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Formulation optimization of mouth dissolving tablets of Meloxicam using mixed hydrotropic solublization technique

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Abstract

The objective of the present study was to develop mouth dissolving tablets of meloxicam in order to achieve rapid release in saliva which may result in enhanced absorption and thereby improved bioavailability. Six batches of mixed hydrotropic solid dispersions and physical mixtures were prepared using different ratios (1:2, 1:4 and 1:6) of hydrotropic blends (urea, Nicotinamide & sodium citrate). The best batch was selected to prepare mouth dissolving tablets comprising solid dispersion of Meloxicam in six preliminary batches using croscarmellose sodium & crospovidone as superdisintegrants and camphor as subliming agent in different ratios along with other excipients. Secondary batches were prepared based on 32 factorial design with amount of superdisintegrant (crospovidone) and camphor (subliming agent) as two independent formulation variables. Two dependent response variables considered were disintegration time and percentage friability. All the batches of mouth dissolving tablets were evaluated for pre-compre sion parameters and post-compression parametes. The results of accelerated stability studies revealed no physical and chemical changes in the tablets during three months.

Keywords: Solubility, Mixed hdrotropy, Mouth dissolving tablets, Factorial design.

Introduction

Solubility, is thus a very important property for pharmaceutical product design because it affects the drug efficacy, its future development and also influences the pharmaco-kinetics, such as the release, transport and the degree of absorption in the organisms. On the other hand, in the pharmaceutical industry, the majority of active pharmaceutical ingredients (APIs) are isolated in the solid form *via* crystallization and hence solubility is important for the design of these processes. The term Hydrotropy was coined in 1916 by Neuberg. Neuberg found that aqueous solutions of certain salts possess the ability to enhance the solubility in water of water-insoluble substances. The phenomenon of increasing the aqueous solubility of substance normally insoluble or sparingly soluble in water by the addition of third component or additive is termed as hydrotropy or hydrotropism. The agent that causes the solubility enhancement is called hydrotrope or hydrotropic agent. Common hydrotropes include urea, citric acid, sodium benzoate, sodium salicylate, aromatic sulfonic acids and their sodium salts etc. This increase in solubility can be as high as 100-200 times and is generally observed to be an exponential function of the concentration of hydrotropes. Mixed hydrotropic solubilization technique is the phenomenon to increase the solubility of poorly water-soluble drugs in the blends of hydrotropic agents which may give miraculous synergestic enhancement effect on solubility of poorly water soluble drugs. The concentration of individual hydrotropic agent can be reduced to minimize the side effects of one hydrotrope. For e.g. in place of using a large concentration of one hydrotrope a blend of 5 hydrotropes can be employed in 1/5th concentrations reducing their individual toxicities.

Mouth dissolving tablets that disintegrates and dissolves rapidly in the saliva within few seconds without the need of drinking water or chewing. A mouth dissolving tablet usually dissolves in the oral cavity within 15 sec to 30 min. Most of the MDTs include certain superdisintegrants and taste masking agents.

Optimization has been defined as the implementation of systematic approaches to achieve the best combination of product and/or process characteristics under a given set of conditions. Development of drug delivery systems invariably involves handling a plethora of drugs, polymers, excipients and

processes. The conventional changing one single variable at a time (COST) approach of drug formulation development suffers from several pitfalls. The trial and error approach can somehow achieve the solution of a specific problem but attainment of the true optimum composition or process is never guaranteed. Optimization techniques using systematic design of experiments represent effective and cost-effective analytical tools to yield the best solution to a particular problem.

Meloxicam is a nonsteroidal anti-inflammatory drug used to relieve the symptoms of arthritis, primary dysmenorrhea, fever and as an analgesic, especially where there is an inflammatory component. It is practically insoluble in water; slightly soluble in acetone soluble in dimethyl formamide; very slightly soluble in ethanol (96%) and in methanol.

