RESEARCH ARTICLE

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Lornoxicam Immediate Release Tablet Using Spray-Dried Cellulose Nanofibers (NFC) as Novel Tablet Excipient

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Abstract: The choice of proper excipients is one of the key factors for successful formulation of pharmaceutical dosage forms. Increasing number of new therapeutic compounds suffers from poor solubility and/or bioavailability, creating a challenge from the drug formulation point of view. Problems have also been encountered in attempts to formulate biological drugs such as peptides and proteins, considering their sensitivity towards certain production processes and routes of administration. In both cases the choice of the right excipient(s) is essential to provide particular processability and development of systems with desirable drug delivery kinetics. The aim of this work was to evaluate pharmaceutical applications of nanofibrillar cellulose (NFC), a renewable, biodegradable and widely available plant based material, as a potential excipient in the production of pharmaceutical dosage forms. Initially, tablets with immediate drug release were manufactured by methods of direct compression using spray dried NFC as a filler material. Addition of NFC improved the flow properties of commercially available and widely used microcrystalline cellulose. The main focus of the thesis was to evaluate NFC material for immediate drug release purposes. This goal was successfully achieved by setting up a spray drying method for the production of drug loaded NFC solid dispersion. System was able to fast the drug release over short periods of time. The purpose of this study was to further clarify and fully understand the mechanisms behind the successful performance of NFC as immediate drug release material. Binding of drugs to NFC due to the electrostatic interactions was observed. This kind of knowledge is beneficial when choosing the proper drug/excipient combination for the formulation process. In conclusion, NFC was shown to be a versatile excipient for the production of pharmaceutical dosage forms, while the comprehensive evaluation of the full potential of NFC in pharmaceutical applications warrants further experiments in the future.

INTRODUCTION

Pharmaceutical excipients have vital roles in drug formulations and dosage forms. Recent trends in drug discovery are leading towards new chemical entities with high molecular weight and increased lipophilicity. Thus, an increasing number of drug candidates suffers from low aqueous solubility and, therefore, requires specialized formulations in order to fulfill their potential. [1-2]

On the other hand biological drugs, such as peptides, proteins and monoclonal antibodies, often possess poor membrane permeability, enzymatic instability, large molecular size and hydrophilic properties, which represent significant challenges for the choice of right excipients for successful formulations. [3-4]

Besides facing the challenges seen in new drug candidates, pharmaceutical industry strives to improve manufacturing processes, reduce costs and improve the performance of existing products by employing proper excipients. [5]

In the area of production of immediate release tablets, direct compression is preferred manufacturing process, in order to improve the manufacturing costs and productivity. Direct compression requires excipients with certain physical characteristics in terms of flowability and compressibility. Thus, the ideal excipient would provide excellent compactibility at low pressures, have a high dilution potential, improve the flowability of powder blend and at the same time have low price. All mentioned challenges explain the constant demand in pharmaceutical industry for development of novel excipients. [6-9]

Cellulosic materials have been thoroughly investigated and reviewed over recent decades as regards their surface modifications and applications. Arising from wood and more especially from cellulose, there has been a growing interest for several years for bio-nanoparticles produced from cellulosic sources. The structure of native cellulosic fibers results in two families of nanocellulose materials. Since the cellulose microfibrils consist of both amorphous and crystalline regions, treatment of them in strongly acidic conditions leads to an extensive hydrolysis of the amorphous fractions and formation of short rod-like cellulose nanowhiskers with high crystallinity and low aspect ratio. Several terms are used in the literature to denote the whiskers, nanowhiskers, nanorods and rod-like cellulose crystals. When the macroscopic cellulose fibers are mechanically disintegrated avoiding the strongly acidic conditions, long nanoscale partly amorphous fibrils are produced. In the literature terms such as cellulose nanofibers, cellulose nanofibrils, microfibrillated cellulose, nanocellulose fibers/fibrils or nanofibrillated cellulose have been used to describe these fibers. [10-12]

As explained above, cellulose possesses high level of organization within plant based materials, where nanoscale fibers are grouped and bound by hydrogen bonding to form macroscopic structures. To isolate NFC from wood, one has to break down its highly organized hierarchical structure. Production processes of NFC include steps, which purpose is to remove the accompanying materials (e.g. lignin). However, the final material contains certain amounts of hemicellulose residues and their contents can vary highly depending on the material origin and production method. The presence of hemicelluloses, which carry carboxylic groups, causes a slight negative charge for the NFC. The negative charge causes repulsion between fibers preventing in this way their aggregation in wet state. Thus, the presence of hemicellulose promotes dispersion of otherwise non-dispersible NFC fibers in an aqueous medium. [12]

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This work focused on evaluation of NFC as a novel versatile excipient for the formulation of pharmaceutical dosage forms. Our aim was to investigate applicability of NFC in formulation of immediate release dosage forms, the specific objectives of this study were study the applicability of NFC as a novel excipient for the production of tablets with immediate drug release properties; in direct compression; physical and chemical interactions between the NFC fibers and lornoxicam; improve the dissolution of lornoxicam by formulation of LC-NFC solid dispersion using spray drying technique; formulatiom and evaluation of LC-NFC fast dissolving tablet of prepared spray dried solid dispersion.

