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OPTIMIZATION, FORMULATION AND EVALUATION OF FAST DISINTEGRATING TABLET OF MELOXICAM

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ABSTRACT

Fast disintegration drug delivery system are intended at enhancing efficacy and drug bioavailability of presented drugs, reduction in drug dosing frequency, minimizes side effect and enhances patient compliance. Fast disintegration dosage forms are disintegrated by saliva. The formulations with lower solubility are a challenge for formulation researchers; solubility enhancement is major issue for ideal bioavailability. Solid dispersions (SDs) are traditional techniques used for enhancing dissolution properties and bioavailability of sparingly soluble drugs. The current study is aimed at formulation SD of selected drugs and incorporating into fast dissolution tablets for enhanced bioavailability.

Meloxicam belongs to the well-known group of Cox-II inhibitors, oxicams, it is a well-established, potent non steroidal anti-inflammatory agent with analgesic actions achieved by inhibiting prostaglandin synthesis. Meloxicam has been found to be approximately 99% protein bound with a mean elimination half-life of 20 h, which allows the administration of a daily single oral dose of 20 mg.

In the present work an attempt has been made to improve the solubility of Meloxicam by solid dispersions using solvent evaporation method along with the aid of novel polymers and further incorporating into fast disintegrating tablets by adopting design of experiment.

The solid dispersions of Meloxicam were prepared with Kollidon CL, PVP K30 and Poloxamer 127, in 1:1:1, 1:2:1 and 1:3:1 by solvent evaporation method. The optimized formulation was selected for fast disintegrating tablets using gellan gum, fenugreek seed mucilage and L-HPC by direct compression method using 3^3 Response surface methods. The optimized product TF13 was selected and performed disintegration, dissolution studies and in vivo bioavailability studies Solid dispersions showed a better dissolution compared to the pure drugs and among all the other formulations SD9 shows high percentage drug release i.e. 99.11±5.17 % and selected as an optimized formulation for the preparation of fast disintegrating tablets of Meloxicam. TF13 was selected as optimized formulation based on its highest disintegration time 36 sec and drug release 99.68±1.52% for 10 min whereas marketed product shows the release of 85.59±1.52%. In vivo studies of optimized formulation (TF 13) and marketed product done in male Wistar rats & pharmacokinetic parameters were calculated. TF 13 shows T_{max} of 1.0 h which was highly significant ($P < 0.05$) when compared with marketed formulation 2.0 h.

From in vivo bioavailability studies solid dispersions incorporated fast disintegrating tablets of Meloxicam can be effectively used for the enhancement of bioavailability with quick onset of time.

It can be concluded that fast disintegrating tablets using Meloxicam solid dispersion could be used to improve better patient compliance with immediate action in the effective management of pain and inflammation.

KEYWORDS: Meloxicam, Solid dispersions, NSAIDS, Fast disintegrating, Bioavailability.

INTRODUCTION

Drugs exhibiting low aqueous solubility have decreased absorption when given orally resulting in poor bioavailability. Drugs whose absorption is limited by dissolution can be subjected to micronization to enhance dissolution rate but this technique is sometimes limited due to poor particles wettability owing to interparticle aggregation. More such techniques that are available for bioavailability enhancement are co-solvent assisted solubilization, salt formation, inclusion complexes formation. Solid dispersion is defined as "dispersion of one or more active hydrophobic ingredients in an inert hydrophilic carrier at solid state formulated by melting (fusion) method, solvent, or melting solvent method". Solid dispersion on encounter with surrounding aqueous medium results in solubilization of carrier that releases the drug with increased surface area which now undergoes absorption at higher rate increasing the bioavailability of drug with poor solubility. Sulfathiazole was the first of its kind to be incorporated in solid dispersions as a eutectic mixture with urea as inert carrier.(1,2)

BCS CLASS BOUNDARIES (3)

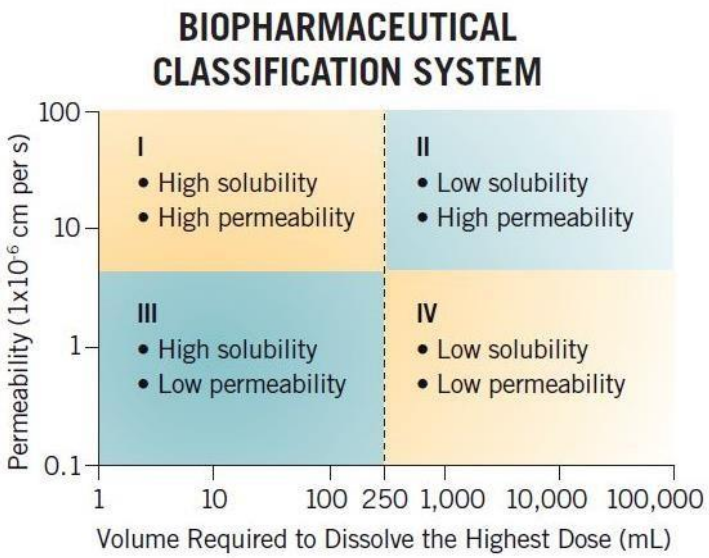

Figure 1: BCS Classification system

Table 1: Type of solubility enhancement techniques

S. No.	Chemical modification	Physical modification	Other
1	Salt Formation	Particle size reduction	Supercritical fluid Method
2	Co-crystallization	Modification of the crystal habit	Spray freezinginto liquid and Lyophillization
3	Co-solvency	Complexation	Evaporative precipitation into aqueous solution
4	Hydrotropic	Solubilization bysurfactants	Solvent evaporation Method

5	Solubilizing agent	Drug dispersion in carriers Solid solution Eutectic mixtures Solid Dispersion	Hot melt Extrusion
6	Nanotechnology	-	Electrostatic spinning method
7	-	-	Direct capsule Filling
8	-	-	Polymeric Alteration

SOLID DISPERSIONS: The term solid dispersion applies to a bunch of solid state particles comprising of two distinct different components, generally a hydrophilic matrix and a hydrophobic drug. Molecular dispersion of drug can be achieved in either amorphous or crystalline matrix.(4)

TYPES OF SOLID DISPERSIONS

Binary solid dispersion: It consists of drug and a polymeric carrier.

Ternary solid dispersion: It consists of drug, a polymeric carrier and a surfactant.

Surface solid dispersion: these comprises of polymers and copolymer prepared by fusion Technique for enhanced solubility.

Eutectic mixtures: An eutectic mixture comprises of binary compounds that are entirely miscible in liquid state but only partially miscible in solid state. These are prepared by quick solidification of combined melt of these components

Solid solutions: Solid solutions are similar to liquid solutions, comprising of single phase regardless component count. In solid solutions, the particle size of drug is minimized to absolute minimum as this determines dissolution rate of drug

- **Substitutional crystalline solutions** -These systems are forms when particle size of solute and solvent within 15% .they exhibit crystalline nature in which the solute molecules substitute for solvent molecules in the crystal lattice.

- **Interstitial crystalline solid solutions** -In these systems, the dissolved particles conquer the interstitial places among the solvent molecules in crystal lattice. The diameter of solute must be <0.59 times than solvent molecules diameter.(5,6)

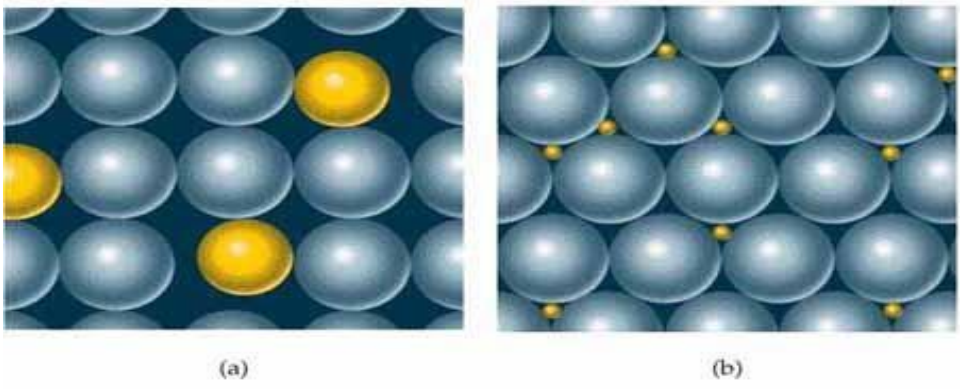

Figure 2: Substitutional Crystalline Solutions and Interstitial Crystalline Solid Solutions

MECHANISM OF BIOAVAILABILITY ENHANCEMENT

Following action modes are involved that are responsible for solid dispersion assisted enhanced rate of dissolution of drugs having poor solubility in water:

•. Reduction in particle size

•Improvement in wettability and dispersibility

•Changing crystalline form of drug to amorphous form

•Reduction in aggregation and agglomeration of drug particles.(7)

ADVANTAGES OF SOLID DISPERSIONS

1.More efficiency than other micronization techniques wherein size of drug is limited to 2-5 mm that is not enough to enhance solubility of drug and release of the same in intestine.

2.Dissolution rate enhancement with increased absorption and reduction in pre systemicmetabolism.

3.Liquid dorm of drug conversion to solid formrans formation of liquid form of drug into solidform.

DISADVANTAGES OF SOLID DISPERSIONS

Absorption of moisture by most polymers used might lead to separation of phase, growth of crystals or amorphous form conversion to crystalline state or to another metastable state to give a enhanced stable structure during storage. Thus this might result in decreased solubility and dissolution rate.(8,9)

FAST DISINTEGRATING TABLETS (FDT)

Orally FDT is one of the recently developed delivery system for the oral drug delivery. Transdermal drug delivery system formed the basis of this advanced technology. These systems on coming in contact with oral mucosal tissue gets hydrated by with saliva It thereby undergoes quick disintegration releasing the drug that undergoes instant absorption into systemic circulation via buccal mucosa.

A FDT system is a tablet that disintegrates rapidly in the oral cavity on coming in contact with saliva, generating drug suspension.FDT dosage forms, also commonly known as fast melt, quick melt, orally disintegrating tablets, and or dispersible systems, have the unique property of disintegrating the tablet in the mouth in seconds.(10)

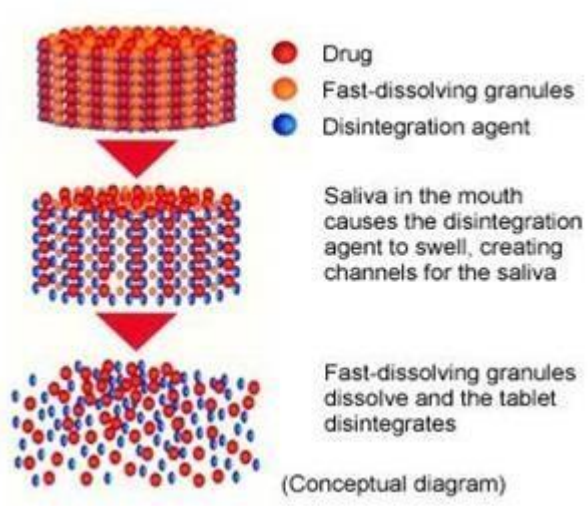

Figure 3: Conceptual diagram of FDTs

REQUIREMENTS OF FAST DISINTEGRATION TABLETS (FDT)

Patient factors: These formulations are suitable for children and geriatric patients who find it difficult to swallow the normal tablets and capsules to be taken with water. This is also suitable for patients who fear chocking of tablets, who has difficulty in swallowing, depression patients, schizophrenic patient, patient with persistent nausea etc.

Effectiveness factor: Enhanced bioavailability and quicker onset of action are asserts of disintegration tablets. Dispersal in saliva leads to pre-gastric absorption from that dissolve the drug instantaneously that bypasses first pass metabolism .this technique also improves safety of drugs that generate toxic metabolites through liver metabolism and gastric metabolism.

Manufacturing and marketing factors: As a drug nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A new dosage form allows a manufacturer to extend market exclusivity, unique product differentiation and extend patent protection. For examples, Eisai Inc. launched Aricept FDT, a line extension of donepezil for Alzheimer's disease, in Japan in 2004 and in the U. S. in 2005 in response to a generic challenge filed in the U. S. by Ranbaxy.(11,12)

ADVANTAGES OF FAST DISSOLVING/DISINTEGRATING TABLETS (FDT)

- Effortlessly administered for pediatric, elderly and depressed patients.
- Accurate dosing.
- Faster dissolution rate and absorption rates.
- Quicker onset of action.
- Enhanced bioavailability of drugs as the dissolved drug directly enters the stomach.
- Ease of administration and transportation.

DESIRED CHARACTERISTICS AND DEVELOPMENT CHALLENGES OF FDT

Taste of active ingredients: Taste is a considerable parameter for oral drugs. Disagreeable taste remains major formulation challenge encountered by many drugs. The formulation of bitter drugs for oral administration is major challenge for manufacturers. The taste masking is obtained by avoiding drug exposure to tongue or by adding taste-masking excipients. Exposure of drug to the oral cavity is prevented by encapsuling in polymers. Taste-masking technology is used for aggressively bitter-tasting drugs and is complex to attain by adding sweeteners only. Hence various techniques including coats, microencapsulation, and granulation were used in combination.(13)

Drug properties: For FDT formulation , the drug should not considerably influence the tablet property. The properties like solubility, crystalinity, particle size, hygroscopic, compressibility of a drug affect formulation characteristics, like strength and disintegration time.

The FDT technique should be flexible to include exclusive characteristics of each drug. The drugs that belong to BCC Class II, are most suitable for FDTs within dosage of 125 and 250 mg.