Materials and methods

Material

Meloxicam was obtained as a gift sample from Vivan Life Sciences (Mumbai). Urea, Nicotinamide, Sodium Citrate, Hydrochloric acid (HCl), Camphor, Aspartame, MCC and Magnesium Stearate, was obtained from CDH Pvt. Ltd (Mumbai). Crosspovidone and Croscarmellose sodium was obtained from Vardha Biotech (Mumbai).

Methods

Drug-excipient compatibility study

Compatibility study using FTIR technique

Drug-excipient compatibility study was carried out by FTIR (Shimadzu, Affinity-1) spectrophotometry. The mixture of drug and KBr (potassium bromide) was ground into fine powder using mortar pestle and then compressed into discs in a hydraulic press at a pressure of 75 kg/cm^2. Each KBr disc was scanned 45 times at a resolution of 2 cm^{-1}. The characteristic peaks were recorded and compared with that obtained with individual formulation.

Thin layer chromatographic method

The drug-excipient compatibility was also studied by densitometric TLC evaluation. The spots of drug and different excipients were obtained on pre-coated silica gel (F_{254}) plates against ammonia: methanol: dichloromethane in the ratio of 1:20:80 (v/v) as mobile phase. The densiometric evaluation of separated spot was performed at 254 nm.

Equilibrium solubility determination at room temperature

Solubility of Meloxicam was determined at 28°±1°C. An excess amount of drug was added to 250 ml conical flask containing different aqueous systems viz. distilled water & 40% solution of blend of hydrotropes. The flasks were shaken mechanically for 12 hrs at 28°±1°C, in an orbital shaker. These solutions were allowed to equilibrate for the next 24 hrs and then centrifuged for 5 min at 2000 rpm. The supernatant of each flask was filtered through Whatman filter paper No. 41. The filtrates were diluted suitably and analyzed spectrophotometrically against corresponding reagent blank.

Enhancement ratios in solubilities were determined by following formula -

$$\text{Enhancement ratio} = \frac{\text{Solubility in hydrotropic solution}}{\text{Solubility in distilled water}}$$

Preparation of Hydrotropic Solid dispersion &Physical Mixture

For preparation of hydrotropic solid dispersion containing Meloxicam and hydrotrope blend in the ratio of 1:2 (w/w), accurately weighed 2.0 gm of hydrotropic blend and 1.0 g of Meloxicam were used. Minimum (possible) quantity of distilled water, at 80°-85°C contained in a 250 ml beaker, was used to dissolve Hydrotrope. Then, Meloxicam was added to the beaker and a teflon coated magnetic bead was dropped in it. Stirring of magnetic bead in beaker was started using a magnetic stirrer. Meloxicam got completely solubilized. Stirring was continued till a semisolid was obtained in the beaker (after evaporation of a large quantity of water) which was spread on watch glasses in thin layers for quick drying. The watch glasses were kept in the oven maintained at 60°-65°C for drying. When mass became pulverizable, it was triturated with the help of pestle mortar and again kept in oven for drying.

After almost complete drying, the powder of solid dispersion was passed through sieve # 100 and kept for 6 days in a desiccator containing blue silica gel. The obtained hydrotropic solid dispersion powder was stored in air-tight glass bottles. Similarly hydrotropic solid dispersions of Meloxicam and hydrotropic blends [1:4 &1:6 (w/w)] were prepared.

To prepare physical mixture containing Meloxicam and hydrotropic blend in the ratio of 1:2 (w/w) accurately weighed 1.0 g Meloxicam & 2.0 g hydrotropic blends were triturated intensely for 10 min using glass pestle &mortar. Then the powder mass was shifted through sieve # 100. Similarly physical mixtures of Meloxicam and hydrotrope [1:4 & 1:6 (w/w)] were prepared (Table 1).

Table 1: Different ratios of Drug and Hydrotrope in PM and HSD

S. No.	Drug / hydrotrope ratio
1.	1:2 (Urea + Nicotinamide + Sodium Citrate)
2.	1:4 (Urea + Nicotinamide + Sodium Citrate)
3.	1:6 (Urea + Nicotinamide + Sodium Citrate)

Based on the data of drug content and the dissolution studies, a suitable mixed hydrotropic solid dispersion was selected for further formulation development (mouth dissolving tablet dosage form).

