Formulation and Dissolution enhancement of Meloxicam tablets using Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer and Povidone in combination

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Abstract: Meloxicam is a poor water soluble drug mostly prescribed in various rheumatic diseases. The present research study was design to formulate and increase the solubility of meloxicam in the tablet dosage form. A 3^2 full factorial design was employed to optimize meloxicam formulations. Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (PVCL-PVA-PEG graft copolymer) and Povidone were taken as independent variables while *cumulative drug release* at 90 minutes was selected as dependent variable. All trial formulations complied with official standards. Multiple regression by Microsoft Excel on cumulative drug release of the selected formulations (F1, F2, F6-F9) showed the positive effect of PVCL-PVA-PEG graft copolymer ($\alpha = 0.05$) and a negative effect of Povidone ($\alpha = 0.05$). Formulation six (F6) (PVCL-PVA-PEG graft copolymer 3 mg and Povidone 22.5 mg / tablet) was considered as the optimal formulation based on its cumulative drug release. Dissolution kinetics by model dependent analysis predicted Weibull (R^2=0.99) as the best fit model in describing meloxicam dissolution kinetics. The role of PVCL-PVA-PEG graft copolymer should be explored with other solubilizers in future studies.

Keywords: Dissolution, Factorial design, Meloxicam tablets, solubility, PVCL-PVA-PEG graft copolymer.

INTRODUCTION

Approximately 70% of the drugs entering in the market possess poor aqueous solubility making it difficult to formulate and the availability at the site of action consequently fails to produce the desired therapeutic response (Kakran *et al.,* 2012). Poor water soluble drugs require more time to dissolve in the gastrointestinal fluids that might delay its absorption into the systemic circulation (Kavitha *et al.,* 2011). Various techniques (micronization, polymeric alteration, hydrotropy, co-solvency, use of surfactant, solid dispersion, pH adjustment, complexation, micro-emulsion, self-emulsification, spray drying and salt formation etc.) are currently in use to overcome the problem of poor solubility which is really a challenge for today's formulating scientists (Sikkara *et al.,* 2012).

Meloxicam is BCS (Biopharmaceutics Classification System) Class II drug (Oliveira *et al.,* 2009) used for the treatment of various inflammatory conditions. Although it possesses excellent bioavailability (89%) its poor water solubility delays dissolution, absorption and onset of action (Singh and Singh, 2009).

Literature survey revealed that previous researchers had selected solid dispersion technique for enhancing solubility of meloxicam. Some used poloxamer 188 (Umesh *et al.,* 2012; Ghareeb *et al.,* 2009), PEG 6000 (Jafar *et al.,* 2010), others tried β-cyclodextrin alone (Ghorab *et al.,* 2004) or with PVP K-30 (Awasthi *et al.,* 2011) and sodium lauryl sulphate (Nandi *et al.,* 2011). Recently, Vinod, 2014 successfully enhanced the solubility and dissolution of meloxicam by using sodium citrate.

PVCL-PVA-PEG graft copolymer is a polymeric solubilizer (amphiphilic in nature). It is a matrix polymer not only design for solid solutions but also possesses strong ability to enhance solubility of poor water soluble drugs in aqueous media (BASF, 2010). It is being used alone or with another solubilizer (β-cyclodextrin) in enhancing solubility and dissolution of poorly soluble drugs such as gliclazide (Sambath *et al.,* 2013), carvedilol (Shamma and Basha, 2013) and efavirenz (Shankar and Chowdary, 2013).

PVP K-30 has been widely used alone or in combination with other solubilizing agents for dissolution enhancement of poor water soluble drugs. In a study Kulkarni *et al.,* 2010 prepared fast dissolving tablets of meloxicam using PVP by solid dispersion technique and found a promising role of PVP as solubility enhancer. Similar results of PVP with β-cyclodextrin-SLS for efavirenz tablets (Chowdary and Naresh, 2011) and HPβCD-poloxamer 407/PVP K30 for etoricoxib tablets (Chowdary and Prakasa, 2012) were also reported in the literature. To the best of our knowledge, the role of PVCL-PVA-PEG graft copolymer and PVP in combination for dissolution enhancement is not available in the current literature. The objective of present work was to fabricate meloxicam tablets by direct compression

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method with the intention of enhancing its solubility using PVCL-PVA-PEG graft copolymer and PVP. The masses of both ingredients were determined based on previous studies (Shankar and Chowdary, 2013; Satyanarayana *et al.,* 2011).

MATERIALS AND METHODS

Materials

Meloxicam BP was obtained from Hilton Pharmaceuticals (Pvt.) Ltd., Pakistan and PVCL-PVA-PEG graft copolymer from BASF, Germany. Other chemicals; polyvinyl pyrrolidone (PVP K-30), sodium starch glycolate, avicel pH 102, lactose, talc, silicon dioxide, magnesium stearate, sodium citrate, methanol, 2-amino-5-methylthiazole, diammonium hydrogen orthophosphate, 2-propanol, orthophosphoric acid, potassium dihydrogen orthophosphate and sodium hydroxide were purchased from Merck, Germany.