Tablet strength and Porosity: On administration of FDTs the drug must be instantly dissolved which comprise of various steps like wetting, disintegration, and dissolution. FDTs that comprise various formulation excipients are implicated beginning with solvent contact with solid and penetrates through tablet matrix. Impact of excipients is understood to be associated with surface property of the particles and structure of solid matrix.
The formulation of FDTs is based on generating porous matrix by water sublimation from pre-frozen formulation comprising matrix-forming agents, preservatives, and flavoring agents.

Moisture sensitivity: Hygroscopicity is major characteristic of powders which is also associated with solubility. FDTs must possess lower sensitivity towards humidity. This is challenging as highly soluble excipients are used to produce superior mouth feel. The excipients are vulnerable to humidity and are deliquesce at higher humidity. A superior packing strategy must be employed for protecting FDTs from

various environmental conditions.(14,15,16)

EXPERIMENTS

Materials And Methods Of Meloxicam: Meloxicam, Gellan Gum, Fenugreek Seed Mucilage, Mannitol, Avicel PH 101, Aspartame, Aerosil, Talc are used during formulations.

PREPARATIONOFCALIBRATIONCURVEFOR MELOXICAM

The calibration curve recorded in 6.8pH buffer comprising 2/10 M sodium hydroxide and 2/10M potassium dihydrogenortho phosphate).

Preparation of 0.2M NaOH: 8gm of NaOH dissolved in minimum water and made upto mark in 1000ml standard flask.

Preparation of 0.2MKH_2PO_4: 27.218 gm potassium di hydrogen ortho phosphate dissolved in water and made upto mark 1000ml standard flask.

Preparation of Meloxicam standard solution **Preparation of stock I :** 0.01g drug dissolved in 6.8 pH buffer and made upto mark in 100ml standard flask with to give 1000 mcg/ml concentration.

Preparation of stock II: 0.01mlof above solution transferred to a 100 ml standard flask and made upto volume using buffer to get 100 mcg/ml concentration.

Plotting Of Standard Curve For Meloxicam : A liquids of 0.2, 0.4, 0.6, 0.8, 1ml withdrawn for Stock II and made up to 10ml using 6.8 pH buffer to obtain concentration of 2, 4, 6, 8, 10 mcg/ml solutions. All the samples analyzed spectrophotometrically at 369 nm.

PRELIMINARY SOLUBILITY STUDIES OF MELOXICAM

Meloxicam dissolved in 25ml solutions of water-soluble carriers like PEG 6000, Kollidon CL, PVPK-30, Soluplus, Aerosil 200, Poloxamer 127, HPMC and Urea. The samples mixed well for 24 hours at 25^0C followed by filtration through Whatman filter paper no 1. The filtered diluted using CH_3OH and evaluated for drug concentration at 369 nm.

Known quantities of Meloxicam and polymers Poloxamer 127, PVPK-30, Kollidon CL and SLS were mixed in varying amounts of1:1:1, 1:2:1 and 1:3:1(table 5.3) and transferred onto porcelain dish. About 9 Meloxicam SD formulations prepared by the solvent evaporation technique.

The physical mixture solubilized in minimum CH_3OH followed by solvent evaporation to dryness at 50ºC. The SDs were pulverized manually and sieved through 45 μm, stored in a desiccators.

Table 2: Composition of Meloxicam SD

Ingredients (mg)	SD1 (1:1:1)	SD2 (1:2:1)	SD3 (1:3:1)	SD4 (1:1:1)	SD5 (1:2:1)	SD6 (1:3:1)	SD7 (1:1:1)	SD8 (1:2:1)	SD9 (1:3:1)
Meloxicam (mg)	20	20	20	20	20	20	20	20	20
Poloxamer127	20	40	60	-	-	-	-	-	-
PVP K 30 (mg)	-	-	-	20	40	60	-	-	-
Kollidon CL (mg)	-	-	-	-	-	-	20	40	60
SLS(mg)	20	20	20	20	20	20	20	20	20
Ethanol(ml)	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs	Qs

EVALUATION OF MELOXICAMSD

Percentage practical yield (PPY): The PPY of Meloxicam SD by collecting and weighing the samples using following formula.

Drug content: The drug content of Meloxicam SD analyzed by dissolving 0.02g of drug in carbinol, and made upto 100ml. The contents filtered and filtrate diluted and measured spectroscopically at 369nm against blank. The actual drug content calculated using the equation.

***In vitro* dissolution study of Meloxicam SD:** 0.02 g of drug dispersed in dissolution medium surface comprising of 0.9litof phosphate buffer at pH 7.4, temperature of 37±0.5ºC, stirred at 50 rpm. The samples withdrawn at predetermined intervals, filtered and diluted with carbinol, analyzed at 369 nm in triplicate for drug contents

CHARACTERIZATION MELOXICAM SOLID DISPERSION

FTIR studies: The IR spectra were recorded using an FTIR spectrophotometer (Shimadzu, Japan) with diffuse reflectance principle .The samples were scanned over the frequency range 4000–400-^{1}cm.(17)

Powder X-ray diffraction (XRD): PXRD recorded using Shimadzu, Japan diffraction instrument utilizing copper target, 40 Kv voltage and 30 mA current. The scanning carried out of range of 5º - 60º.(18)

Differential Scanning Calorimetry (DSC): Differential Scanning Calorimetry (DSC) studies were carried out using DSC 60, having TA60 software, Shimadzu, Japan. Samples were accurately weighed and heated in sealed aluminum pans at a rate of 10°C/ min between 40 and 350°C temperature rang under nitrogen atmosphere. Empty aluminum pan was used as a reference.(19)

SEM studies: The SEM analysis carried out using SEM (Hitachi, Japan) by dispersion of minimum drug on carbon tape adheres to aluminum stubs.

Stability Studies The optimized SD sealed 40cc HDPE container and placed in restricted environment in stability chamber (Thermo Lab, India) at 75%±5%RH and 40 ^{0}C±2^{0}C. Samples analyzed at the end of 1st, 2nd and 3rd months for drug content and drug release.(20)

PREPARATION AND EVALUATION OF MELOXICAM FDT

Experimental methodology: Meloxicam drug was selected, which is required to show immediate therapeutic action. The basic approach used to study and evaluation of Meloxicam FDT. For this study different super is integrants like gellan gum, fenugreek seed mucilage and L-HPC were selected to formulate the Meloxicam FDT by direct compression technique.

Preparation of Meloxicam FDT: Total27 formulations of (TF1-TF27) for active layer prepared by direct compression method using3^{3} RSM with super disintegrates like gellan gum, fenugreek seed mucilage and L-HPC. The formulation prepared with varying concentration of superdisintegrants, and magnesium stearate. The contents sieved via #60 and mixed manually. The final mixture compressed with8 mm flat punches using eight station rotary tablet press (Table 5.4). The prepared tablets analyzed for drug dissolution.

Table 3: Formulation trials of Meloxicam of Fast disintegrating tablets

F.NO	Meloxicam	Gellan gum	Fenugreek Seed Mucilage	partae	anni tol	MC C	Magnesium stearate	al c	ero sil	TOT AL
TF1	20	14	26	8	50	32	4	4	4	**200**
TF2	20	18	26	8	50	28	4	4	4	**200**
TF3	20	14	30	8	50	28	4	4	4	**200**
TF4	20	16	28	8	50	28	4	4	4	**200**
TF5	20	14	26	8	50	28	4	4	4	**200**
TF6	20	18	26	8	50	24	4	4	4	**200**
TF7	20	14	30	8	50	24	4	4	4	**200**
TF8	20	16	30	8	50	22	4	4	4	**200**
TF9	20	14	30	8	50	24	4	4	4	**200**
TF10	20	18	28	8	50	24	4	4	4	**200**
TF11	20	16	26	8	50	28	4	4	4	**200**
TF12	20	16	30	8	50	24	4	4	4	**200**
TF13	**20**	**18**	**30**	**8**	**50**	**20**	**4**	**4**	**4**	**200**
TF14	20	16	28	8	50	24	4	4	4	**200**
TF15	20	16	28	8	50	26	4	4	4	**200**
TF16	20	16	26	8	50	26	4	4	4	**200**
TF17	20	16	26	8	50	30	4	4	4	**200**
TF18	20	16	30	8	50	24	4	4	4	**200**
TF19	20	18	26	8	50	26	4	4	4	**200**
TF20	20	16	30	8	50	26	4	4	4	**200**
TF21	20	18	28	8	50	26	4	4	4	**200**
TF22	20	18	28	8	50	24	4	4	4	**200**
TF23	20	18	30	8	50	22	4	4	4	**200**
TF24	20	14	28	8	50	28	4	4	4	**200**

TF25	20	18	28	8	50	22	4	4	4	**200**
TF26	20	14	28	8	50	30	4	4	4	**200**
TF27	20	16	28	8	50	28	4	4	4	**200**

Design of Experiment

Of late, the response surface methodology (RSM) used by proper experimental designs are widely employed for formulation optimization. RSM is generally applied to experimental situations where several independent variables influence a response variable.

Central composite designs (CCD) is frequently used optimization designs that employs5 level of each input factor with a reduced experiment number compared to three-level full factorial design.

This method is mainly used to explain the effect of one factor on other factor, whether this effect is significant or not, if significant how it influences the response. In this present work the effect of one factor (gellangum) on other two factors (fenugreek seed mucilage and L-HPC) was explained.

Statistical analysis: Data were analyzed using Stat-Ease Design Expert ® software V8.0.1 to obtain analysis of variance (ANOVA), regression coefficients and regression equation. Mathematical relationships were generated by multiple linear regression analysis for the mentioned variables that demonstrates the effects of amount of gellan gum(A), amount of fenugreek seed mucilage (B) and amount of L-HPC (C) and their interaction on %CDR and DT.(22,23)

EVALUATION OF MELOXICAM FDT

Pre Compression Evaluation Tests

Angle of repose: Angle of repose signifies highest angle achievable between tablet surface and the horizontal plane. A rough and irregular surface exhibit larger angle of repose. Weight accurately 100gm of the blend and are cautiously poured through funnel with tip placed 2.5cm height over the graph paper that is positioned on a horizontal surface. The powder is poured till apex of pile just reaches funnel tip.(24)

Angle of repose is calculated by the following formula

$$\Theta = \mathbf{Tan^{-1}(h/r)}$$

Where Θ = angle of repose, r=radius of pile, h= height of the pile

Bulk density: Bulk density is powder mass divided by the bulk volume. It is analyzed by pouring the powder blend into graduated cylinder to determine volume (V*) and powder(M) .The bulk volume calculated as.(25)

$$b = M/V^*$$

Tapped density: This is calculated by tapping a cylinder containing accurately weighed powder blend for about 250 times.(26)
Tapped density is calculated as

$$^*t = M/V_t$$

Compressibility Index (Carr's Index): Carr's index (CI) signifies the easiness with which a material can be courage to flow. CI value <10 indicates excellent powder flow while value between 26-31 indicates power flow(27)
The CI calculated as follows

$$C.I\ (\%) = \frac{Tappeddensity - Bulkdensity}{Tapped\ density} \times 100$$

Hauser's Ratio: Hauser's ratio is an indicator of easiness of powder flow calculated as follows

$$Hausner's\ ratio = *dt/*db$$

Where*dt = tapped density,*db =bulk density

Post compression evaluation tests

Weight variations: 20 random FDTs weighed and average weight determined. Then individual tablet weighed separately to obtain % deviation from the average. The accepted deviation for tablets with average weight ≤ 130mg is 10%, for ≥130mg is 7.5%.

Thickness: Thickness of tablet is crucial for patient acceptance and packaging hence to be controlled at±5% deviation from standard value. Vernier Calipers used for measurement of thickness of 10 FDTs .the average and SD values recorded.

Hardness: Monsanto hardness tester was used for determination of hardness of randomly picked 10 tablets and average of measured values reported.

Friability: 20 tablets randomly picked were weighed and subjected to friability test in Roche friabilator that rotated at 25rpm for duration of 4min. the tablets were then reweighed after de-dusting and following equation was used to calculate percent loss in weight due to impact and abrasion,

%Friability= (Loss in weight/Initial weight) X 100.

Content uniformity: Randomly picked 20 tablets were powdered in a glass mortar after calculating their average weight and amount equal to 10 mg was dissolved in 100ml of phosphate buffer pH 6.8 and filtered followed by spectrometric determination of drug content at 369 nm.

In-vitro disintegration time (DT): The DT of FDT analyzed in USP device with six glass tubes measuring "3 long, open at the top, and held against 10" screen at lower end of the basket rack congregation. One tablet positioned in each tube with basket rack positioned in 1000ml beaker containing buffer at 37± 2 ^{0}C, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker.(28,29,30)

Accelerated Stability Studies Of Meloxicam Fdt: Accelerated three months stability tests were carried out for the optimized FDT in a stability chamber at 40^{0}C 75% RH post wrapping the FDT sin aluminum foil and sealing into ambered bottles.

Pharmacokinetic Studies Of Meloxicam Fdt: Animal preparation: Healthy male rabbits (weighing 2-3 kg) selected for this study were maintained at room temperature 25^{0}C, Relative Humidity 45% and 12 h alternate light and dark cycle with 100 % fresh air exchange in animal rooms. The water and power supply were not interrupted. They were fed with standard diet and water. The protocol was approved by Institutional animal ethics committee with no: 1292/ac/09/CPCSEA/58/A.