Formulation composition for tablets of preliminary trial batches:

The formulation was divided into six batches prepared by different superdisintegrants as depicted in the table 2.

Experimental Design

Factorial design is an experimental design technique by which the factor involved and their relative importance can be assessed.

A 3^2 full factorial design containing 2 factors evaluated at three levels and the experimental trials were performed at all possible combinations (Table 3).

The two independent formulation variables evaluated included:

Factor A: % of superdisintegrant (crospovidone) (X_1) (4, 8&12)
Factor B: % of subliming agent (camphor) (X) (0, 5&10)
In total, 9 experiments were conducted with three replicates of center point.

Table 2: Formulation chart for preliminary trial batches

Name of Ingredients	T_1	T_2	T_3	T_4	T_5	T_6
HSD	49.35	49.35	49.35	49.35	49.35	49.35
CP	8	-	4	8	-	4
CCS	-	8	4	-	8	4
Camphor	0	0	0	10	10	10
Talc	3	3	3	3	3	3
Aerosil	2	2	2	2	2	2
Aspartame	2	2	2	2	2	2
Magnesium Stearate	2	2	2	2	2	2
MCC	133.65	133.65	133.65	123.65	123.65	123.65
TOTAL	200	200	200	200	200	200

Table 3: Actual and coded values of the factors

Model	Actual values			Coded values		
Factor	**Low level**	**Mid level**	**High level**	**Low**	**Mid**	**High**
Factor -A	4	8	12	-1	0	+1
Factor-B	0	5	10	-1	0	+1

Statistical Analysis

The effect of formulation variables on the response variables were statically evaluated by applying one-way ANOVA at 0.05 level using a commercially available software package Design of Experiments® 6.05 (Stat Ease, USA). The design was evaluated by quadratic model bearing the form of equation (1).

$$Y= b_0 + b_1 X_1 + b_2 X_2 + b_3 X_1 X_2 + b_4 X_1^2 + b_5 X_2^2 \quad \text{…… eq-1}$$

Where y is the response variable, b_0 the constant and b_1, b_2, $b_3 \ldots b_5$ is the regression coefficient. X_1 and X_2 stand for the main effect; X1&X2 are the interaction terms showing how response changed when two factors were simultaneously altered. X_1^2, X_2^2 were quadratic terms of the independent variables to evaluate the nonlinearity. Using the regression coefficient of the factors, the polynomial equation for the response was constructed. Only significantly, contributing factors were considered for the equation generation.

Desirability Details

The method made use of an objective function, D (X), called the desirability function. It reflected the desirable ranges for each response (di). The desirable ranges were from zero to one (least to most desirable respectively). The simultaneous objective function is a geometric mean of all transformed responses.

If any of the responses or factors fell outside their desirability range, the overall function became zero. For simultaneous optimization, each response must have a low and high value assigned to each goal.

Maximum:

di = 0 if response < low value
$0 \leq di \leq 1$ as response varies from low to high
di = 1 if response > high value

Minimum:

di = 1 if response < low value
$1 \leq di \leq 0$ as response varies from low to high
di = 0 if response > high value

Target:

di = 0 if response < low value
$0 \leq di \leq 1$ as response varies from low to target
$1 \leq di \leq 0$ as response varies from target to high
di = 0 if response > high value

Range:

di = 0 if response < low value
di = 1 as response varies from low to high
di = 0 if response > high value

Result and Discussion

Table 4: UV-Spectrophotometric characteristics of Meloxicam using different solvent systems