Methods

Experimental design

A 3^2 full factorial design at low, mid and high level was used to formulate meloxicam tablets (table 1). PVCL-PVA-PEG graft copolymer and PVP K-30 were selected as independent variables while *in-vitro* dissolution as the dependent variable. Direct compression method was employed for the fabrication of nine trial formulation batches of meloxicam 7.5 mg tablets.

Formulation of meloxicam tablets

Meloxicam was added into a porcelain mortar followed by Povidone and triturated well. Subsequently PVCL-PVA-PEG graft copolymer was added, and mixture triturated for 5 minutes more. It was collected into a polythene bag after sieving through sieve no. 30. Remaining excipients e.g. lactose, avicel pH 102, sodium starch glycolate and sodium citrate were transferred to the mixture and subjected to tumbling for 10 minutes. Finally, silicon dioxide, talc and magnesium stearate after passing through sieve number 80 were added into the polythene bag. The powder mixture was blended for 5 minutes. Tablets were compressed onto a single punch machine (KORSCH Erweka, Frankfurt, Germany) using spherical and biconvex punches at the target weight of 200mg±7.5% (185mg-215mg) according to USP specifications (table 2). The compression weight of each formulation was adjusted by avicel pH 102.

Evaluation of preformulation parameters

Angle of repose

Angle of repose was determined through fixed funnel and free standing cone method. The tip of funnel adjusted at 1cm height from graph paper positioned on flat and even surface. The powder blends then allowed, passing freely through the funnel making a conical heap just touching the tip of the funnel. The height of cone and diameter of powder blend measured and the angle of repose was determined using equation (Rangasamy *et al.,* 2008):

$\text{Tan } \theta = h/r.$

where θ is the angle of repose, r is radius of base of conical heap and h is the height of funnel.

Carr's index and Hausner's ratio

Approximately 40g powder blend was taken into a 100 ml graduated cylinder. The volume of powder was noted after leveling the powder blend (apparent volume). Tapping of powder blend carried out manually until no more change in powder volume was taken place (tapered volume). Carr's index and Hausner's ratio calculated by using formulas (USP 30/NF 25, 2007):

Carr's index (C.I.) = $100^{*}(V_o-V_f)/V_o$

Hausner's Ratio = V_o/V_f

Where V_o is the apparent volume

V_f is the final tapered volume.

Physicochemical evaluation

Tablets of each trial formulation were randomly selected and visually inspected for organoleptic properties and tableting defects.

Physical tests

Weight Variation

Randomly 20 tablets were taken and individually weighed on a balance (Shimadzu AEG 220, Japan) the average weight was calculated and compared with the official limits (USP 30/NF 25, 2007).

Thickness, Diameter and hardness

Randomly selected 10 tablets were subjected to thickness and diameter tests using Vernier caliper (Seiko brand, China) to ascertain their dimensions and further exposed to hardness test using a hardness tester (Fujiwara, Seisukusho Corporation, Japan).

Friability

20 tablets were randomly selected, placed in a friabilator (Erweka GmbH, Germany), tumbled for 4 minutes and accounted for any loss in weight (USP 30/NF 25, 2007).

Disintegration

800 ml purified water was taken in a 1000ml beaker, maintained at 37°C±2°C. Six tablets were placed separately in each tube with discs and the basket rack assembly (Erweka Zt-2, Germany) operated for 15 minutes (BP, 2009).

Chemical test evaluation

Assay and Content Uniformity (CU)

These tests were performed using BP, 2005 guidelines and described briefly below.

Solution 1

20 tablets of meloxicam were crushed in a mortar. Meloxicam equivalent to 30mg added into a 100ml

volumetric flask followed by 10ml sodium hydroxide (1 M) and 80ml methanol in portions (40 ml each), sonicated and shaken for 3 hours and the volume was made by methanol.

Table 1: A 3^2 full factorial design used for the formulation of meloxicam tablets

Formulation codes*	X1**	X2***
F1	+1	+1
F2	+1	-1
F3	+1	0
F4	-1	+1
F5	-1	-1
F6	-1	0
F7	0	+1
F8	0	-1
F9	0	0

*Formulation codes= F1-F9, **X1= PVP K-30, ***X2 = PVCL-PVA-PEG graft copolymer**.** Factor level, +1 = High level, 0 = Mid. level, -1 = Low level

Solution 2

4.5mg of 2-amino-5-methylthiazole taken and equal volume (20ml each) of 1M sodium hydroxide and methanol added into 200ml volumetric flask. The flask was shaken, cooled and made up to the mark with methanol. 2ml of this solution transferred to 100ml volumetric flask and volume made up with methanol.

Solution 3 (Final sample solution)

Both solutions (Solution 1 and Solution 2) mixed together equally to form Solution 3.