MATERIALS AND METHODS

The materials including Lornoxicam, Kollidon VA64, Neusilin US2, Avicel PH 101, Avicel PH 102, Ac-di-sol was received as a gift sample from Shreya Pharmaceuticals. Aurangabad. Citric Mannitol, Mg. Stearate, Mango flavor, Methanol (HPLC grade), Distilled water (HPLC grade); DMSO, Ethanol, Methanol and aspartame were obtained from Unique Biologicals, Kolhapur. The reagents 0.1 N Sodium Hydroxide, Phosphate buffer were used of analytical grade.

Nanofibrillar Cellulose

The nanofibrillar cellulose was produced and kindly donated by UPM-Kymmene Corporation, Finland. Bleached birch pulp was used as the NFC source. Purified pulp fibers were diluted with sterilized, ultra high quality water before the fibrillation. Fibers isolation was conducted via controlled homogenization process using an industrial fluidizer. The applied process resulted in the production of nanofibrillar cellulose hydrogel with the fiber content typically 1.7 wt%. The product also contains some soluble hemicelluloses, i.e. 23 wt% of xylan, due to the birch based raw material.[106] Method of production of NCF includes to disintegrate cellulose fibers to the level of nanofibers. These methods include mechanical force using super grinder treatment or high-pressure refiner, microfluidizer and high-pressure homogenizer treatment. All these methods lead to a production of gel-like water suspension with high water content, which can be further processed into powder by spray drying. [10-12]

The aim of this study was to evaluate the usability of spray-dried NCF as novel tabletting material for immediate release formulations. For the purpose, NCF material was compared to two commercially available grades of MCC: Avicel PH 101 and Avicel PH 102. MCC was chosen for comparison due to its similarity to CNF in chemical structure. Determination of powders main physical characteristics was done as well as examination of their precompression behavior. [13-14]

Solid Dispersions of Lornoxicam

1. Preparation of Suspension for Spray Drying

All the suspensions were prepared in the same manner. Physical mixtures of lornoxicam with NFC, Avicel PH 101 and Avicel PH 102 were prepared separately by thoroughly mixing the components in a mortar for 15 min until a homogeneous mixture was obtained. First, the Lornoxicam was dissolved in a [Methanol: NaOH] (10:1) solvent system. [15-17] The solution was then mixed with NFC suspension so that the total concentration of the both, dissolved and suspended material, was 0.5%. The ratios, in which the NFC and drug were mixed, were 1:1, 1:2 and 1:3. Since the used NFC was in a form of 1.66% water dispersion. The prepared suspensions were sonicated for 15 min using a high intensity ultrasound processor (QE-194; Quality Instruments and Equipments, Kudal) equipped with a 13 mm probe and then mixed with a mechanical stirrer for 15 min at a speed of 1800 rpm. [18-19]

2. Spray Drying

The suspensions were dried using a (LSD-48; JISL Pvt. Ltd., Mumbai) spray dryer. The spray dryer was equipped with a fluid nozzle and operated in a co-current mode (the feeding suspension and the drying air flow in the same direction). The drying was performed using the following parameters: inlet temperature 220°C, outlet temperature in a range from 120–127°C, spray flow 700 l/h, air pressure 7 bar, aspirator setting 95% and pump setting 18%. The feeding suspension was mixed continuously during the drying process using a magnetic stirrer to prevent sedimentation of the suspended cellulose fibers. The spray dried powder were collected from the dryers' collection vessel and stored in closed vials at room temperature. Aiming to improve the dissolution behavior of lornoxicam in gastric conditions, solid dispersions of lornoxicam with Avicel PH 101 and Avicel PH 102 were prepared at three molar ratios, namely1:1, 1:2 and 1:3(drug: polymer), using spray drying technique. [20-21]

Tabletting

Spray dried NFC powder was compared to two commercially available grades of microcrystalline cellulose (MCC); Avicel PH 101 and Avicel PH 102 for the comparisons due to its similarity to NFC in chemical structure and these are the two most commonly used grades of MCC. Determination of the powders' main physical characteristics was done as well as examination of their compression behavior. Tablets were compressed from dry powder mixtures for direct compression studies, dry powder mixtures were prepared by mixing the ingredients with Lornoxicam SD using a teflonized metal jar in all purpose mixer (Shakti corp., Mumbai) at 90 rpm for 24 h (Table 1).