S. No	Hydrotrope in D.W	Regression equation	R^2
1.	Urea	Y=0.022X-0.010	0.998
2.	Sodium citrate	Y=0.024X-0.013	0.996
3.	Sodium benzoate	Y=0.023X+0.059	0.996
4.	Nicotinamide	Y=0.023X-0.040	0.996
5.	Urea + Nicotinamide	Y=0.024X+0.028	0.998
6.	Urea +Sodium citrate	Y=0.022X+0.045	0.997
7.	Nicotinamide + Sodium citrate	Y=0.024X+0.037	0.999
8.	Urea+ Nicotinamide + Sodium citrate	Y=0.025X+0.020	0.998
9.	Urea+ Nicotinamide + Sodium benzoate	Y=0.023X-0.049	0.998

Full factorial design: A 3^2 randomized full factorial design was used to optimize the variables in the present study. The two independent formulation variables were evaluated, each at 3 levels, and experimental trials were performed for all 9 possible combinations. The amount (4,8 &12 mg) of crospovidone (X_1), and camphor (0, 5&10 mg) of tablets (X_2), were selected as independent variables. The percentage friability and D.T. were selected as dependent variables.

Table 5: 3^2 Full Factorial Design Layouts

Batch Code†	Variable Levels in Coded Form		D.T. (sec)	Friability %
	X_1 (mg)	X_2 (mg)		
F-l	-1	-1	120	0.235
F-2	-1	0	90	0.168
F-3	-1	1	60	0.137
F-4	0	-1	50	0.266
F-5	0	0	32	0.213
F-6	0	1	25	0.203
F-7	1	-1	40	0.400
F-8	1	0	30	0.257
F-9	1	1	20	0.223
Coded values	**Actual value**			
	X_1(mg)	X_2 (mg)		
-1	4	0		
0	8	5		
1	12	10		

Table 6: Calculations for Testing the Model in Portions

	For D.T.(sec)				
	DF	**SS**	**MS**	**F**	**R^2**
Regression					
FM	5	8828.44	1765.69	59.89	0.990
RM	3	8421.72	2807.24	28.35	0.944
Error					
FM	3	88.44	29.48		
RM	5	495.17	99.03		
	For % friability				
	DF	**SS**	**MS**	**F**	**R^2**
Regression					
FM	5	0.042	8.40	10.54	0.946
RM	2	0.038	0.019	18.87	0.862
Error					
FM	3	2.391	7.97		
RM	6	6.089	1.101		

*DF indicated: degrees of freedom; (SS), sum of squares; (MS), mean of squares; (F), Fischer's ratio; (R^2) regression coefficient; (FM), full model; and (RM), reduced model

Table 7: Summary of Regression Analysis Results

For D.T.(sec)						
Response	**Bo**	**b_1**	**b_2**	**b_{12}**	**b_{11}**	**b_{22}**
FM	0.21	-0.056	0.057	-0.020	0.031	9.33
RM	0.23	-0.056	0.057	-	-	-
For % friability						
Response	**Bo**	**b_1**	**b_2**	**b_{12}**	**b_{11}**	**b_{22}**
FM	34.44	-17.50	-30.00	10.00	1.83	24.33
RM	35.67	-17.50	-30.00	-	-	24.33

*(FM) indicated full model; and (RM), reduced model.

Table 8: Optimized formula obtained and their desirability

Name	Goal	Lower limit	Upper limit
Factor A	In range	4	12
Factor B	In range	0	10
D.T.(sec)	Targeted(70)	20	120
% friability	Targeted(0.2685)	0.137	0.4

Table 9: Predicted solution

Factor A	Factor B	Disintegration time (sec)	% Friability	Desirability	Remarks
1	0.98	70	0.2685	1.000	Selected

A checkpoint batch (optimized formulation) was prepared at X_1= 1 and X_2= 0.98 to confirm the predicted responses of disintegration time and percentage friability.

Response surface graph

Interpretation: - Disintegration time and % friability increased from blue to red region in contour graph, the prediction points were determined.