Mobile phase

650 ml methanol and 100 ml 2-propanol was taken in a suitable flask. Diammonium hydrogen orthophosphate (0.2%w/v) was prepared separately (pH adjusted to 7.0 with dilute orthophosphoric acid). Both solutions mixed as 370 ml and 630 ml respectively.

Nucleoside C_{18} column (250 mm x 4.6 mm) was used at 40°C for high pressure liquid chromatography. Mobile phase was run at a flow rate of 0.8 ml / minute with ultraviolet detection at 254nm.

The same above procedure was followed for CU determination. For which 10 randomly selected meloxicam tablets weighed individually and tested in 50 ml volumetric flask.

Following formulas were utilized for assay and CU calculations:

$$Assay\ (\%) = \frac{Peak\ area\ of\ sample \times weight\ of\ standard \times 50 \times 100 \times 100 \times Average\ weight \times 130}{Peak\ area\ of\ standard \times 100 \times 100 \times weight\ of\ sample \times 50 \times Factor \times 7.5}$$

$$CU\ (\%) = \frac{Peak\ area\ of\ sample \times Weight\ of\ standard \times 50 \times 50 \times 100}{Peak\ area\ of\ Standard \times 100 \times 100 \times 7.5 \times factor}$$

In-vitro drug release study

The *in-vitro* dissolution was performed by following BP, 2005 guidelines with USP paddle apparatus II (Erweka GmbH, Germany). Briefly, potassium dihydrogen orthophosphate buffer pH 7.5 taking as dissolution medium at 37±0.5°C and the apparatus operated at 50 rpm. An aliquot of 10 ml sample withdrawn after 5, 10, 15, 30, 45, 60 and 90 minutes time interval with volume of media compensated after each removal to maintain sink condition. Aliquot samples then filtered using 0.45µm membrane filter and analyzed by spectrophotometer (Shimadzu UV-1800, Japan) at 362 nm using dissolution medium as blank. Percent drug release determined from the standard calibration curve of meloxicam (fig. 1).

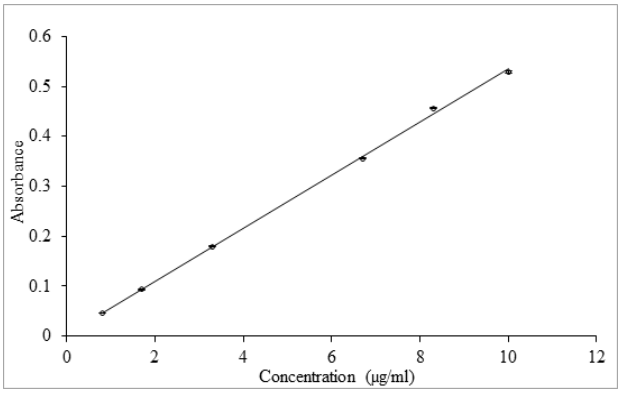

Fig. 1: Mean calibration curve of meloxicam in phosphate buffer pH 7.5 (Mean±SD) and optical parameters; y=0.053x+0.006, R^2 = 0.999, Accuracy = 99.44±3.02%, % Recovery min. = 94.36% & max. = 102.63%, Standard error of slope = 0.0008, Standard error of intercept = 0.0049, LOD = 0.74µg/ml, LOQ = 2.25 µg/ml.

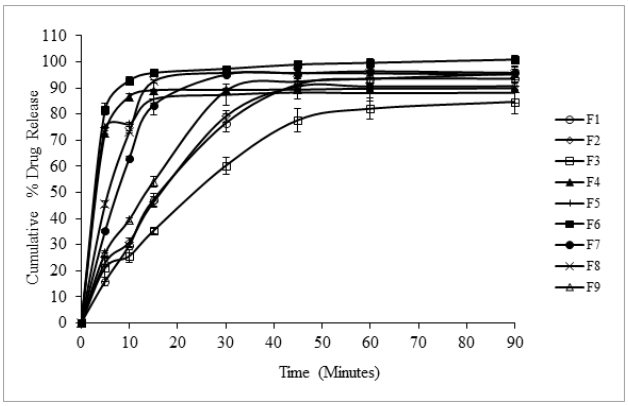

Fig. 2: Cumulative *in-vitro* dissolution profiles of meloxicam tablets in phosphate buffer pH 7.5 (F1-F9), Mean±SD

Standard preparation

Accurately weighed 100mg meloxicam BP reference standard was placed into a 100ml volumetric flask. Methanol was poured about 17ml followed by 3.5ml 0.1 M sodium hydroxide in order to dissolve API (meloxicam) and dissolution medium was added up to the

mark (1000µg/ml). The stock solution was diluted serially to get a working standard of 50µg/ml. From this standard solution six working standard dilutions were prepared (0.8, 1.6, 3.3, 6.6, 8.3 and 10µg/ml) (fig. 1).