1. Mixture Homogeneity

The content of Lornoxicam was used to express the quality (i.e. heterogeneity) of the mixtures. Samples of each mixture weighing 130 mg were withdrawn with aid of sample thieves/Spatula. The amount of Lornoxicam in the samples was measured spectrophotometrically (Shimedazu corp. Japan) at a wavelength of 378 nm. [22]

2. Immediate Release Tablet

Before tablet preparation, the mixture blend of the formulations were subjected to compatibility studies (IR)

and Precompression parameters like Angle of repose, bulk density, tapped density, compressibility index and hausner's ratio. Lornoxicam-Kollidon VA64 (Avicel PH 101, Avicel PH 102 and NFC) spray dried solid dispersion was selected; Neusilin US2 (adsorbent) was mixed thoroughly with lornoxicam solid dispersion. Mannitol and Ac-Di-Sol were added as tablets diluent and superdisintegrants, respectively and mixed with above mixture in a glass mortar using pestle for 30 min (Table 1). Magnesium stearate was then added as lubricant to above mixture and mixed for another 30 min. The resultant powder blend was then compressed under constant pressure using multi-punch rotary tableting machine into 130 mg tablets, each containing a total of 10 mg Lornoxicam. [23-25]

Evaluation of Powder Blend

To develop an immediate release tablet with the simple and low cost direct compression method, it was necessary to find suitable excipient with good compactability and disintegrating ability. All the ingredients were passed through mesh no 60. Required quantity of each ingredient was taken for each specified formulation (Table 1) as per procedure mentioned. [26]

1. Angle of Repose

The angle of repose of powder blend was determined by the funnel method. The 10 gm of accurately weighed powder blends were taken in funnel. The height of the funnel was adjusted 2 cm above the tip of the funnel which just touches the heap of the powder blend. The powder blends were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

$$\theta = \tan^{-1}\ \frac{h}{r}$$

Where 'h' and 'r' are the height and radius of the cone.

2. Bulk Density

Bulk density Pb is defined as the mass of the powder divided by the bulk volume and is expressed as g/cm^3. Accurately weighed 10 gm of powder blend from each formulation was taken in a measuring cylinder and the initial volume of the powder blend in the measuring cylinder was noted. This was calculated by using the following formula:

$$Pb = \frac{M}{Vb}$$

Where, Pb - Bulk density, M - Weight of sample in g, Vb- Final volume of blend.

3. Tapped Density

It is the ratio of total mass of the powder to the tapped volume of powder. The volume was measured by tapping the powder blend for 100 times. Tapped density was calculated by using the following formula:

$$Pt = \frac{M}{Vt}$$

Where, Pt-Tapped density, M - Weight of the sample in g, Vt - Tapped volume of blend.

4. Compressibility Index and Hausners Ratio

The compressibility index of the powder blend was determined by Carr's compressibility index and the Hausners ratio is calculated by using the following formula:

$$\text{Hausner Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

$$\text{Carr}'\text{s Index} = \frac{\text{Tapped Density} - \text{Bulk Density}}{\text{Tapped Density}} \times 100$$

5. Porosity

It is defined as the ratio of void volume to the bulk volume of the packaging. The porosity of powder was determined by:

$$\text{Porosity } (\varepsilon) = \frac{\text{Bulk Volume} - \text{True Volume}}{\text{True Volume}}$$

The porosity was expressed in percentage (%)

$$\text{Percentage Porosity } (\varepsilon) = \frac{\text{Bulk Volume} - \text{True Volume}}{\text{True Volume}} \times 100$$

Mainly it indicates the types of packaging a powder undergoes when subjected to vibration.

