research*, *69*(2).
14. Elder, D.P., Kuentz, M. and Holm, R., 2016. Pharmaceutical excipients quality, regulatory and biopharmaceutical considerations. *European journal of pharmaceutical sciences*, *87*, pp.88-99.
15. Gohel, M., Patel, M., Amin, A., Agrawal, R., Dave, R. and Bariya, N., 2004. Formulation design and optimization of mouth dissolve tablets of nimesulide using vacuum drying technique. *AAPs PharmSciTech*, *5*(3), pp.10-15.
16. Chang, J.S., Huang, Y.B., Hou, S.S., Wang, R.J., Wu, P.C. and Tsai, Y.H., 2007. Formulation optimization of meloxicam sodium gel using response surface methodology. *International journal of pharmaceutics*, *338*(1-2), pp.48-54.
17. Singh, J. and Singh, R., 2009. Optimization and formulation of orodispersible tablets of meloxicam. Tropical Journal of Pharmaceutical Research, 8(2).
18. Aly, A.M., Semreen, M. and Qato, M.K., 2005. Superdisintegrants for solid dispersion: to produce rapidly disintegrating Tenoxicam tablets via camphor sublimation. Pharmaceutical technology (2003), 29(1), pp.68-78.
19. Abd Elbary, A., Ali, A.A. and Aboud, H.M., 2012. Enhanced dissolution of meloxicam from orodispersible tablets prepared by different methods. *Bulletin of Faculty of Pharmacy, Cairo University*, *50*(2), pp.89-97.
20. Kalpana, P., Manish, S., Dinesh, S.K. and Surendra, J.K., 2010. Solid Dispersion: Approaches, Technology involved, Unmet need & Challenges. Drug invention today, 2(7).