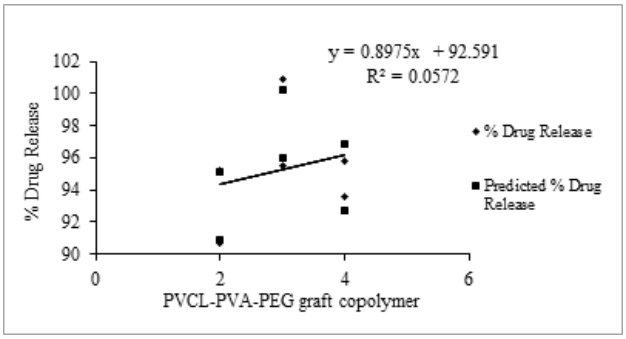

Fig. 3: Line Fit plot for PVCL-PVA-PEG graft copolymer

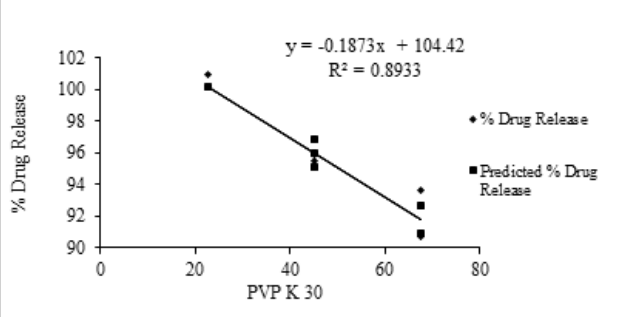

Fig. 4: Line Fit plot for PVP K-30

STATISTICAL ANALYSIS

Microsoft Excel 2007 used for statistical evaluation of the data. Dissolution data was interpreted by multiple regression analysis at 0.05 level of significance using Microsoft Excel 2007. Model dependent methods including zero order, first order, Weibull, Hixson-Crowell, Korsmeyer-Peppas were applied on *in-vitro* dissolution data using DD solver® software.

RESULTS

Pre-formulation studies

Among the nine formulations, F6 and F8 showed lower angle of repose (27.75° and 30.25° respectively) whereas F2 showed the highest angle of repose (34°). All trial formulation batches presented a good flow character on the basis of Carr's index (11.17% to 14.0%) and Hausner's ratios (1.12 to 1.17). It is apparent from the results that all trial formulations possessed good flow characteristics and showed comparable results. Nevertheless, F6 appeared to be better as compared to other trial formulations based only on its lower angle of repose value (table 3).

Physicochemical evaluation

All compressed tablets of meloxicam (F1-F9) appeared glossy and shiny with even surface. The tablets were free from pitting, sticking, lamination and any other tableting defects.

Physical tests

The trial formulations of meloxicam complied USP limits set for weight variation (198.18±3.16mg to 200.88±1.88 mg). F6 showed lesser weight variations while F9 showed slightly higher weight variation according to upper and lower compression control limits. The hardness of tablets ranged from 4.60±0.66kg to 5.71±0.94kg. All the trial formulations were within friability limits (<1%). All compressed tablets disintegrated within 15 minutes and hence followed BP specifications (BP 2009). The formulations F4-F7 exhibited lower while F1- F3 showed higher disintegration time (table 4).

Chemical tests

Assay and CU

All meloxicam formulations complied to assay (95.2±0.25% to 100.5±0.78%) and CU (95.1±1.10% to 100.6±0.80%) tests according to BP, 2005. Lower assay and active content found in F3 whereas higher in F6 (table 4).

In-vitro drug release

Likewise assay and content uniformity, trial formulations met BP dissolution specifications that states for each of the 6 tablets tested, the amount of active ingredient in solution within 45 minutes should not be less than 70% of the prescribed or stated amount (BP, 2005). The cumulative drug release at 45 minutes ranged from 77.74±3.42% to 99.02±1.01% thus complying official limits (table 5).

Statistical evaluation

Multiple regression analysis of the dissolution data of Meloxicam tablets (at 90 minutes) for F1, F2, F6, F7, F8 and F9 were carried out by Microsoft Excel 2007. Regression statistics of ANOVA showed calculated R^2 of 0.95 with F value greater than significance F value (table 6 and table 7). The regression coefficient of Povidone was found as -0.19±0.03 and that of PVCL-PVA-PEG graft copolymer was 0.90±0.48. Further model dependent methods were applied to determine the mechanism of drug release kinetics. The Weibull model showed high determination coefficient (R^2 ranging from 0.84 to 0.99) than rest of the models analyzed (table 8).

DISCUSSION

The present work was aimed to formulate meloxicam tablets by direct compression method and to enhance its dissolution. PVCL-PVA-PEG graft copolymer and Povidone with conventional excipients used in fabrication of meloxicam tablets using 3^2 full factorial design and subjected to physicochemical tests required for compressed tablets.