***In vivo* study design:** Random division of rabbits into two groups of six animals each was done. Group A and B were administered orally with Meloxicam FDT (2.5 mg) and marketed product (2.5 mg) with equivalent dose of animal body weight respectively.

At pre-determined time intervals of 0, 0.5, 1, 1.5,2, 4, 6, 8, 12, 16, 20 and 24hrs post dose, blood sample (approximately 0.5ml) collected by marginal ear vein was mixed with heparin for clotting prevention. This was followed by centrifugation of blood at 5000rpm for 5-10min of blood to separate plasma which was then stored frozen at −20°C for further analysis.(33,34)

HPLC study

Preparation of plasma samples for HPLC analysis: About 2.5ml of ice cold absolute ethanol was used for precipitation of protein for each 0.5ml of rabbit plasma samples for chromatography followed by separation of ethanol into a clean tube after centrifugation. Resuspension of precipitate with 1ml of aceto nitrile was done by vortex in git for 1min. Addition of aceto nitrile was done to ethanol after centrifugation (5000 – 6000 rpm for 10 min), followed by taking the organic mixture to near dryness by a steam of nitrogen at room temperature.

Pharmacokinetic Analysis: Various pharmacokinetic parameters (Table 5.6) were analysed by non compartmental analysis using Win Nonlin 3.3® pharmacokinetic software (Pharsight Mountain View, CA USA). All values reported as mean ±SD. Statistical analysis was performed with Graph Pad InStat software (version 3.00, Graph Pad Software, San Diego, CA, USA) using one-way analysis of variance (ANOVA) followed by Tukey–Kramer multiple comparison test. Difference with $p<0.05$ was considered statistically significant.(36,37)

RESULT AND DISCUSSION

UV CALIBRATION CURVE: The UV spectra of Meloxicam scanned between 200-400 nm denoted absorption maximum peaks at 346 nm (figure 6.1). The calibration curve exhibited good linearity within concentration of 2-10 mcg/ml with correlation coefficient value of 0.999 (table 6.1and figure 6.2).

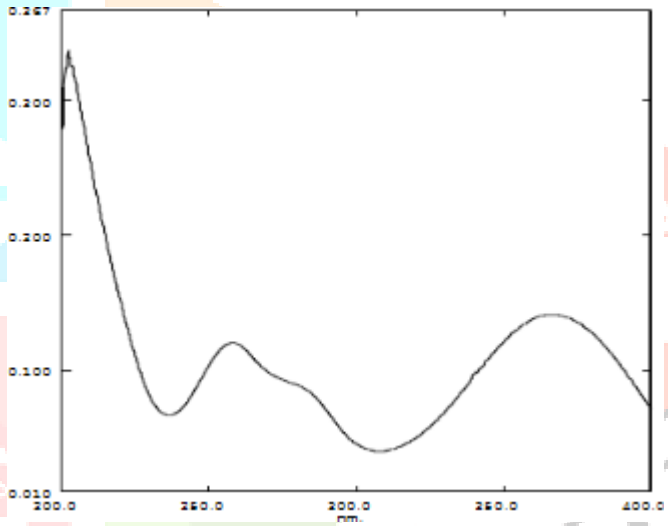

Figure 4: UV spectra of Meloxicam pure drug

Table 4: Calibration curve of Meloxicam

Concentration (mcg/ml)	Absorbance
0	0
2	0.196
4	0.388
6	0.601
8	0.82
10	0.996

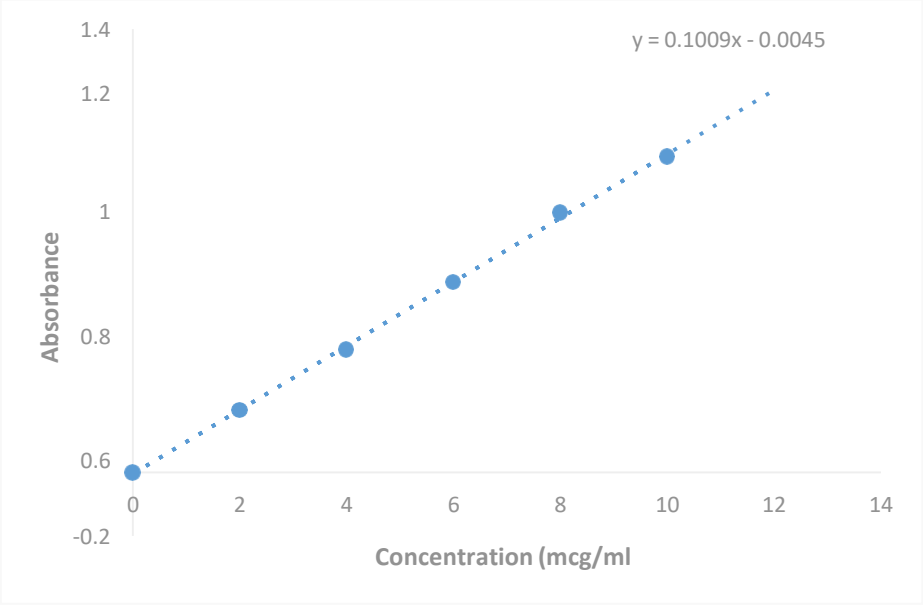

Figure 6.2: Calibration curve for Meloxicam

Preliminary Solubility Data Of Meloxicam: The solubility data indicate that Meloxicam pure drug solubility is 0.068±0.14mg/ml. the mixture of Meloxicam and Kollidon CL in equimolar ratio displayed maximum drug solubility of 1.116±0.21mg/ml that is almost 18-fold the solubility of pure drug itself. The PEG 6000, Soluplus, Urea, HPMC and Aerosil 200 that displayed poor solubility were excluded from formulation of Meloxicam SD. (table 6.2 and figure 6.3)

Table 5: Preliminary solubility studies of Meloxicam in different polymers

Physical Mixture (1:1)	**Solubility(mg/ml) ***
Meloxicam Pure drug	0.068±0.14
Drug + Kolliwax GMS II	0.682±0.11
Drug + Poloxamer127	0.93±0.04
Drug + Aerosil 200	0.744±0.09
Drug + PEG 6000	0.558±0.20
Drug + PVP K 30	0.868±0.14
Drug +Soluplus	0.62±0.08
Drug + Kollidon CL	1.116±0.21
Drug + Urea	0.496±0.07

PREPARATION OF MELOXICAM SD

Nine formulations of Meloxicam SD prepared by solvent evaporation technique usingKollidon CL, Poloxamer 127 and PVPK-30 in 3 different drug: polymer: SLS in varying concentration (1:1:1, 1:2:1 and 1:3:1). All the formulations were fine and free flowing powers (figure 6.4).

Figure 5: Optimized formulation of Meloxicam SD

EVALUATION OF MELOXICAM SD

Solubility studies of Meloxicam SD: All the nine Meloxicam SD formulations subjectedto solubility study. Results show that formulation (SD9) comprising of drug: Kollidon CL (1:3) added with SLS displayed maximum solubility of 4.216±0.19mg/ml, which is 68 times than solubility of pure drug (0.068±0.14 mg/ml) .(figure 6.5 and table 6.3)

Table 6: Solubility studies of Meloxicam SD

S No	Formulation code	Solubility (mg/ml) *
1	Pure drug (Meloxicam)	0.068±0.14
2	SD1	3.472±0.04
3	SD2	3.596±0.06
4	SD3	3.72±0.11
5	SD4	3.224±024
6	SD5	3.348±0.14
7	SD6	3.410±0.27
8	SD7	3.906±0.17
9	SD8	4.092±0.05
10	SD9	4.216±0.19

Percent practical yield and drug content of Meloxicam SD: The Meloxicam SD (SD9) displayed maximum PPY and drug content of 98.87% and 99.09%. (Table 6.4)

Table 7: Percent practical yield and drug content for Meloxicam SD

S. No	Formulation	% Practical Yield	% Drug content
1	SD1	93.26±0.19	90.44±0.11
2	SD2	92.49±0.12	93.44±0.25
3	SD3	94.77±0.33	92.11±0.31
4	SD4	96.16±0.11	94.55±0.27
5	SD5	91.44±0.41	95.34±0.07
6	SD6	96.68±0.08	96.11±0.49
7	SD7	97.19±0.04	95.77±0.70
8	SD8	97.99±0.27	97.52±0.44
9	SD9	98.87±0.51	99.09±0.55

In vitro dissolution studies

The dissolution results of SD1 to SD9 indicate enhanced Meloxicam release from all SDs when compared to pure drug itself. The formulation SD9 comprising drug: Kollidon CL :SLS (1:3:1) displayed maximum release of 99.11±5.17 %. (Table6.5 And figure 6.6)

Table 8: In vitro dissolution profile of pure drug and different formulations of SD (SD1-SD9)

Puredrug	SD1	SD2	SD3	SD4	SD5	SD6	SD7	SD8	SD9
0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
8.11± 0.01	18.55 ±1.42	20.21 ±1.12	22.42 ±1.07	23.31 ±1.37	25.12 ±1.24	26.17 ±1.72	28.47 ±1.63	31.42 ±1.25	33.42 ±1.94
16.42 ±1.44	25.58 ±1.88	28.86 ±1.44	30.29 ±1.68	32.60 ±1.98	33.86 ±1.79	35.93 ±1.88	36.23 ±1.67	38.23 ±1.45	41.23 ±2.04
22.89 ±1.93	38.37 ±2.07	39.86 ±2.12	41.80 ±2.00	44.40 ±2.25	45.81 ±2.44	47.72 ±2.18	49.12 ±2.26	52.12 ±2.76	55.12 ±2.96
28.22 ±2.04	55.89 ±2.14	58.94 ±3.04	61.50 ±3.42	63.50 ±3.25	64.49 ±3.11	65.77 ±3.42	67.72 ±3.18	68.72 ±3.58	69.92 ±3.28
32.89 ±2.49	71.44 ±3.12	73.68 ±3.65	69.69 ±3.59	72.76 ±3.78	74.57 ±3.05	78.36 ±3.59	77.45 ±3.19	75.45 ±3.19	78.45 ±3.69
35.68 ±2.88	83.20 ±4.34	80.14 ±4.75	82.69 ±4.85	86.27 ±4.18	88.21 ±4.11	84.23 ±4.78	80.56 ±4.52	81.56 ±4.12	86.56 ±4.52

40.11 ±2.97	90.38 ±5.15	91.14 ±5.55	93.81 ±5.86	92.08 ±5.58	94.04 ±4.78	94.31 ±5.11	93.89 ±5.32	95.89 ±5.32	99.11 ±5.17

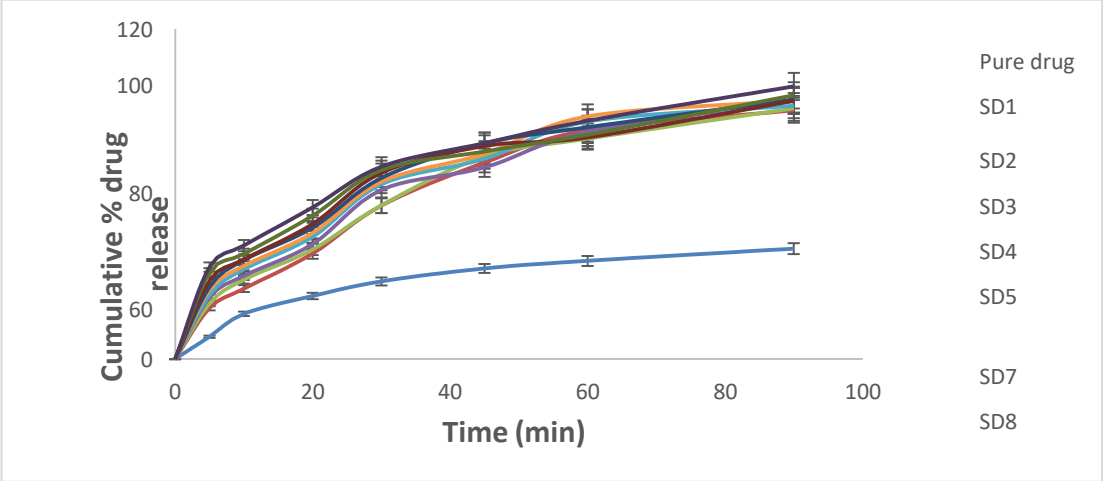

Figure 6: In vitro dissolution profile of pure drug and different formulations ofMeloxicam SD (SD1-SD9)

CHARACTERIZATION OF MELOXICAM SD

FTIR studies: The IR spectra are shown in Figure6.7-6.9. Pure meloxicam (A) exhibited peaks at 3126 cm^{-1} and 3088 cm^{-1} (NH and OH stretching), 1635 cm^{-1} (aromatic C=C), 1521 cm^{-1} and 1510 (Amide – C = O, C=N), 1440 cm^{-1} (C-H deformation), 1369 cm^{-1}(- CH3 deformation). The optimized formulation of solid dispersion also exhibited the same characteristic peaks representing

withholding of Meloxicam chemical identity. Hence, there exists no interaction among drug and the carriers used in SD formulation.

Ray Diffraction patterns

The existence of several distinct peaks in the XRD of pure Meloxicam specifies that Meloxicam is in crystalline form (Figure 6.10). The PXRD of SD9 was described by the absolute lack of any diffraction peak, indicating its existence in amorphous state (Figure 6.11). The augmentation in drug release from SD9 is due to reduction in drug crystallinity.