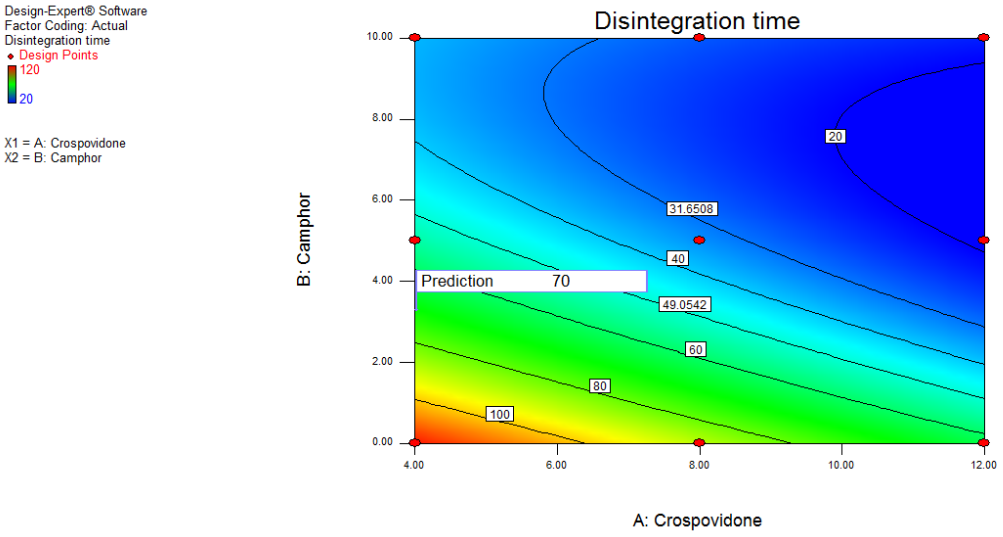

Figure 1: Contour plot showing the influence of crospovidone and camphor on disintegration time

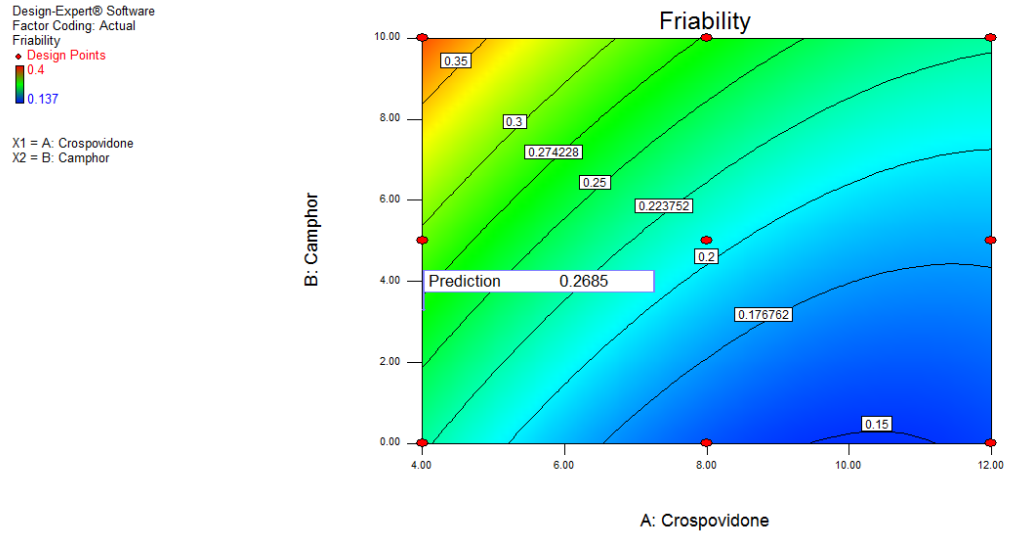

Figure 2: Contour plot showing the influence of Crospovidone and camphor on friability. Interpretation: Friability was affected both by % of camphor and crospovidone in the response graph. Disintegration time decreased from blue to orange region owing to increased concentration of camphor in the response surface graph