Table 2: Composition of ingredients used in the formulation of meloxicam 7.5 mg tablets

Ingredients	Amount (mg/tablet)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Meloxicam	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Povidone K-30	67.5	67.5	67.5	22.5	22.5	22.5	45	45	45
PVCL-PVA-PEG graft copolymer	4	2	3	4	2	3	4	2	3
Sodium starch glycolate	8	8	8	8	8	8	8	8	8
Lactose	58	58	58	58	58	58	58	58	58
Avicel pH 102**	48	50	49	93	95	94	70.5	72.5	71.5
Silicon dioxide	1	1	1	1	1	1	1	1	1
Sodium citrate	1	1	1	1	1	1	1	1	1
Magnesium stearate	2	2	2	2	2	2	2	2	2
Talc	3	3	3	3	3	3	3	3	3
Total compression weight (mg/tablet)	200	200	200	200	200	200	200	200	200

*F1-F9=Formulation codes, ** Total compression weight of each formulation adjusted by Avicel pH 102

Table 3: Preformulation studies of meloxicam trial formulations

Formulation Code	Angle of Repose (°)	Compressibility Index (%)	Hausner's Ratio	Flow Property
F1	32.61	13.51	1.16	Good
F2	34.00	14.00	1.17	Good
F3	33.69	11.76	1.13	Good
F4	33.69	12.82	1.14	Good
F5	32.00	11.17	1.12	Good
F6	27.75*	13.33	1.15	Good
F7	32.00	13.45	1.15	Good
F8	30.25*	11.90	1.13	Good
F9	32.00	12.12	1.13	Good

*Excellent

Table 4: Physicochemical tests of meloxicam 7.5 mg tablet formulations prepared by direct compression method

Physico-chemical Test	Weight variation (mg)	Thickness (mm)	Diameter (mm)	Hardness (Kg)	Friability (%)	Disintegra-tion (min.)	Assay (%)	Content uniformity (%)
	Limits							
Formulations	±7.5% (USP)	±5%	±5%	5kg	<1% (USP)	< 15min. (BP)	95.0-105.0% (BP)	95.0-105.0% (BP)
F1	200.78±2.56	3.83±0.31	8.24±0.24	5.22±1.04	0.22±0.02	8.68±0.71	99.3±0.31	98.6±1.02
F2	200.73±1.37	3.34±0.35	8.28±0.28	4.60±0.66	0.35±0.02	8.36±0.18	99.9±0.90	99.2±1.49
F3	200.57±1.71	3.50±0.41	8.25±0.30	5.06±0.67	0.20±0.02	8.17±0.44	95.2±0.25	95.1±1.10
F4	200.88±1.88	3.65±0.46	8.37±0.32	4.65±0.70	0.53±0.03	3.89±0.39	96.8±0.10	96.4±1.44
F5	200.30±2.54	3.82±0.42	8.31±0.32	5.71±0.94	0.78±0.02	3.63±0.23	98.5±1.11	98.9±1.34
F6	200.00±1.43	3.92±0.42	8.39±0.28	5.42±0.81	0.77±0.02	2.74±0.16	100.5±0.78	100.6±0.80
F7	199.46±2.80	3.84±0.47	8.24±0.29	5.46±0.69	0.33±0.04	3.17±0.17	99.8±2.11	99.4±1.62
F8	199.71±2.83	3.86±0.34	8.07±0.01	5.13±0.57	0.35±0.03	4.28±0.18	99.6±1.35	99.6±1.40
F9	198.18±3.16	3.80±0.47	8.25±0.23	5.69±0.89	0.34±0.03	6.00±0.49	98.0±0.72	99.5±1.58

*F1-F9=Formulation codes, values (Mean±SD).

Table 5: Cumulative % drug release of meloxicam trial formulations

Formulation codes*	Cumulative % drug release						
	Time (min.)						
	5	10	15	30	45	60	90
F1	16.00±1.65	29.73±0.83	47.18±2.28	76.54±3.36	91.40±2.26	93.55±1.88	93.60±1.87
F2	23.10±1.68	30.99±1.71	46.20±2.07	79.12±2.30	90.64±2.09	90.60±1.03	90.67±1.59
F3	21.20±5.42	25.60±2.35	35.30±0.96	60.26±3.15	77.74±3.42	82.10±3.97	84.75±4.64
F4	72.95±0.69	86.77±0.89	89.15±0.35	89.29±0.30	89.40±0.51	89.76±0.63	89.88±0.8
F5	74.85±0.45	76.12±0.87	85.74±6.16	87.43±4.12	88.31±2.68	88.02±3.00	88.24±4.00
F6	81.80±2.18	92.82±1.43	95.80±0.39	97.37±0.57	99.02±1.01	99.67±1.69	100.93±1.69
F7	35.24±0.63	63.00±0.76	83.37±0.83	95.18±0.57	95.64±1.70	96.37±1.57	95.83±2.03
F8	45.54±1.32	73.16±0.36	92.54±0.55	95.86±0.48	95.76±0.94	95.64±1.78	95.17±2.19
F9	26.72±1.09	39.51±0.79	54.01±2.02	88.89±0.84	92.46±1.14	93.56±1.82	95.50±3.05