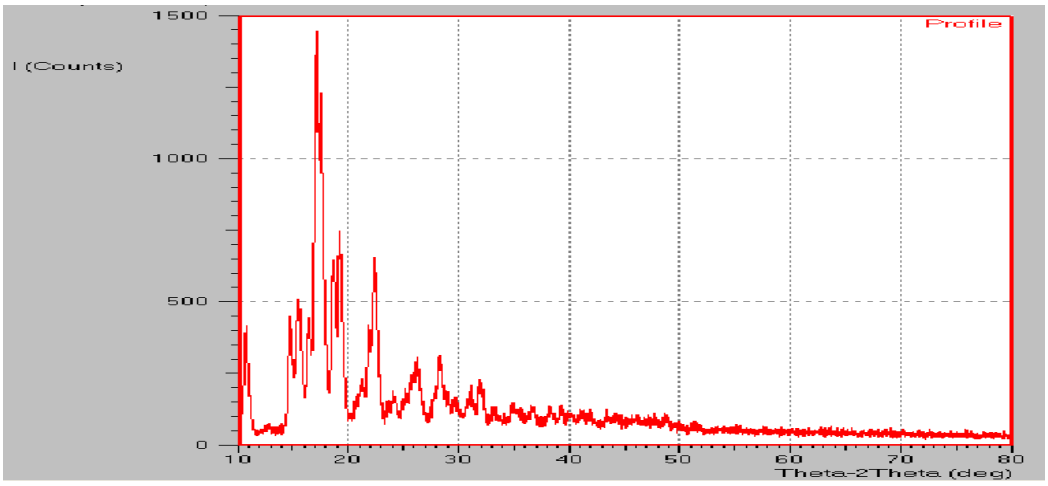

Figure 7: X-Ray powder diffractogram of Meloxicam pure drug

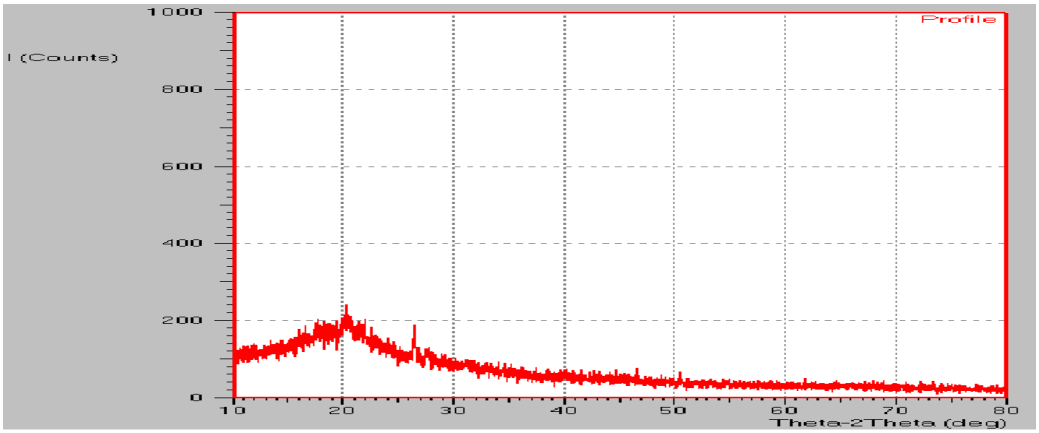

Figure 8: X-Ray powder diffractogram of Meloxicam optimized formulation

DSC studies: The DSC thermo grams of Meloxicam displayed (Figure 6.12) sharp endothermic peak at 209 ^{0}C, demonstrating crystalline state of the drug. The nonappearance of this peak in SD9 thermo gram demonstrates amorphous form of drug. Crystallization inhibition is attributed to the entrapment of the drug molecules in the polymer matrix during solvent evaporation.

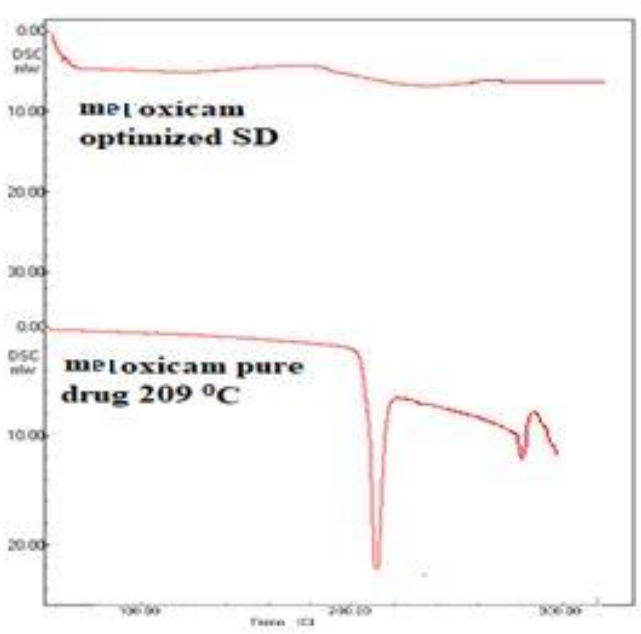

Figure 9: DSC thermo grams of Meloxicam pure drug and SD9

SEM studies: SEM data of Meloxicam and SD9 (figure 6.13) indicate that drug crystals are smooth and irregular in shape. The SEM of SD9 could not display the presence of drug crystals. The drug surface is porous and SD is uniform which appeared as homogeneously mixed mass with wrinkled surface. The drug crystals are successfullyincorporated into matrix.

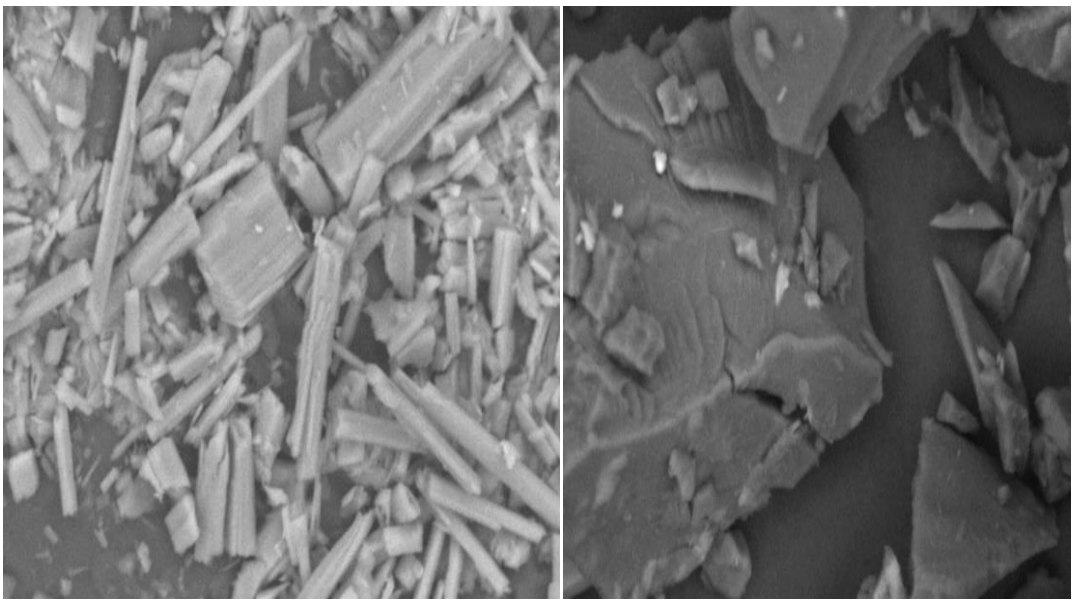

Figure 10: SEM photographs of Meloxicam pure drug (a) and SD9 (b.)

Stability studies: Stability data of SD9 formulation carried out for 3 months as per ICH guidelines. The results conclude that the formulation was stable with retention of its properties with minor variations (table 6.6).

Table 9: Evaluation parameters of SD9 stored at 40 ±2^{0}c /75 ±5%RH

Retest time for optimized formulation	**% Drug content**	***In-vitro* drug release (%)**
0 days	98.87	99.09
30 days	98.55	98.44
60 days	97.49	97.76
90 days	96.32	96.34

PHYSICO-CHEMICAL EVALUATION OF MELOXICAM FDT

The results of precompresion evaluation of all the formulations indicate that the bulk densities formulations bearing TF1 to TF27 reported being in the range of 0.50g/cc to 0.59g/cc. The findings of tapped density formulations TF1 to TF27 reported being in the range of 0.50g/cc to 0.69g/cc. The angle of repose of all the formulations was found a satisfactory result. The formulation TF13 was found to be 21.09 having good flow property. The compressibility index values were found to be in the range of 8 to 11.29 %. These findings indicated that the all the batches of formulations exhibited good flow properties. The Hausner's ratio values in the space of 1.10 to 1.14 %. These findings designated that the all the batches of formulations advertised good flow criterions. (table 6.7)

Table 10: Physical properties of prepared powder blends of Meloxicam FDT

Formulation	Bulk density (g/cc)	Tapped density (g/cc)	Angle of repose(Ɵ)	Carr^{2}s index(%)	Hausnerratio
TF1	0.52±0.15	0.51±0.56	22.56±0.27	09.41±0.49	1.13±0.03
TF2	0.54±0.34	0.50±0.28	23.30±0.17	11.48±0.24	1.13±0.05
TF3	0.50±0.68	0.68±0.02	25.56±0.25	10.23±0.39	1.15±0.04
TF4	0.56±0.22	0.69±0.17	24.67±0.36	11.31±0.13	1.13±0.09
TF5	0.60±0.76	0.54±0.34	25.56±0.31	09.62±0.49	1.12±0.03
TF6	0.50±0.21	0.63±0.34	21.66±0.22	10.22±0.41	1.11±0.02
TF7	0.53±0.06	0.68±0.23	25.34±0.24	10.42±0.31	1.14±0.09
TF8	0.55±0.39	0.62±0.22	24.34±0.43	09.62±0.22	1.10±0.03
TF9	0.59±0.97	0.59±0.33	21.67±0.33	11.42±0.86	1.13±0.06
TF10	0.52±0.28	0.63±0.34	26.54±0.16	11.90±0.34	1.12±0.03
TF11	0.53±0.37	0.62±0.24	23.89±0.22	11.459±0.62	1.13±0.01
TF12	0.57±0.19	0.67±0.33	22.45±0.43	10.11±0.54	1.11±0.03
TF13	0.59±0.95	0.69±0.56	21.09±0.32	11.03±0.45	1.13±0.032
TF14	0.50±0.57	0.60±0.33	23.05±0.25	09.31±0.22	1.14±0.09
TF15	0.52±0.49	0.61±0.02	25.06±0.26	10.61±0.42	1.11±0.052
TF16	0.55±0.37	0.52±0.31	22.78±0.44	09.69±0.61	1.12±0.064
TF17	0.51±0.77	0.67±0.77	22.45±0.43	11.27±0.57	1.14±0.01
TF18	0.53±0.66	0.64±0.35	25.09±0.34	09.31±0.59	1.13±0.06
TF19	0.57±0.44	0.61±0.67	23.05±0.23	11.09±0.79	1.12±0.02
TF20	0.53±0.06	0.60±0.16	25.06±0.24	09.23±0.83	1.11±0.06
TF21	0.57±0.11	0.60±0.69	24.78±0.13	08.29±1.01	1.11±0.04
TF22	0.56±0.19	0.69±0.07	25.34±0.44	10.11±0.74	1.10±0.05
TF23	0.54±0.18	0.67±0.49	23.42±0.32	11.34±0.62	1.12±0.09
TF24	0.57±0.17	0.63±0.49	22.99±0.52	11.29±0.82	1.11±0.04
TF25	0.55±0.13	0.67±0.06	25.14±0.34	10.20±0.56	1.10±0.04
TF26	0.52±0.4	0.64±0.37	24.09±0.23	10.39±1.07	1.12±0.06
TF27	0.54±0.47	0.66±0.19	22.78±0.46	09.13±0.82	1.10±0.04

Above parameters are communicated as Average ± Standard Deviation; (n=6)

The post compression evaluation of Meloxicam FDT indicate that the Weight variation of all formulations witnessed to be in the limit allowed that is ± 5% of total tablet weight. The suitable hardness for compressed tablets is considered as a vital function for the end user. The deliberated crushing strength of fabricated tablets of formulations TF1-TF27 trended between 4.0-4.9 kg/cm^2 and magnitudes of crushing strength .The thickness of all the formulations between the ranges 4.0-4.4 mm. The friability of all prepared formulation between 0.52-0.89.the friability properties limits are in between 0-1%. The drug content of all formulation is in between 94.11- 99.45 %, drug content depends on the angle of repose since the angle of repose indicates uniform flow nature of powder blend which makes the drug to evenly distribute in all the formulation and to maintain content uniformity in all batches. (table 6.8)