6. Kawakita Plot

Kawakita equation was developed to study the powder compression using the degree of volume of reduction 'C'. Parameter equivalent to the engineering strain of the particle bed and is expressed 'ab'.

$$\frac{P}{C} = \frac{P}{a} + \frac{1}{ab}$$

Where, C= Degree of volume reduction; Vo= Initial volume of powder bed. Vp= Powder volume after compression. a and b=Constants obtained from slope and intercept of P/C Vs. P plot respectively;

Physical Characterization of Immediate Release Tablet

1. General Appearance

Mainly it includes the visual identity, elegance, consumer acceptance and the size and shape of the tablet. [26]

2. Thickness, Diameter and Volume

The thickness and diameter of the tablets were measured with a screw gauge micrometer that had a 0 to 25 mm scale and was capable of differentiating up to 0.01 mm. The tablet thickness is expressed as averages of 5 measurements made at 5 different points between the 2 surfaces of the compact. [26] The volume of the compact at a given pressure was calculated according to the equation:

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$$V = \pi r^2 h$$

Where V is the volume, r is the radius and h is the thickness of the compact.

3. Tablet Hardness

Hardness of the tablet of each formulation was determined using Pfizer hardness tester. Three tablets from each formulation batch were tested randomly and the average reading was noted. [26]

4. Weight Variation Test

Randomly selected 20 tablets were weighed individually and together in a single pan balance. As per IP this method is satisfactory to determine the drug content uniformity. The average weight was noted and standard deviation was calculated. [26]

$$\text{Percentage deviation} = \frac{\text{Average weight of tablet} - \text{Individual weight of tablet}}{\text{Average weight of tablet}} \times 100$$

Where, PD = Percentage deviation, W_{avg}= Average weight of tablet, $W_{initial}$= Individual weight of tablet.

5. Uniformity of Content

The test for uniformity of drug content is carried out by collecting a sample of 10 tablets from a batch and determining their individual amount of drugs in each tablet. The average drug content is calculated and the content of the individual tablets should fall within specified limits in terms of the percentage deviation from the mean. [26]

6. Friability

Roche friabiliator was used for the friability. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of 4 inches with each revolution. Pre-weighed 20 tablets were placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed. [26]

$$\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial Weight}} \times 100$$

7. Drug Content

Ten tablets from each formulation were weighed individually and powdered. The Powder equivalent to 10mg of Lornoxicam was weighed and dissolved in 10 ml of Methanol: NaOH and volume was adjusted to 100ml with pH 6.8 simulated salivary fluids. From this solution 1 ml was taken and made up to 100 ml using same dilution media, solution was filtered and analyzed at 378 nm by UV–visible spectrophotometer using simulated salivary fluid as the blank and % drug content were calculated. [27]

8. Disintegration Time

Nine hundred milliliters of water maintained at 37°C. DT was determined at the point at which the tablet disintegrated and passed through the screen of the sinker completely (opening of mesh of the sinker: 3–3.5 mm in height and 3.5–4 mm in width). The mean±standard deviation values of DT were calculated. [28]

9. *In-Vitro* Dispersion Time

In vitro dispersion time i.e. time required to breakdown the tablet into small particles and make dispersion was measured by dropping a tablet in a beaker containing 50 ml of simulated salivary fluid pH 6.8. [28]

10.Wetting Time and Water Absorption Ratio

Although a wetting test is not a standard test, it is useful for quality control and provides supportive evaluation of IR tablets. A piece of tissue paper folded twice was kept in a Petri dish containing 6 ml of purified water. A tablet having a small amount of amaranth powder on the upper surface was placed on the tissue paper. The time required to develop a red color on the upper surface of the tablet was recorded as the wetting time. The same procedure without amaranth was followed for determining the water absorption ratio. The wetted tablet was weighed and the water absorption ratio, R, was determined. [28]

$$R = \frac{Wa - Wb}{Wb} \times 100$$

Where, Wb and Wawere the weights of the tablet before and after study.

11.Measurement of Tablet Tensile Strength

A diametric compression test was performed according to European Pharmacopoeia (resistance to crushing of tablets) (n = 35). The tablet crushing load, which is the force required to break a flat-faced tablet into halves by compression in the radial direction, was measured using a tablet hardness tester. [26-28] Tensile strength for crushing (Ts) was calculated using the following equation:

$$Ts = \frac{2F}{\pi . dt}$$

Where, F is the crushing load and d and t denote the diameter and thickness of the tablet, respectively.