*F1-F9=Formulation codes, values (Mean±SD), n=6

Table 6: Regression Statistics of meloxicam dissolution data at 90 minutes

Multiple R	0.97
R Square	0.95
Adjusted R Square	0.92
Standard Error	0.96
Observations	6

Table 7: ANOVA applied to meloxicam dissolution data at 90 minutes

Source	df	SS	MS	F	Significance F
Regression	2	53.57	26.78	28.77	0.01
Residual	3	2.79	0.93	-	-
Total	5	56.36	-	-	-

$p < 0.05$

Table 8: Model dependent *in-vitro* dissolution kinetics (90 minutes) of various Meloxicam formulations in official medium (pH 7.5 Phosphate Buffer)

Formulations	Zero order $F=k_0.t$		First order $F=100.[1-Exp(-k_1.t)]$		Korsmeyer-Peppas $F=k_{KP}.t^n$			Hixson-Crowell $F=100.[1-(1-k_{HC}.t)^3]$		Weibull $F=100.\{1-Exp[-((t-Ti)^\beta)/\alpha]\}$	
	Parameter										
	R^2	k_0	R^2	k_1	R^2	k_{KP}	n	R^2	K_{HC}	R^2	β
F1	0.35	1.44	0.98	0.04	0.88	13.29	0.46	0.99	0.01	0.99	1.13
F2	0.15	1.41	0.97	0.05	0.87	15.48	0.42	0.96	0.01	0.97	1.18
F3	0.45	1.25	0.97	0.03	0.93	10.65	0.48	0.93	0.01	0.98	0.94
F4	-79.29	1.52	-1.28	0.23	0.57	73.45	0.05	-25.81	0.02	0.99	0.04
F5	-77.27	1.48	-3.21	0.2	0.78	69.19	0.06	-24.56	0.02	0.84	0.14
F6	-82.22	1.68	0.87	0.32	0.82	78.59	0.06	-27.51	0.02	0.99	0.31
F7	-2.51	1.57	0.97	0.1	0.74	36.96	0.23	0.51	0.02	0.98	0.74
F8	-5.63	1.59	0.95	0.13	0.65	48.28	0.17	-0.37	0.02	0.96	0.50
F9	-0.18	1.49	0.98	0.06	0.86	19.95	0.37	0.96	0.02	0.98	1.43

*F= Fraction (%) of drug release at time t, k_0=Zero order rate constant, k_1= First order rate constant, k_{KP}= Release constant showing structural and geometric characteristics of drug-dosage form, n=diffusional exponent indicative of drug release mechanism, k_{HC}= Hixson-Crowell rate constant, α = scale parameter defining time scale of dissolution process, β = shape parameter characterizes the curve, Formulation codes = F1-F9

Both PVCL-PVA-PEG graft copolymer and Povidone caused no hindrance in the flowability of powdered blends set for compressing meloxicam tablets as revealed from their flow behavior thus resulted in minimum weight variation. Previously, Ghorab *et al.,* 2004 used β-cyclodextrin to increase the poor water solubility of meloxicam. A decrease in flowability reported as the concentration of β-cyclodextrin increased, resulting in weight variation above 50% β-cyclodextrin.

All formulations met minimum requirement of hardness (5 kg) generally desirable for making satisfactory tablets. This is in line with Vinod, 2014 who reported hardness uniformity by preparing meloxicam tablets using wet granulation method or Nandi *et al.,* 2011 by direct compression method. The friability of compressed tablets found as less than 1%. This indicates that compressed tablets possessed sufficient hardness to endure abrasion. It is evident from the results that as concentration of PVP

and hardness increased, friability get decreased that might because of strong binding property of PVP.

Although in the present study, tablets compressed by direct compression but strong binding property of PVP delayed tablet disintegration which is evident from the formulations behaviour. Formulation F6 showed earlier disintegration (low PVP concentration) while formulation F1 showed a delayed disintegration owing to high PVP concentration. This is in agreement with Kulkurni study who also reported delayed meloxicam disintegration with increasing PVP concentration (Kulkarni *et al.,* 2010).

Uniformity of active ingredient (assay and CU) was found in all formulations. F6 showed higher assay and content uniformity for API followed by F2, F7 and F8 respectively. Nevertheless, results are closer and comparable. This collaborates with previous studies that reported uniformity in content of meloxicam tablets made by solid dispersion technique using PVP as carrier (Kulkarni *et al.,* 2010) or poloxamer 188 (Ghareeb *et al.,* 2009).