Table 11: Physico-chemical parameters Meloxicam FDT

F.NO	*Weight variation (mg)	#Thickness (mm)	#Hardness (Kg/Cm^2)	#Friability (%)	#Content uniformity (%)	DT (Sec)
TF1	298.29±1.23	4.1±0.29	5.4±0.13	0.74±0.03	94.11±0.37	51±1.23
TF2	300.28±0.87	4.3±0.59	5.1±0.062	0.75±0.02	97.23±0.3	72±1.51
TF3	301.37±0.56	4.3±0.49	5.2±0.09	0.78±0.01	96.13±0.97	65±1.40
TF4	299.97±0.03	4.2±0.55	5.3±0.19	0.79±0.01	95.23±0.27	55±1.19
TF5	301.17±0.46	4.2±0.34	4.9±0.03	0.82±0.01	97.97±0.93	65±1.25
TF6	298.96±0.43	4.3±0.27	5.0±0.01	0.84±0.03	97.45±0.75	48±1.87
TF7	299.37±0.35	4.3±0.99	5.7±0.13	0.63±0.03	94.11±0.37	57±1.63
TF8	300.27±0.23	4.1±0.43	4.7±0.45	0.66±0.02	97.23±0.93	68±1.37
TF9	302.44±0.36	4.4±0.21	3.4±0.02	0.53±0.03	96.13±0.27	56±1.19
TF10	300.27±0.24	4.2±0.20	3.9±0.42	0.76±0.05	95.23±0.27	58±1.24
TF11	301.37±0.42	4.2±0.47	3.8±0.02	0.74±0.03	97.97±0.63	63±1.19
TF12	302.37±0.35	4.3±0.95	3.5±0.06	0.73±0.02	97.45±0.44	56±1.40
TF13	**300.66±0.29**	**4.3±0.49**	**4.9±0.32**	**0.52±0.02**	**99.45±0.48**	**36±1.73**
TF14	299.72±0.30	4.1±0.26	3.4±0.22	0.76±0.05	96.98±0.93	55±1.87

TF15	300.31±0.24	4.4±0.54	3.8±0.22	0.43±0.08	96.45±0.41	68±1.35
TF16	298.37±0.37	4.2±0.34	3.4±0.22	0.67±0.02	96.45±0.41	54±1.81

TF17	299.22±0.46	4.5±0.73	4.0±0.39	0.72±0.89	96.34±0.63	53±1.56
TF18	301.41±0.19	4.5±0.57	3.7±0.32	0.89±0.03	96.29±0.71	52±1.12
TF19	302.22±0.32	4.0±0.63	3.9±0.12	0.52±0.01	97.18±0.17	57±1.33
TF20	299.71±0.24	4.0±0.27	5.0±0.1	0.55±0.02	96.27±0.9	58±132
TF21	298.27±0.43	4.2±0.93	5.1±0.36	0.63±0.03	96.78±0.42	55±1.27
TF22	300.27±0.14	4.2±0.72	5.2±0.92	0.72±0.01	96.14±0.79	60±1.61
TF23	300.26±0.13	4.0±0.57	3.8±0.27	0.62±0.02	96.29±0.31	68±1.49
TF24	301.10±0.57	4.3±0.67	3.7±0.21	0.66±0.01	97.16±0.19	53±1.31
TF25	299.12±0.66	4.3±0.92	3.6±0.19	0.58±0.02	96.23±0.02	51±1.39
TF26	300.46±0.89	4.1±0.47	3.9±0.27	0.69±0.01	97.34±0.27	69±1.40
TF27	300.69±0.15	4.4±0.63	4.2±0.49	0.89±0.03	97.10±0.44	53±1.77

*Values are expressed in mean± SD :(n=20)#Values are expressed in mean± SD :(n=3)

PERCENTAGE CUMULATIVE DRUG RELEASE

The % CDR of all the formulations TF1-TF27 are tabulated in table 6.9-6.12 and figure 6.15 - 6.18.The study indicate that the drug release of all the formulations ranged between 84.73±1.61 to 99.68±1.52% in 10 hours .the maximum drug release is exhibited by TF13 (99.68±1.52%) that is higher than the release value of marketed formulation(92.77±1.52%).

Table 12: % CDR OF Meloxicam FDT(TF1-TF7)

Time(h)	TF1	TF2	TF3	TF4	TF5	TF6	TF7
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
1	13.01±0.25	19.04±1.24	15.71±2.25	15.01±0.21	18.15±0.88	16.95±0.29	14.12±1.29
2	22.51±0.47	25.16±1.11	27.29±2.29	26.54±0.24	27.86±0.15	24.93±0.32	23.23±1.32
3	28.49±1.24	32.05±1.28	33.24±1.75	36.58±0.45	38.18±0.78	30.09±1.29	28.34±1.82
4	37.32±1.78	40.06±1.78	38.80±1.52	45.38±1.78	44.81±1.75	39.72±1.16	39.12±2.29
5	45.83±2.44	47.94±1.44	46.50±0.52	53.87±1.89	52.49±1.28	51.77±1.29	51.72±1.27
6	53.49±1.78	54.88±1.26	52.69±0.86	61.89±1.16	55.57±1.19	59.36±1.63	55.45±1.19
7	64.28±0.89	68.74±1.25	63.11±1.77	72.28±1.89	63.21±1.32	67.23±1.45	66.56±1.27
8	72.21±1.52	79.34±1.61	71.23±1.16	81.49±1.21	72.34±1.25	73.14±1.29	72.48±1.22
9	77.01±1.22	86.34±1.18	77.45±1.16	88.54±1.57	77.68±1.02	82.34±1.92	78.55±1.78
10	84.55±1.17	90.34±1.53	83.34±1.16	90.78±1.37	85.79±1.67	88.34±1.78	85.29±1.13

Table 13: *%CDR of* Meloxicam FDT (TF8-TF13)

Time(h)	TF8	TF9	TF10	TF11	TF12	TF13	Marketed
0	0±0	0±0	0±0	0±0	0±0	**0±0**	0±0
1	16.95±1.96	13.89±1.46	11.77±2.29	17.08±1.28	19.15±0.26	**19.05±1.52**	17.35±1.78
2	23.93±1.42	24.46±1.98	22.90±1.18	28.76±2.94	30.86±0.32	**29.60±1.16**	27.87±1.68
3	32.09±1.44	32.35±1.74	31.79±1.11	39.89±2.28	41.18±0.52	**42.30±1.25**	32.64±0.18
4	40.72±174	44.67±1.78	42.58±1.75	49.87±2.23	52.81±0.58	**59.40±1.19**	47.56±1.15
5	54.77±1.75	51.97±1.18	50.70±1.56	56.97±1.16	60.49±1.89	**68.50±1.27**	51.78±1.98
6	70.36±1.86	59.89±1.85	57.09±1.86	65.76±1.78	65.57±1.75	**79.76±0.28**	54.69±1.77
7	74.23±1.22	65.78±1.18	65.79±1.22	75.69±1.18	77.21±1.24	**85.89±1.28**	68.89±1.65
8	79.86±1.01	73.73±1.21	70.29±1.21	80.43±1.15	82.19±1.05	**89.21±1.23**	77.43±1.52
9	85.21±1.58	79.73±1.01	78.47±1.85	85.37±1.65	88.58±1.27	**91.27±1.18**	86.78±1.52
10	89.33±1.46	84.73±1.61	85.36±1.21	90.69±1.38	94.13±1.79	**99.68±1.52**	92.77±1.52

Above parameters are communicated as Average ± Standard Deviation; (n=3)

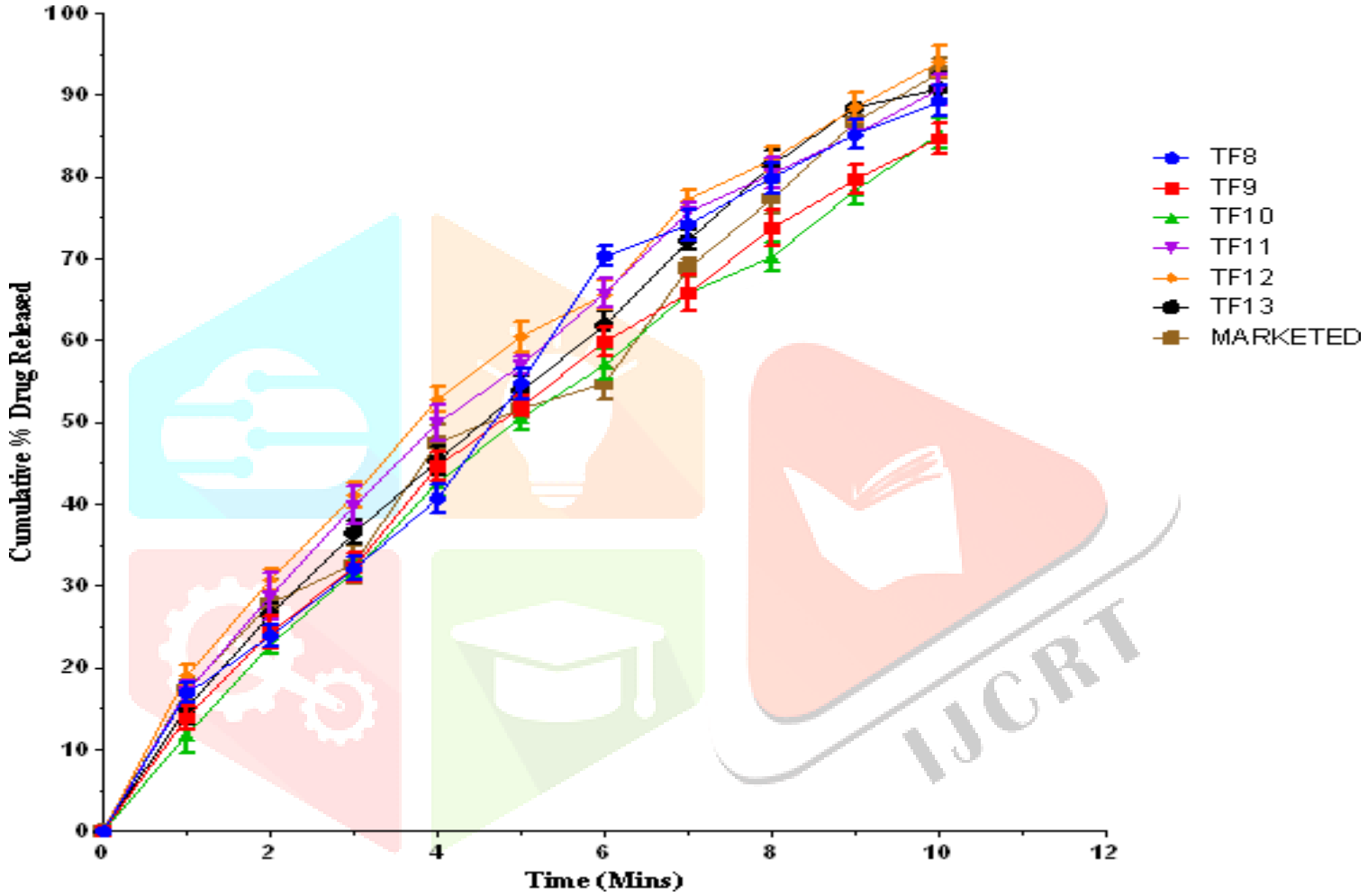

Figure 11: ***% CDR of*** **Meloxicam FDT Meloxicam TF8-TF13**

Table 14: *% CDR of* Meloxicam FDT (TF14-TF20)

Time(h)	TF14	TF15	TF16	TF17	TF18	TF19	TF20
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
1	11.77±0.52	17.04±2.22	13.35±1.14	20.05±1.14	16.34±1.78	14.46±2.24	12.12±3.21
2	22.64±0.18	29.16±1.18	23.87±1.17	30.60±1.63	26.46±1.23	25.87±2.26	30.23±1.24
3	32.54±1.18	40.05±1.17	32.64±1.86	43.30±1.98	36.78±1.28	36.97±2.22	41.34±2.289
4	41.58±2.22	48.06±1.82	43.56±1.89	52.40±1.82	46.78±1.24	47.67±1.75	57.12±2.41
5	53.28±2.29	59.94±1.96	54.78±1.75	66.50±1.78	57.66±1.75	59.89±1.96	69.72±2.11
6	61.54±2.85	68.88±1.48	65.69±1.44	73.76±1.44	63.56±1.22	65.67±1.18	73.45±1.75
7	73.78±1.86	76.74±1.27	76.89±2.45	79.27±1.47	72.65±1.16	74.78±2.28	78.56±1.78
8	78.16±1.04	81.28±1.14	80.65±1.25	84.43±1.32	80.74±1.09	81.11±1.13	85.45±1.10
9	84.22±1.16	88.39±1.07	86.22±1.45	87.98±1.17	85.29±1.11	87.29±1.08	89.56±1.28
10	89.33±1.24	93.87±1.11	90.05±1.85	94.17±1.12	92.15±1.29	93.18±1.33	94.45±1.34

