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A VITAL OF FAST DISINTEGRATING IN THE THERAPY OF NSAIDs

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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)

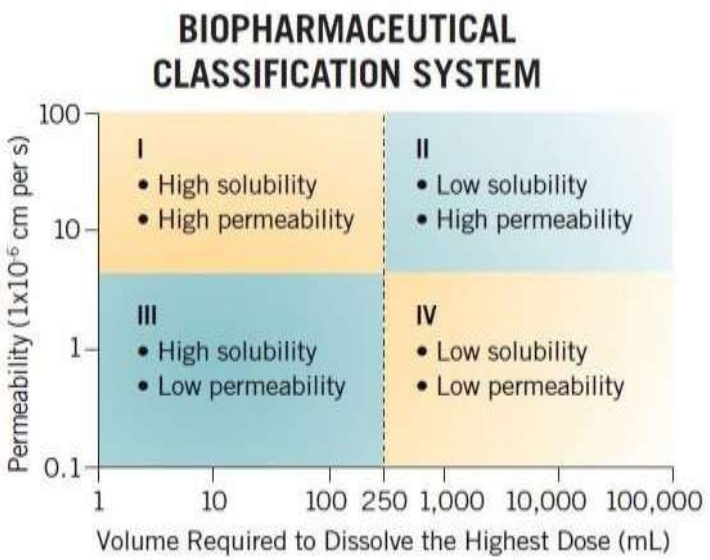

Figure 1: BCS Classification system

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 freezing into liquid and Lyophillization
3	Co-solvency	Complexation	Evaporative precipitation into aqueous solution
4	Hydrotropic	Solubilization b ysurfactants	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)

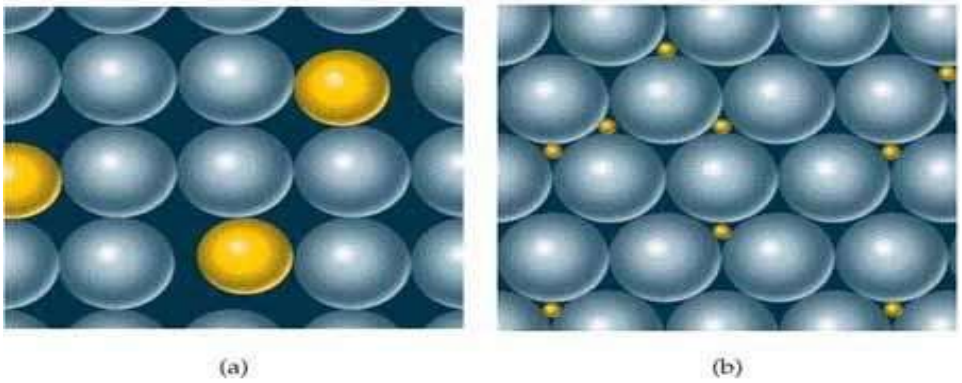

Figure 2: Substitutional Crystalline Solutions and Interstitial Crystalline Solid Solutions

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)

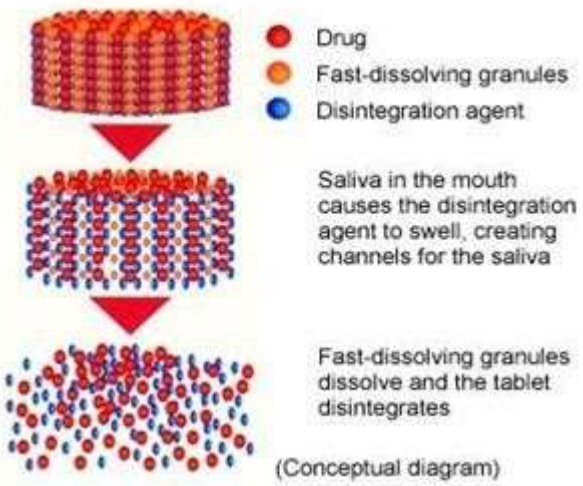

Figure 3: Conceptual diagram of FDTs

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±0.5^{o}C, 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 5° - 60°.(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	Gellangum	Fenugreek Seed Mucilage	Aspartae	Mannitol	MCC	Magnesium stearate	Talc	Aerosil	TOTAL
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

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

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)

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

$$\text{Hausner's ratio} = {}^*dt/{}^*db$$

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

POST COMPRESSION EVALUATIONS

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.

***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)

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