In case of cumulative % drug release, formulations F1-F3 that contained PVP at higher level (67.5mg/ tablet) with PVCL-PVA-PEG graft copolymer as 2%, 1% and 1.5% respectively; an increase in dissolution rate was observed. Although F1 and F2 profiles were found to be super imposable at most of the sampling times yet the dissolution rate can be ordered F1>F2>F3. In case of formulations F4-F6 that contained PVP at lower level (22.5 mg / tablet) and PVCL-PVA-PEG graft copolymer in the similar concentration as stated in first set of formulations, the highest dissolution rate achieved in F6 followed by F4 and F5. The order of cumulative % drug release was F6>F4>F5. In formulations, F7-F9, PVP used as 45mg/tablet whereas PVCL-PVA-PEG graft copolymer added in the similar strength as described above, the dissolution rate can be ordered in terms of enhancing dissolution as F7>F9>F8. The overall order of cumulative % drug release can be stated as F6>F7>F9>F8>F1>F2>F4>F5>F3 (fig. 2).

Moreover multiple regression analysis confirmed the significant difference in % drug release of selected formulations F1, F2, F6-F9 at 90 minutes sampling time. From the ANOVA results the F value found to be significantly greater than significance F value. Thus null hypothesis was rejected and it is concluded that the factor levels has a significant effect on the meloxicam dissolution. The regression coefficient of PVCL-PVA-PEG graft copolymer found to be positive which indicated as the concentration of PVCL-PVA-PEG graft copolymer increased, dissolution rate also get increased and vice versa. This behavior of PVCL-PVA-PEG graft copolymer was further verified by line fit plot (fig. 3). In case of PVP K-30, regression coefficient found to be negative. This indicated that as the concentration of PVP increased, dissolution tends to be decreased as evident from the line fit plot (fig. 4). PVCL-PVA-PEG graft copolymer in high concentration showed positive response in enhancing dissolution of meloxicam which might be suppressed when used with high concentration of PVP.

Model dependent methods like zero order, first order, Hixson-Crowell, Korsmeyer-Peppas and Weibull highlighted drug release mechanisms. Results showed that only Weibull gave highest R^2 value in official medium. The Weibull β parameter describes shape parameter of dissolution curve. Among all formulations F1, F2 and F9 showing sigmoidal shape curve with β>1 (Jitendra and Deshpande, 2014) while in remaining formulations β was less than 1 showed initially steeper slope having parabolic curve than is consistent with exponential shown in table 8. Various studies showed Weibull a good model to characterize dissolution kinetics (Israr *et al.,* 2016).

Our findings confirm previous studies reported so far in the literature. Shankar and Chowdary, 2013 used PVCL-PVA-PEG graft copolymer with β-cyclodextrin to accelerate the solubility and dissolution rate of efavirenz and efavirenz tablets and found positive response in solubility and dissolution enhancement. Similar results also reported for gliclazide (Sambath *et al.,* 2013). Likewise PVCL-PVA-PEG graft copolymer, PVP K-30 used to increase dissolution rate of fast dissolving tablets of meloxicam. A profound decrease in dissolution rate observed as concentration of PVP increased (Kulkarni *et al.,* 2010).

Hence dissolution data with other quality control attributes including earlier disintegration, high assay and content uniformity clearly advocates superiority of formulation F6 over other formulations and might be regarded as best (optimized) formulation in the present study. Thus PVP in lower concentration and PVCL-PVA-PEG graft copolymer (middle value) appeared to be the most appropriate combination for enhancing solubility and dissolution of meloxicam.

CONCLUSION

Immediate release meloxicam tablets with enhanced water solubility successfully formulated by direct compression method using PVCL-PVA-PEG graft copolymer and PVP. All formulations showed compliance to official standards. Among nine formulations, F6 appeared to be superior not only because of maximum % drug release but also in terms of other physicochemical tests conducted, especially assay, content uniformity and disintegration which are better predictive of *in-vivo* bioavailability. A rapid dissolving tablet of meloxicam is required in clinical practice of instant pain reliever. The role of PVCL-PVA-PEG graft copolymer alone or in combination with other solubility enhancers should be explored in future research studies.

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REFERENCES

Awasthi SS, Kumar TG, Manisha P, Preeti Y and Kumar SS (2011). Development of meloxicam formulations utilizing ternary complexation for solubility enhancement. *Pak. J. Pharm. Sci.,* **24**(4): 533-538.

BASF (2010). Soluplus® technical information. Pharma ingredients and services. pp.1-8.

British Pharmacopeia (2009). British Pharmacopeia Commission, London, UK: The stationery office, p. 6582.

British Pharmacopeia. (2005). British Pharmacopeia Commission, London, UK: The stationery office, pp. 2626, A273, A274.

Chowdary KPR and Naresh A (2011). Formulation development of efavirenz tablets employing β cyclodextrin-PVP K30-SLS: A factorial study. *J. App. Pharm. Sci.,* **1**(9): 130-134.