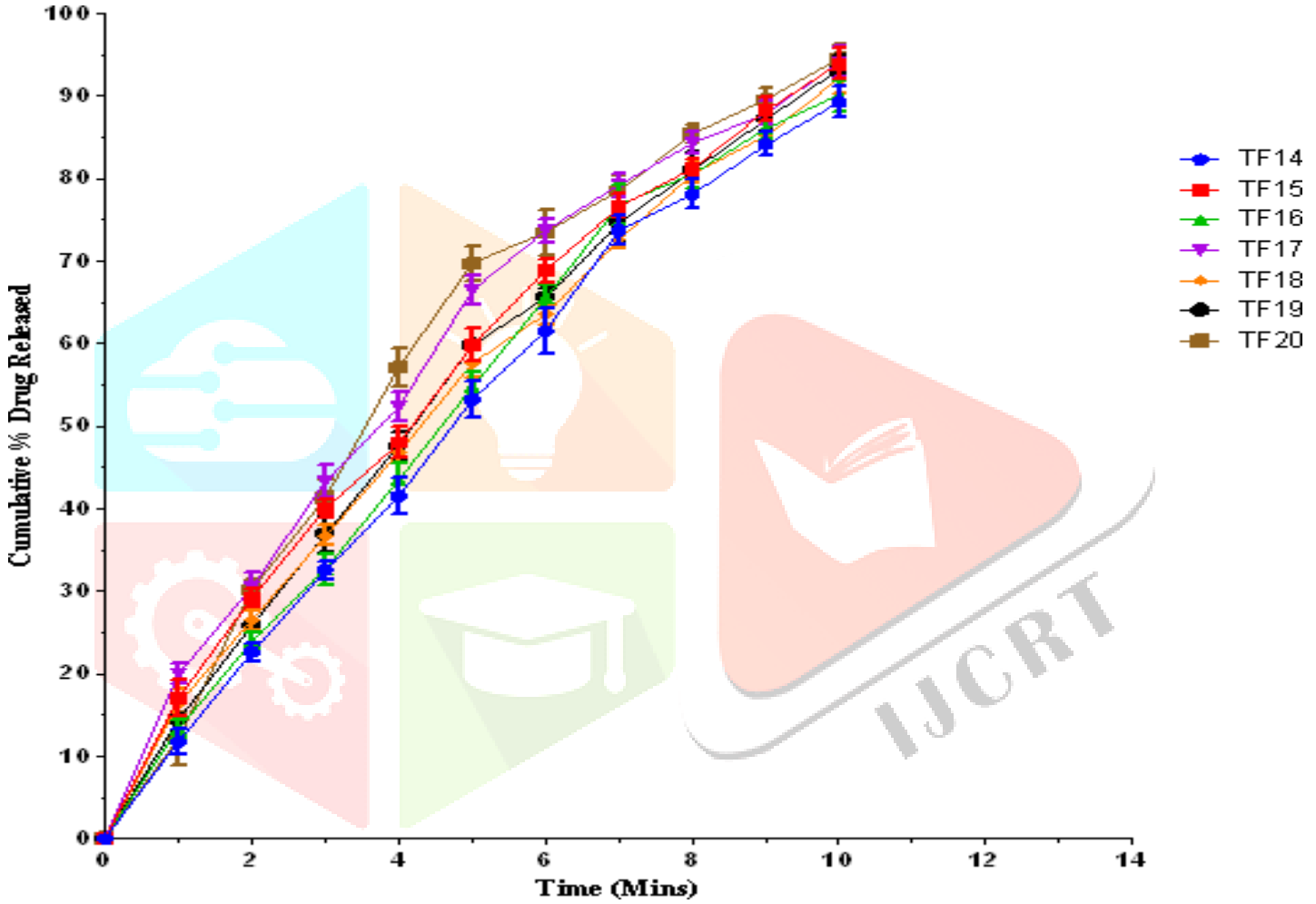

Figure 12: *% CDR of* Meloxicam FDT TF14-TF20

Table 15: *% CDR* of Meloxicam FDT (TF21-TF27)

Time(h)	TF21	TF22	TF23	TF24	TF25	TF26	TF27
0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
1	13.01±1.18	17.53±1.11	11.66±1.28	20.05±2.18	15.47±3.14	14.95±2.22	12.12±1.12
2	24.51±1.14	27.67±1.75	22.76±1.18	30.60±1.89	25.67±2.18	24.93±2.27	21.23±1.28
3	34.49±2.22	40.68±1.18	31.65±1.75	43.30±2.22	36.78±2.17	28.09±1.78	36.34±1.75
4	43.32±2.22	48.78±1.65	42.65±1.72	52.40±2.15	42.87±2.41	37.72±1.28	57.12±1.86
5	55.83±1.96	55.56±0.18	54.32±1.98	66.50±1.74	53.66±2.44	49.77±1.32	69.72±1.74
6	64.49±1.58	67.08±1.34	62.39±1.56	69.76±1.74	63.86±2.74	67.36±2.26	73.45±2.28
7	72.28±1.75	76.98±1.41	71.67±1.42	77.27±1.85	71.47±1.95	75.23±1.29	79.56±1.23
8	80.58±1.19	83.76±1.77	80.45±1.44	82.86±1.98	77.45±1.14	82.48±1.17	84.02±1.15
9	86.33±1.21	89.98±1.18	88.17±1.89	89.66±1.65	85.17±1.15	89.43±1.09	89.56±1.03
10	91.18±1.29	94.76±1.07	93.25±1.14	94.16±1.11	90.23±1.88	92.55±1.12	94.02±1.65

Above parameters are communicated as Average ± Standard Deviation; (n=3)

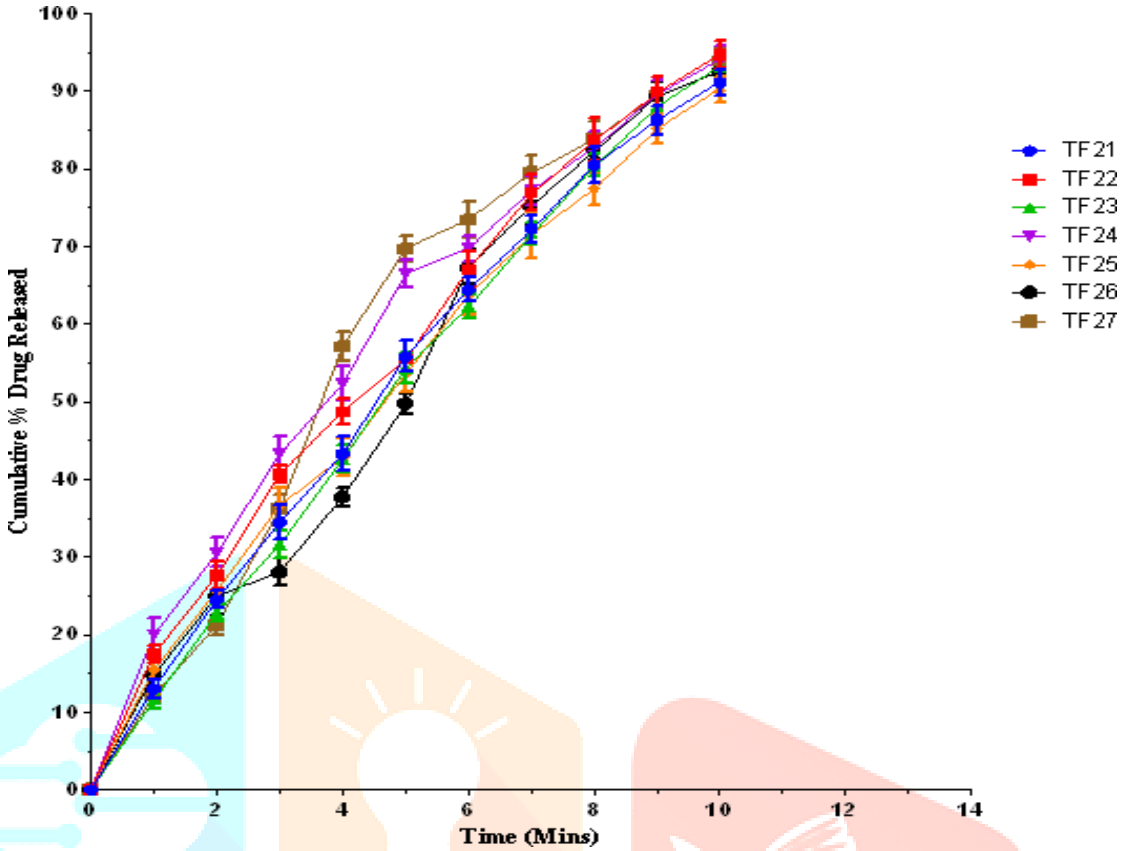

Figure 13: *% CDR of* Meloxicam FDT TF21-TF27

DESIGN OF EXPERIMENT

This method is mainly used to explain the effect of one factor on other factor and its influence on the response. The study explains the effect of L-HPC on gellan gum andfenugreek seed mucilage..

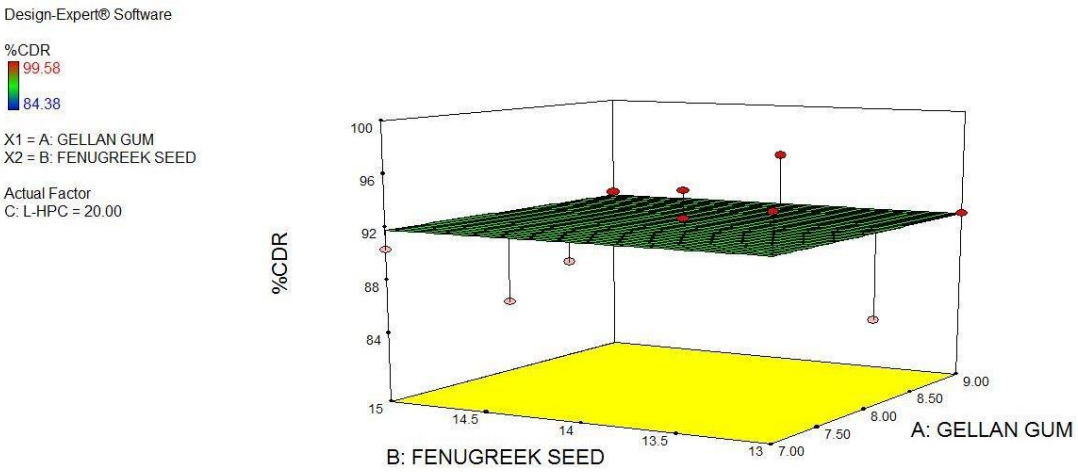

Figure 14: Response surface plot showing the influence of amount of Superdisintegrants on the release profile of Meloxicam for % CDR

The graph demonstrates effect of L-HPC on % CDR demonstrating significant effect of L-HPC on % CDR. The drug release indicated that as concentration of superdisintegrants increase, the % CDR also increases to specific level beyond which it starts decreasing . But forecast of % CDR results show the common effect of superdisintegrants concentration (figure 6.19).

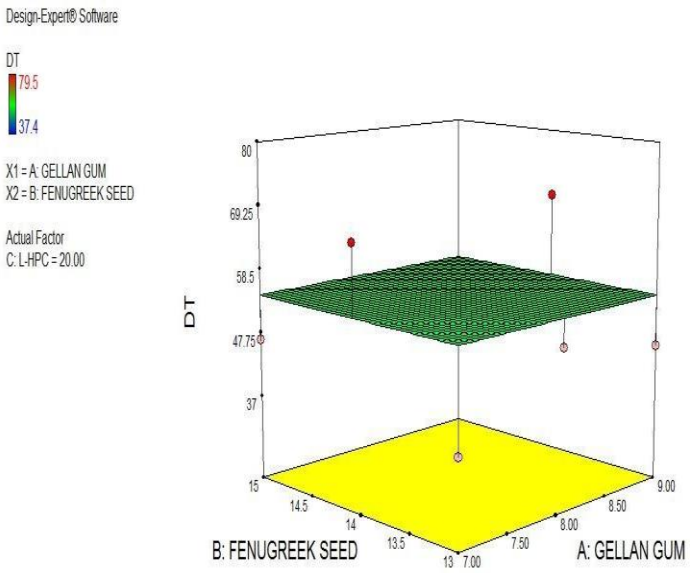

Figure 15: Response surface plot showing the influence of amount ofsuperdisintegrants on Disintegration Time of Meloxicam

Figure 6.20 indicates the effect of L-HPC on DT which indicates a very significant effect of L-HPC on DT. The graph indicates that as as concentration of superdisintegrants increase, the DT decreases.

Response 1 %CDR

ANOVA for Response Surface Mean Model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	0.000	0				
Residual	458.63	27	16.99			
Lack of Fit	*456.24*	*26*	*17.55*	*7.32*	*0.2854*	*significant*
Pure Error	*2.40*	*1*	*2.40*			
Cor Total	458.63	27				

Figure 16: ANOVA for Response Surface Mean Model of release profile ofMeloxicam for % Cumulative Drug Release.

Response 2 DT

ANOVA for Response Surface Mean Model

Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-value Prob > F	
Model	0.000	0				
Residual	3365.77	27	124.66			
Lack of Fit	*3364.49*	*26*	*129.40*	*101.10*	*0.0785*	*significant*
Pure Error	*1.28*	*1*	*1.28*			
Cor Total	3365.77	27				

Figure 17: ANOVA for Response Surface Mean Model of release profile ofMeloxicam for Disintegration Time.