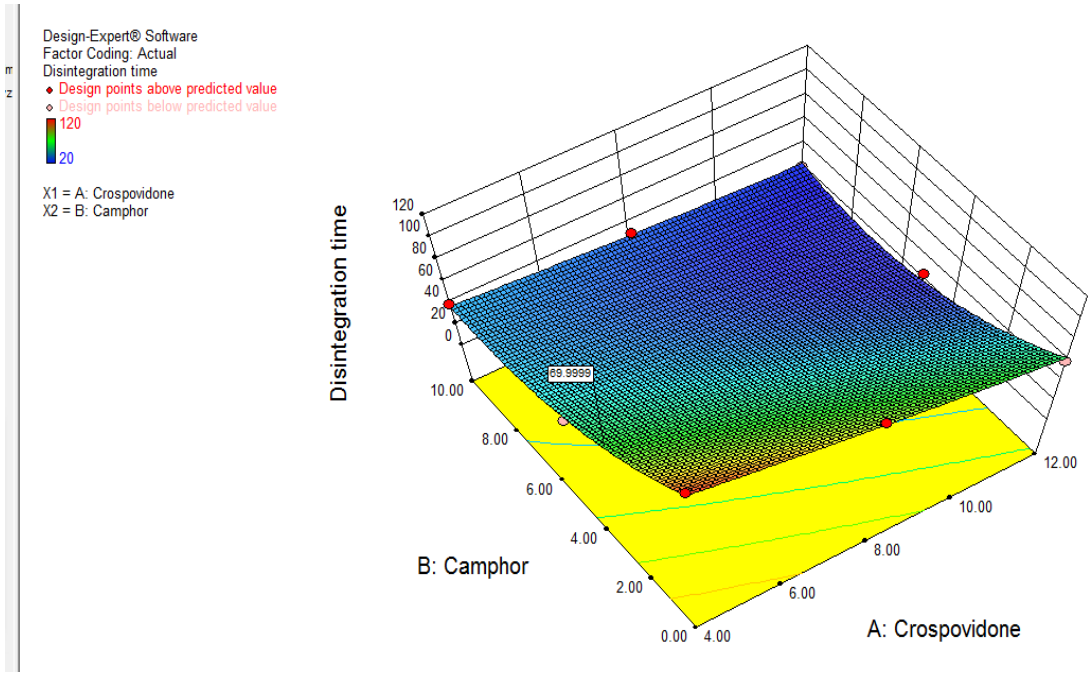

Figure 3: Response surface plot showing the influence of crospovidone and camphor on disintegration time

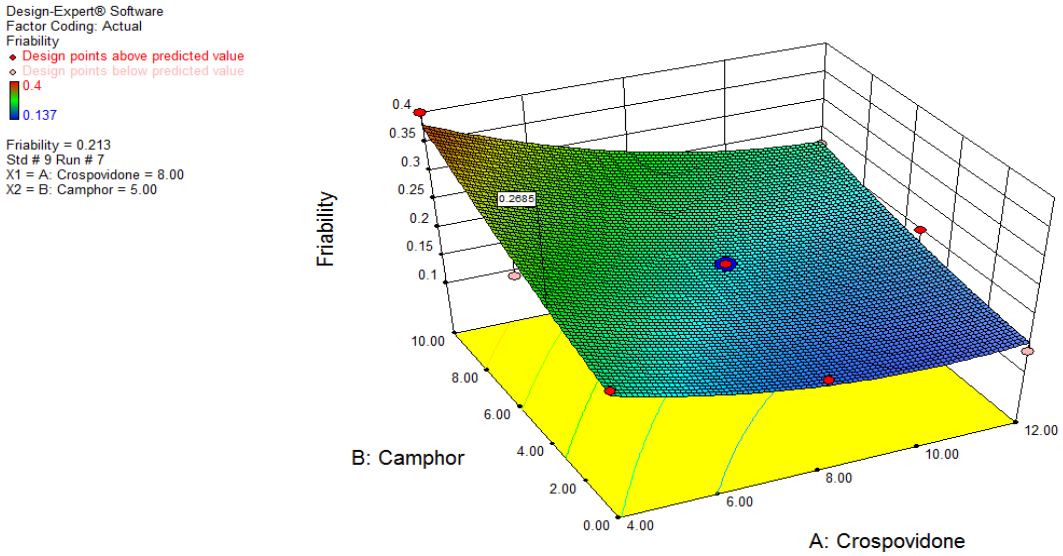

Figure 4: Response surface plot showing the influence of crospovidone and camphor on friability

Stability study of optimizd formulation

The stability studies were performed on prepared formulations as per as ICH guidelines at accelerated conditions ($40^{o} \pm 2^{o}$ C/75% ±5%RH) which showed that formulations suffered no physical-chemical changes and there was no significant reduction in drug contents also.