Chowdary KPR and Prakasa RKS (2012). Formulation development of etoricoxib tablets employing HP β cyclodextrin-poloxamer 407-PVP K30: A factorial study. *Asian J. Pharm. Clin. Res.,* **5**(1): 161-164.

Ghareeb MM, Abdulrasool AA, Hussein AA and Noordin MI (2009). Kneading technique for preparation of binary solid dispersion of meloxicam with poloxamer 188. *AAPS Pharm. Sci. Tech.,* **10**(4): 1206-1215.

Ghorab MM, Abdel-Salam HM, El-Sayad MA and Mekhel MM (2004). Tablet formulation containing meloxicam and β-cyclodextrin: Mechanical characterization and bioavailability evaluation. *AAPS Pharm. Sci. Tech.,* **5**(4): 63-68.

Israr F, Mahmood ZA, Hassan F and Hasan SMF (2016). Pharmaceutical evaluation of cefuroxime axetil tablets available in drug market of Pakistan. *Indian J. Pharm. Sci.,* **78**(1): 17-26.

Jafar M, Dehghan MHG and Shareef A (2010). Enhancement of dissolution and anti-inflammatory effect of meloxicam using solid dispersions. *Int. J. Appl. Pharm.,* **2**(1): 22-27.

Jitendra CS and Deshpande A (2014). Kinetic modeling and comparison of *invitro* dissolution profiles. *World J. Pharm. Sci.,* **2**(4): 302-309.

Kakran M, Lin L and Müller RH (2012). Overcoming the challenge of poor drug solubility. *Pharm. Eng.,* **32**(4):1-7. Available at: www.ispe-pcc.org/pe-ja12/kakran.pdf

Kavitha K, Raju KNSL, Ganesh NS and Ramesh B (2011). Effect of dissolution rate by liquisolid compact approach: an overview. *Pharm. Lett.,* **3**(1): 71-83.

Kulkurni U, Patil BS, Hariprasanna RC, Borgaonkar PA, Hogade MG and Rabbani G (2010). Formulation and development of fast dissolving meloxicam tablets by solid dispersion technique: For the effective treatment of dental pain. *Int. J. Curr. Pharm. Res.*, **2**(3): 82-85.

Nandi S, Debnath S, Manjunath SY, Mallareddy V, Babre NP and Rao MG (2011). Improvement of dissolution characteristics of meloxicam by complexation with cyclodextrins. *Int. J. Pharm. Sci. Nanotech.,* **3**(4): 1263-1270.

Oliveira EFS, Azevedo RCP, Bonfilio R, Oliveira DB, Ribeiro GP and Araújo MB (2009). Dissolution test optimization for meloxicam in the tablet pharmaceutical form. *Braz. J. Pharm. Sci.,* **45**(1): 67-73.

Rangasamy M, Balasubramaniam A and Gummadevelly S (2008). Design and evaluation of β-cyclodextin of meloxicam tablet. *Res. J. Pharm. Tech.,* **1**(4): 484-486.

Sambath L, Muthu AK, Kumar MA, Phaneendra K and Shalini (2013). Physicochemical characterization and *in-vitro* dissolution behavior of gliclazide –soluplus solid dispersions. *Int. J. Pharm. Pharm. Sci.,* **5**(Suppl 2): 204-210.

Satyanarayana T, Mohideen S, Kumar PS, Krishnan SN, Pavani S and Rao MG (2011). Polyvinyl pyrrolidine-An approach to enhance the solubility and dissolution of valdecoxib tablets. *Int. J. Biopharmaceutics.,* **2**(2): 72-79.

Shamma RN and Basha M (2013). Soluplus®: A novel polymeric solubilizer for optimization of Carvedilol solid dispersions: Formulation design and effect of method of preparation. *Powder Technol.*, **237**: 406-414.

Shankar KR and Chowdary KPR (2013). Factorial studies on enhancement of solubility and dissolution rate and formulation development of efavirenz tablets employing ß cyclodextrin and soluplus. *BioMedRx.,* **1**(3): 299-303.

Sikarra D, Shukla V, Kharia AA and Chatterjee DP (2012). Techniques for solubility enhancement of poorly soluble drugs: an overview. *J. Med. Pharm. Allied. Sci.*, **1**: 1-22.

Singh J and Singh R (2009). Optimization and formulation of orodispersible tablets of meloxicam. *Trop. J. Pharm. Res.,* **8**(2): 153-159.

Umesh M, Naveen S, Amit C and Bhatt DC (2012). Physical properties and dissolution behaviour of meloxicam / poloxamer solid dispersions prepared by hot melt method and microwave assisted method. *Int. J. Res. Pharm. Sci.,* **2**(2): 64-74.

United States Pharmacopeia (USP 30 / NF 25). (2007). The United States Pharmacopeial Convention, pp. 643, 674, 731.

Vinod J (2014). Formulation and *in vitro* evaluation of immediate release meloxicam tablets. *Adv. Res. Pharm. Biol.,* **4**: 612-617.