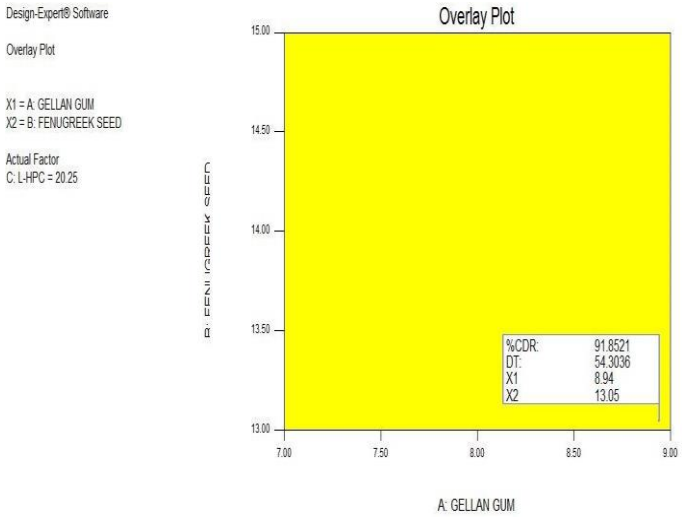

Figure 18: Overlay Plot of Meloxicam

STABILITY STUDIES: The stability studies carried out for optimized Meloxicam FDT formulation for 6 months according to ICH guidelines. The results indicate that the formulation is stable and withheld the properties like hardness, disintegration test and *in vitro* dissolution studies with minor differences. (table 6.13)

Table 16: Stability studies of optimized formulation (TF13)

Retest Time For Optimized formulation (F24)	**Hardness (Kg/Cm^2)**	**Disintegration test (Sec)**	***In-vitro* drug release profile (%)**
0 days	3.3±0.45	42±1.55	99.68±1.22
30 days	3.2±0.25	42±0.39	99.68±1.13
60 days	3.2±0.17	42±0.24	99.50±1.25
120 days	3.2±0.29	42±0.19	99.48±1.37
180 days	3.2±0.15	42±0.12	99.48±1.22

*Values are expressed in mean± SD :(n=6)

PHARMACOKINETIC STUDIES: The HPLC analysis of Meloxicam and internal standard in rabbit plasma is carried out as per the procedure followed in 5.11.3.The retention times of Meloxicam and Maloxicam (Internal standard) are 3.53 and 2.61 minutes, respectively.(figure 6.24 and 6.25)

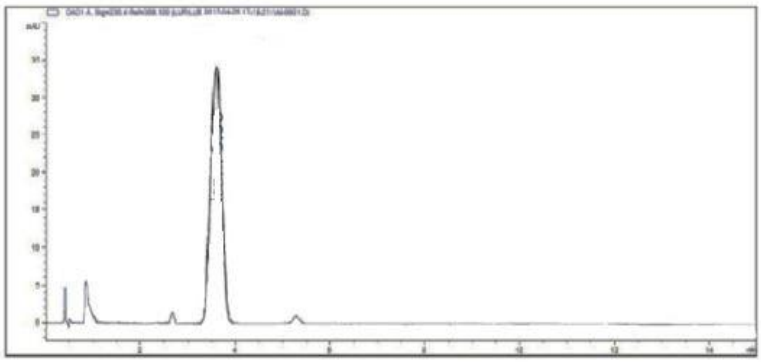

Figure 19: Standard chromatogram of Meloxicam in rabbit plasma by HPLC

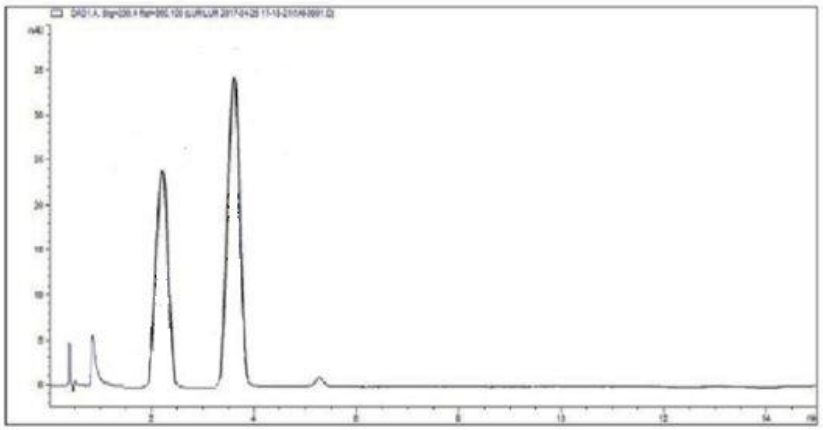

Figure 20: chromatogram of optimized formulation Meloxicam with internalstandard in rabbit plasma by HPLC

Table 17: Standard calibration curve of Meloxicam

S. No	Concentration(ng)	Area
1	0	0
2	1	4643.85
3	2	9687.7
4	3	13831.6
5	4	18465.4
6	5	23219.3
7	6	27893.3

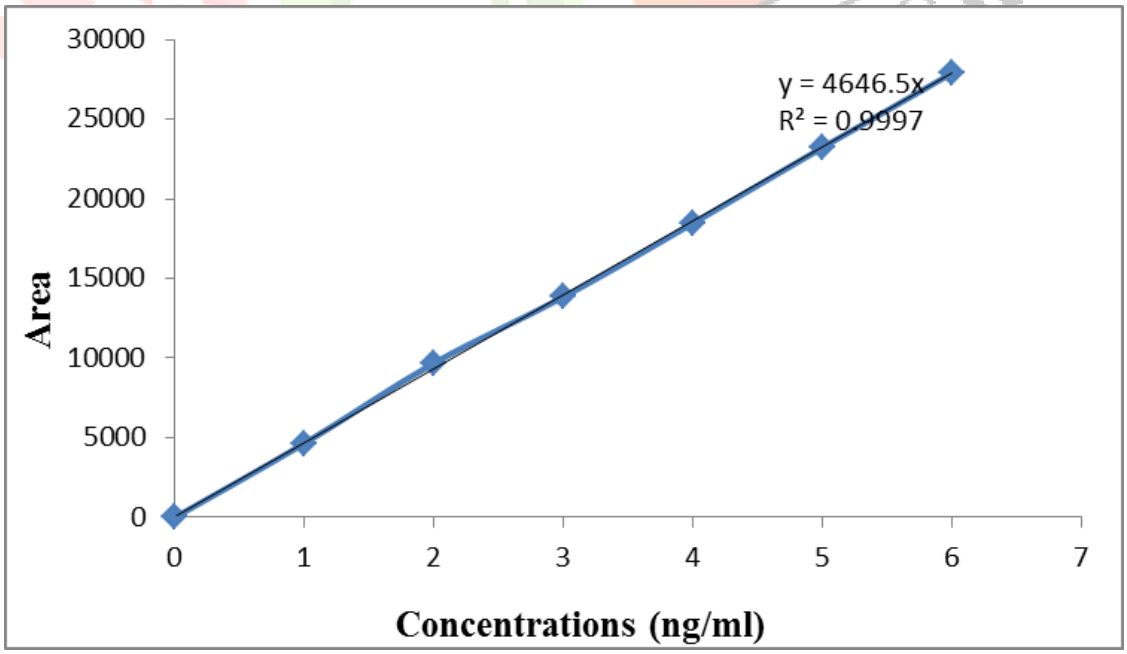

Figure 21: Standard calibration curve of Meloxicam in rabbit plasma

Bioavailability Parameters

Mean plasma concentration profiles of prepared Meloxicam optimized formulation and Meloxicam marketed product are presented in figure 6.26. Meloxicam optimized formulation exhibited immediate release *in vivo* when compared with marketed product. All the pharmacokinetics parameters displayed in table 6.16. The T_{max} of the optimized formulation was (1.50±0.04h) and Meloxicam marketed product T_{max} was (4.00±0.01h). This show the immediate absorption of optimized formulation compared with marketed product. On the other hand, the C_{max} of test formulation (4.21±0.03ng/ml) was significantly higher compared with marketed product (3.00±0.01ng/ml). However, the $AUC_{0-\infty}$ values for the two formulations were significantly different test formulation (35.12±7.12ng h/ml) and marketed product (25.18±6.82ng h/ml). This suggests that the Meloxicam contained in the test product was using completely absorbed showing more bioavailability when compared with marketed product.

CONCLUSION

Meloxicam, is used for treatment of osteoarthritis and control acute pain. The drug inhibits enzyme cycooxygenase which lead to prostaglandin synthesis inhibition .Total 27 Meloxicam FDTs were formulated with gellan gum, fenugreek seed mucilage and L-HPC with varying concentrations and optimized using the design of experiment tool.

All the twenty-seven FDTs evaluated for pre and post compression parameters.The formulation TF13 showed highest drug release of 99.68±1.22 % at 10 mins. On the basis of different evaluation parameters and *in vitro* dissolution studies TF13 was found to be optimized formulation which contains different concentrations of gellan gum, fenugreek seed mucilage and L-HPC. FTIR analysis revealed that there was no interaction between the drug and superdisintegrants. From DSC studies it was concluded that there is no considerable change observed in melting endotherm of the drug in the optimized formulation. It also indicates that there is no interaction between drug & excipients used in the formulation. Results of SEM indicated that the particles are crystal and morphology with a rough surface.

In vitro drug release of optimized fast disintegrating tablets (TF13) was much higher than that of Meloxicam marketed formulation. Hence it was concluded that fastdisintegrating tablets can be efficiently formulated.

It favours rapid onset of action of dosage units to be consumed by the patients thereby improves patient compliance. It may be concluded that fast disintegrating tablets using natural superdisintegrants like Gellan Gum, Fenugreek Seed Mucilage and L-HPC were suitable candidature for fast disintegrating tablets for Meloxicam based on information reported here in. Hence the same composition of superdisintegrants might be used for the bulk development after the clinical trials.

REFERENCES

1. Alladi Saritha, Nalini Shastri and Alladi Saritha. Preparation, Physico Chemical Characterization of Solid Dispersions of Meloxicam with Poloxamer. Journal of Pharmaceutical Science and Technology 2010;2(9):308-311.2.
2. Anroop N and Rachana G. In Vitro Controlled Release of a Alfuzosin Hydrochloride using HPMC-Base Matrix Tablets and Its Comparism with Marketed Product. Pharmaceutical Developments Technology 2007; 12: 621-625.3.
3. Armando Y, Schramm S, Silva M, Kano E, Porta V and Serra C. Bioequivalence assay between orally disintegrating and conventional tablet formulations in healthy volunteers. IntJ Pharm 2009;366:149-153.
4. Arun Prasad K, Narayanan N, Rajalakshmi G..Preparation and evaluation of solid dispersion of terbinafine hydrochloride. International Journal of Pharmaceutical Sciences Review and Research 2010;3(1).

5. Arya A, Chandra A, Sharma V and Pathak K. Fast Dissolving Oral tablets: An Innovative Drug Delivery System and Dosage Form. Int J Chem Tech Res 2014;2(1):576-583.
6. Ashish Masih, Amar Kumar, Shivam Singh and Ajay Kumar Tiwari. Fast Dissolving Tablets: A Review. Int J Curr Pharm Res 9(2):8-18.
7. Bahman Homayun, Xueting Lin, and Hyo-Jick Choi. Challenges and Recent Progress in Oral Drug Delivery Systems for Biopharmaceuticals Pharmaceutics 2019;11(3):129.
8. Battu SK, Repka MA, Majumdar Sand Rao YM. Formulation and Evaluation of Rapidly Disintegrating Fenoverine Tablets: Effect of Superdisintegrants. Drug Development and Industrial Pharmacy2007;33(11):1225–1232.
9. Bhowmik D, Chiranjib B, Krishna kanth Pankaj and Chandira RM. Fast dissolving tablet: an overview. J Chem Pharm Res 2009;1:163-77.
10. Bhupathi SK, Jithendra R, Bandaru S and Bhupathi VV. Design and evaluation of fast dissolving tablet of terbutaline sulphate. Research Journal of Pharmaceutical, Biological and Chemical Sciences. 2012;3:138-154.
11. Bolla Nagamani, Chandra Sarat, Rao GSN Koteswara and Devi P Uma. Improvement of simvastatin solubility using natural polymers by solid dispersion technique. International journal of pharmaceutical research and biomedical analysis 2013;2(2):01-06.
12. Brahmankar DM, Sunil B and Jaiswal. Bioavailability and Bioequivalence, Biopharmaceutics and pharmacokinetics A treatise, II edtn, Vallabh prakashan 2009;349-357.
13. Breitenbach J. Melt extrusion from process to drug delivery technology. Eur J Pharm Biopharm 2002; 54:107–117.
14. Chandrasekhar R, Hassan Z, AlHusban F, Smith A and Mohammed A. The role of formulation excipients in the development of lyophilized fast-disintegrating tablets. Eur J Pharm Biopharm 2009;72:119-29.
15. Chang RK, Guo X, Burnside BA and Couch RA. Fast dissolving tablets. Pharma Tech 2010; 24(6):52-58.
16. Chaturvedi Ashwani and Verma Amita. Solubility enhancement of poorly water soluble drugs by solid dispersion. Journal of Pharmaceutical Sciences and Research 2012;3:26-34.
17. Chaulang Ganesh, Patel Piyush, Hardikar Sharwaree, Kelkar Mukul, Bhosale Ashok and Bhise Sagar. Formulation and Evaluation of Solid Dispersions of Furosemide in Sodium Starch Glycolate. Tropical Journal of Pharmaceutical Research 2009;8(1): 43-51.
18. Chinnala KM, and Vodithala S. “Formulation Development And Evaluation Of Fast Disintegrating Tablets Of Cinitapride Hydrogen Tartarate By Using Direct Compression Technique”. International Journal Of Current Pharmaceutical Research2017;9(6):98-103.
19. Corniello C. Quick dissolving strips: from concept to commercialization. Drug Del Technol 2016;6(2):68–71.
20. Daniel Mark and Axel Zeitler J.A Review of Disintegration Mechanisms and Measurement Techniques. Pharm Res 2017;34(5):890–917.

21. Darwish MK and Foad MM. Enhancement of the dissolution profile of Meloxicam by a solid dispersion technique and its analytical evaluation using HPLC. Drug DiscovTher 2009;3(1):27-36.

22. Dharshini Swapna B, Ashok N. Formulation and Evaluation of Immediate Release Tablets of Nebivolol Hydrochloride. World J Pharm Pharm Sci. 2015;4(1):687–698.