Table 10: Observations of parameters for stability studies at accelerated conditions (40 ± 2 °C/ 75% ±5%RH)

	Time			
Parameters	**0 Days**	**30 Days**	**60 Days**	**90 Days**
Appearance	No change	No change	No change	No change
Hardness (Kg/cm^2)	2.1	2.1	2.0	2.0
Disintegration time (seconds)	20	22	22	23
Percent friability	0.223	0.223	0.224	0.224

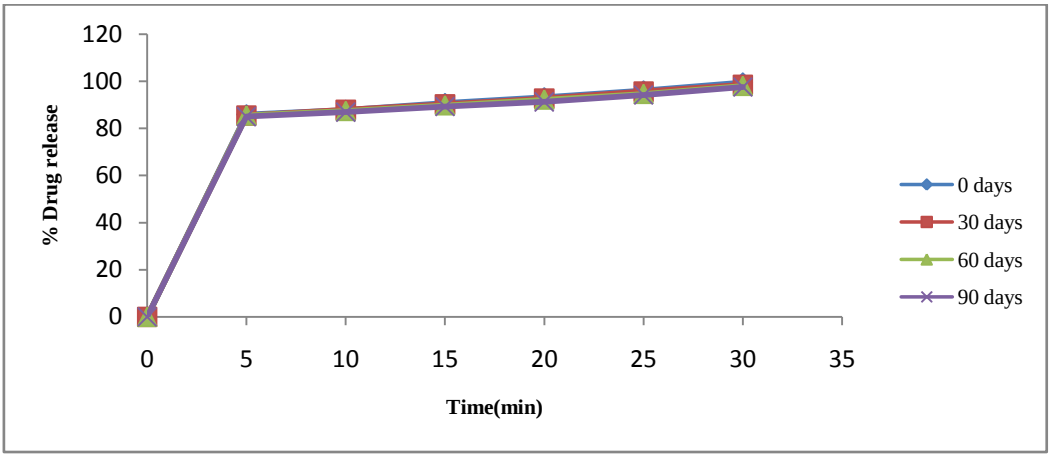

Figure 5: Comparative release profile formulation at different time intervals (0, 30,60 and 90 days) on stability

Conclusion

The study conducted so far on formulation optimization of mouth dissolving tablets of Meloxicam using mixed hydrotropic solubilization technique. Equilibrium solubility studies were performed and its results concluded that by exploiting hydrotropy, the solubility of Meloxicam got enhanced from 24.96 to 133.23 times as compared to its aqueous solubility. Amongst the trial batch formulations, the optimized results were obtained with T_4 which was further fitted into factorial design and such designed formulations named as (F_1-F_9).Other pre-compression parameters determined with the powdered blends were bulk density (0.725-0.784 gm/cc), tap density(0.785-0.835 gm/cc), angle of repose (23.55-27.82),hausner's ratio (1.05-1.09) & carr's index (5.70-8.58),These formulations were subjected to study of post compression parameters various evaluation parameters and the results inferred were: hardness (2.1-3.7 Kg/cm^2), thickness (2.51-2.92 mm), friability (0.137-0.400%), weight variation (Passed), disintegration time (20-120 sec) and in-vitro drug release determination (98.93%).The optimized values obtained from the design expert version (8.5.0.1) software were 3.30 mg of camphor and 4.03 mg of crospovidone at1.00 desirability. The in-vitro release of the optimized formulation (F_9) in pH 6.8 phosphate buffers and simulated salivary fluid was found to be 97.93 % and 98.93 % respectively in 30 minutes.

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