23. Dhirendra K, Lewis S and Udupa N. Solid Dispersions: A Review. Pak J Pharm Sci 2009; 22(2):234-246.

24. Dhirendra K, Lewis S, Udupa N andAtin K. Solid dispersions: a review. Pak J Pharm Sci 2009;22(2):234-246.

25. Dixit RP and Puthli SP. Oral tablet technology. J Controlled Release 2009;139(2):94-107.

26. Dwija Trivedi, Veera Venkata Satyanarayana Reddy Karri, Asha Spandana KM and Gowthamarajan Kuppusamy. Design of Experiments: Optimization and Applications in Pharmaceutical Nanotechnology. ChemSci Rev Lett2015; 4(13):109-120.

27. Florence E Eichie and Roland S Okor. Parameters to be Considered in the Simulation of Drug Release from Aspirin Crystals and their Microcapsules Tropical. Journal of Pharmaceutical Research 2002;1(2):99-110.

28. Fu Y, Yang S, Jeong SH, Kimura S and Park K. Orally fast disintegrating tablets: Developments, technologies, taste-masking and clinical studies Crit Rev Ther Drug Carrier Syst 2004;21:433-76.

29. George Traian Alexand Burcea Dragomiroiu, Adina Cimpoieşu, OctavGinghină, Corneliu Baloescu, Maria Bârcă, Daniela Elena Popa, Annemarie Ciobanu and Valentina Anuţa. The Development And Validation Of A Rapid HPLC Method For Determination Of Piroxicam. FARMACIA 2015;63(1):123-131.

30. Hadi MA, Rao Nand Rao A. Formulation and evaluation of compression Coated tablets of Lornoxicam for Targeting early morning peak symptoms of Rheumatoid arthritis. Dhaka University Journal of PharmaceuticalSciences 2014;12(2):109-117.

31. Hariharan M and Bogue A. Orally dissolving film strips (ODFS): the final evolution of orally dissolving dosage forms. Drug Del. Technol 2013;9(2):24–29.

32. Harshitha M S, Senthil Kumar K, Gulzar Ahmed M. Formulation and Evaluation of Fast Dissolving Tablets of Nebivolol Hydrochloride. IJAPBR.2016; 1(2):78- 86.

33. Higuchi T and Connors K. Phase-solubility techniques: Adv Anal Chem Instrum 1965;4:117-212.

34. Horat KR and Laware RB. Formulation and evaluation of Lornoxicam loaded Lyotropic liquid crystalline gel. JDDT 2019;9(6):116-25.

35. Ismat U. Moisture-activated dry granulation. Pharm Tech Eur 2011;23(3):1-3.

36. Janaki B and Sashidhar RB. Physico-chemical Analysis of Gum Kondagogu (Cochlo spermum gossypium): A Potential Food Additive. Food Chemistry 1998;61(1/2):231-236.

37. Jinichi F, Etsuo Y, Yasuo Yand Katsuhide T. Evaluation of rapidly disintegrating tablets containing glycine and carboxymethylcellulose. Inter J Pharm2006;310:101-109.

38. Kale SA and Dr. Bajaj VH. Role of statistics in quality by design product development for pharmaceutical industry: a review. Int J Pharm 2014;4(3):171-173.

39. Karia I, Parmar RB and Thakkar SJ. Formulation And Evaluation Of Fast Dissolving Tablets Of Olmesartan Medoxomil By Using Co- Processed ExcipientsTechique 2015.

40. Kaur T, Gill B, Kumar S, Gupta GD. Mouth dissolving tablets: a novel approach to drug delivery. Int J Curr Pharm Res 2011;1:1-7.

41. Keshari R, Bharkatiya M, Rathore KS, Shyama S, Kumar, Sirvi G and somani N. Fast disolving tablet drug delivery system-an overview. Int J Pharm 2015;5:577- 89.

42. Khaja nayub Rasool, Satheesh kumar E, Shubhrajit Mantry, Anil Kumar S. Formulation and Evaluation of Fast dissolving oral films containing Losartan potassium. IJIPSR 2014;2(3):688-702.

43. Khan AB, Tripuraneni A. Fast dissolving tablets–a novel approach in drug delivery. Rguhs J Pharm Sci 2014;1:7-16.

44. Kulkarni AS, Deokule HA, Mane MS and Ghadge DM. Exploration of different polymers for use in the formulation of oral fast dissolving tablets. J CurrentPharm Res 2010;2(1):33-35.

45. Kumari Beenaand Bishnoi Harish. Review Article Solid Dispersion: Its Types And Mechanism Of Enhancement Of Solubility By Solid Dispersion2019;65-71.

46. Lakshmi K, Pranavkumarreddy M and Rajesh kaza. Dissolution enhancement of telmisartan by surface solid dispersion technology. International Journal of Innovative Pharmaceutical Research 2012; 3(4): 247-251.

47. Lala II MK , Prajapati BG, Patel VM, Shah DA and Modasiya MK. Design and Characterization of Fast Disintegrating Tablets of Piroxicam Modasiya.Int J PharmTech Res 2009;1(2).

48. Leuner C and Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm 2000;50(1):47-60.

49. Levy G. Effect of Particle Size on Dissolution and Gastrointestinal Absorption Rates of Pharmaceuticals. American Journal of Pharmacy and Sciences 1963;135:78–92.

50. Liang CA and Chen HL. Fast dissolving intraoral drug delivery systems. Expert Opin. Ther. Patents 2011;11:981-986.

51. Lipinsky C. Poor aqueous solubility: an industry wide problem in drug discovery. Am Pharm Rev 2002;5:82–85.

52. Mai G El-Hennawy, Sally A Abdel Halim, Alia Badawy and Mohammed A Effat. Preparation, Characterization and Evaluation of Meloxicam Gels and Microemulsion Gels for Topical Drug Delivery. Inventi Impact: Pharm Tech 2013;4.

53. MandalDipika, Ojha Kumar Probir, Nandy Chandra Bankim and Ghosh Kanta Lakshmi. Effect of Carriers on Solid Dispersions of Simvastatin (Sim): Physico- Chemical Characterizations and Dissolution Studies. Scholars Research Library; Der Pharmacia Lettre 2010;2(4): 47-56.

54. Mangesh Machhindranath Satpute and Nagesh Shivaji Tour. Formulation and in vitro evaluation of fast dissolving tablets of metoprolol tartrate. Brazilian Journal of Pharmaceutical Sciences 2013;49:4.

55. Methker Vishal, Kumar Anuj, Pathak Naveen, Papdee Kumud and Sahoo Sangram "Formulation and Evaluation of Orodispersible tablets of Lornoxicam". Int. J. Drug Dev. & Res 2011;3(1):281-285.

56. Metkar Vishal, Kumar Anuj, Pal Deepti, Shurngarpure Mansee, Pant Pankaj and Madhusudan Dutta. "Formulation development and evaluation of Bilayer tablets of Lornoxicam". IntJ Drug Dev. & Res 2012;4(2):173-179.

57. Misal NV and Chemate SZ: Formulation and evaluation of Lornoxicam mouth dissolving tablet by using natural superdisintegrants. Int J Pharm Sci& Res 2019;10(4):1848-55.

58. Mishra R and Amin A. Quick API Delivery. Pharm Tech Eur 2013;19(10):35-39.

59. Mishra US, Prajapati SK, Bhardwaj P. A review on formulation and evaluation for mouth dissolving tablet. World J Pharm Pharm Sci 2014;8:1778-810.

60. Mishra US, Prajapati SK, Bhardwaj P. A review on formulation and evaluation for mouth dissolving tablet. World J Pharm Pharm Sci 2014;8:1778-810.

61. Montgomery and Douglas C. Design and Analysis of Experiments: Response surface method and designs, John Wiley and Sons, Inc. New Jersey 2015;210- 256.

62. Nautiyal U, Singh S, Singh R, Gopal and Kakar S. Fast dissolving tablets as a novel boon: a review. J Pharm Chem Biol Sci 2014;2:5-26.

63. Negus SS and Banks ML. Pharmacokinetic-Pharmacodynamic (PKPD) Analysis with Drug Discrimination. Curr Top Behav Neurosci 2018;39:245-259.

64. NerurkarJayanti, Jun HW, Price JC and Park MO. Controlled-release matrix tablets of ibuprofen using cellulose ethers and carrageenan. Effect of formulation factors on dissolution rates. European journal of pharmaceutics and bio pharmaceutics. Official JAPV 2005;61:56-68.

65. Odd G Nilsen. Clinical Pharmacokinetics of Meloxicam. Clinical Pharmacokinetics1994;26:16-43.

66. Pagar R, Ahirrao S, Yallatikar T and Wagh M. Review on dispersible tablets. Int J Res Dev Pharm L Sci 2014;3:949-58.

67. Patel Anuradha, Prajapati Parixit, Boghra Rikisha and Shah Dipti. Solubility enhancement of poorly aqueous soluble Furosemide using peg-4000 by solid dispersion. Asian Journal of Pharmaceutical Sciences and Clinical Research (AJPSCR) 2011;2(1):1-9.

68. Patel KH, Pillai RS, Patel KH and Pillai RS. Solid Dispersion Compositions. U.S. Patent 2008;7:423.

69. Patel TS, Sengupta M. Fast dissolving tablet technology. World J Pharm Sci 2013;2:485-508.

70. PDB and RRNG. "Formulation And Evaluation Of Valsartan Fast Disintegrating Tablets By Vacuum Drying Technique". Asian Journal of Pharmaceutical and Clinical Research2016;9(2):73-79.

71. Pratik Swarup das. Fast dissolving tablet using solid dispersion technique: a review. Int J Curr Pharm Res2017;9(6):1-4.

72. Pujari, Vijayanand & Patil, Jagadevappa , Reddy, M.Formulation characterization and in-vitro/in-vivo evaluation of dispersible tablets of Nebivolol HCl. Der Pharmacia Sinica 2015; 6:103-114.

73. Rama swamy Ravi kumar, Mani ganesh, Ranganathanhariprasaad and Hyun Tae Jang.Preparation of immediate release tablets of Repaglinide by a solubility enhancer and hot-melt extrusion method. Int J Res Ayurveda Pharma 2016;7(5).

74. Ramesh KVRNS, ShahnazUsman, Omar Sarheed, Fasiha Shah, Tahera Parveen, Venkata Kameswara Rao B and Vinay Kumar M. Formulation and evaluation of fast dissolving tablets of meloxicam. Indo American Journal of Pharmaceutical Research 2014;4(10).

75. Reddy LH and Ghosh BR. Fast dissolving drug delivery systems: A review of literature. Indian J Pharm Sci 2012;64(4):331-336.

76. Sethia S and Squillante E. Solid dispersions: revival with greater possibilities and applications in oral drug delivery. Critical Reviews of Therapeutic Drug Carrier System 2003;20(2-3):215-247.

77. Shah JC, Chen JR and Chow D. Preformulation study of etoposide. Increased solubility and dissolution rate by solid dispersions. International Journal of Pharmaceutics 1995;113:103-111.

78. Shashidhar Reddy Dodda and Prakash Rao Boggrapu. Development and in Vitro- in Vivo Evaluation of Controlled Release Matrix Tablets of Desvenlafaxine,Pharmacology & Pharmacy 2012;3:15-19.

79. Shimizu T, Sugaya M, Nakano Y, Izutsu D, Mizukami Y, Okochi K and Igari Y. Formulation Study for Lansoprazole Fast-disintegrating Tablet. III. Design of Rapidly Disintegrating Tablets. Chemical & PharmaceuticalBulletin2003;51(10):1121–1127.

80. Siddiqui M, Garg Garima and Sharma Pramod. A Short Review on A Novel Approach in Oral Fast Dissolving Drug Delivery System and Their Patents.Adv Biol Res.2010;5.

81. Siddiqui N, Garg G, Sharma PK. Fast dissolving tablets: preparation, characterization and evaluation: an overview. Int J Pharm Sci Rev Res 2010;2:87-96.

82. Sohi H, Sultana Y and Khar RK. Taste masking technologies in oral pharmaceuticals: Recent developments and approaches. Drug DevInd Pharm 2004;30:429-48.

83. Sohi. HY and Sultana RK Khar. Taste masking technologies in oral pharmaceuticals: recent developments and approaches. Drug Dev Ind Pharm 2014;30:429–448.

84. Sonam Ranga, Manish Jaimini, Sanjay Kumar Sharma, Bhupendra Singh Chauhan and Amit Kumar.A Review on Design of Experiments (DOE). IJPCS 2014;3(1):216-224.

85. Tiwari R, Gaurav T, Birendra S and Rai A. Solid Dispersions an Overview on Solubility Enhancement of Poorly Water Soluble Drugs. International Journal of Pharma Tech Research 2014;5(3): P7–P25.

86. Todd PA and Clissold SP. Meloxicam: an update of its pharmacology and therapeutic efficacy in rheumatic diseases. Drugs 1991;41:625–646.

87. Uppala L and Pranusha P. Development and Evaluation of Fast Disintegrating Tablets of Ondansetron with Natural and Synthetic Super Disintegrating Agents. SOJ Pharm PharmSci 2015;2(3):1-7.

88. Varalakshmi TSNS, Siva Ramesh Ch, Jyothi I, JyothiY, Bharathi G and Chinni Babu P. Formulation and evaluation of solid dispersions of valsartan for dissolution rate enhancement. Journal of Pharmacy Research 2015;9 (2):139- 144.

89. Verma Navneet, Chhatrapati Shahuji and Maharaj. (2014). A review on patent related technologies of orally disintegrating tablets.