12.Measurement of Tablet Porosity

The tablet porosity was calculated from the dimensions and weight of the tablet and the apparent particle density of the mixture. The apparent density (ρapp) of the compact, were calculated from the ratio of the tablet mass to the volume of the compact.

$$(\rho app) \text{of compacts} = \frac{\text{Mass of tablet}}{\text{Volume of compact}} = \frac{gm}{\pi r2h}$$

The porosity of the compacts was calculated using the relationship

$$\text{Porosity } (\varepsilon) = 1 - \frac{\rho \text{ app density of compacts}}{\rho \text{ true density of particles}}$$

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Where, ε is the porosity of the compacts, ρ_{app} is the apparent density of the compact and ρ true is the true density of the particles. The ratio of ρ_{app}/ρ_{true} is a measure of the relative density or the solid fraction of the compact. [26-28]

13.Permeability Study

The in vitro drug transport through the artificial cellulose acetate membrane (molecular weight cut off 1000 Da) was carried out using a vertically static type Franz diffusion cell. Franz diffusion cells are characterized by an effective diffusion surface area of 4.9 cm^2 and a receptor cell volume of 30 ml. The receptor cell was filled with 30 ml simulated salivary fluid (pH 6.8) and was stirred with a small magnetic bar at a speed of 100 rpm for uniform mixing. The receptor compartment was maintained at 37±0.5°C using a circulating water bath. Formulation J containing 10 mg of lornoxicam in IR tablets were placed on the cellulose membrane surface facing the donor compartment and 1ml samples were withdrawn from the receptor compartment at predetermined time points of 5, 10, 20, 30, 60, 90, 120, 150, 180, 210, 240, 270 and 330 min. The 1 ml sample withdrawn was replaced by fresh simulated salivary fluid (pH 6.2) and maintained at 37±0.5°C. The drug content in the collected samples was determined by an UV visible spectrophotometer at 378 nm (UV/visible spectrophotometer, Shimadzu-120, Japan). [29-33]

a. Permeability Coefficient

The permeability coefficient through the membrane (Kp) was determined according to the following equation:

Permeability coefficient *(Kp) = (Jss.H)/C0*

Where, H is the thickness of membrane and, C0 is the initial drug concentration.

b. Steady-State Flux

Flux is defined as the rate of diffusion or transport of a substance across a permeable membrane. After drug permeation has reached steady state, the steady-state flux was calculated:

Steady state flux *(Jss) = dM/S.Dt*

Where, dM is the amount of drug that permeates through a unit cross section area, S, per unit time, t. The slope of the steady-state portion of the permeation curve created by plotting the cumulative amount of drug permeated in micrograms versus time in hours is the flux.

14.*In-Vitro* Dissolution Test

The release rate of Lornoxicam from IR tablets was determined using USP dissolution testing apparatus II (paddle method, Electrolab, TDT-06T, Mumbai, India). The dissolution test were performed using 900 ml of simulated salivary fluid (pH=6.8), at 37±0.5°C and 50 rpm. A sample (1 ml) of the solution was withdrawn from the dissolution vessel at 1, 2, 3, 4, 5, 10 and 20 min time intervals. The samples were replaced with fresh dissolution medium of same quantity. The samples were filtered through a whatman filter. Absorbance of these solutions was measured at 378 nm using a Shimadzu UV-1700 UV/Vis double beam spectrophotometer. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve. [34-37]

15. Model-Independent Methods to Compare Dissolution Profiles

The difference factor (f1) and similarity factor (f2) was used as a basis to compare dissolution profile. The dissolution profiles of products were compared using f1 and f2.

$$f_1 = \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} X\ 100$$

$$f_2 = 50\ X \log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n} w_f\ |R_t - T_t|^2\right]^{-0.5} \text{X } 100\right\}$$

According to the FDA guidance, in both equations, R and T represent the dissolution measurements at P time points of the reference and test, respectively. f1 values of 0–15 and f2 values of 50–100 ensure sameness or equivalence of the two dissolution profiles. [34]

Accelerated Stability

The optimized formulation was kept in 5 ml of glass vial and closed. The vials were kept at 40±2°C/75± 5% RH for three months in a stability chamber. After end of stipulated period, tablets were evaluated for mean drug content. The values given were at end of the three months. [38-39]

Pharmacokinetic

The animal study protocol was approved by the institutional animal ethics committee (IAEC) and submitted to CPCSEA, New Delhi.

Nine rats (200 +20 gm) were divided into three groups (Controlled, test and marketed). The prepared fast release tablet and marketed rapid release tablet were triturated separately and powder equivalent to 0.4 mg lornoxicam were administered orally as a solution to each of two groups. Blood samples (1 ml) were collected at 0 (pretreatment), 1/2, 1, 2, 4, 6, 8 and 24 hours. The plasma was separated by centrifuging the blood samples at 5000 rpm for 10 min and kept at - 20°C until analysis. The plasma was mixed with chloroform then vortex for 10 min and then filtered. The filtrate was evaporated and the residue was then reconstituted with 1 ml of mobile phase [Methanol: NaOH] (10:1) and the 20 µl of the resulting solution was analyzed by HPLC (Agilent Corp, Germany).

Lornoxicam Estimation by HPLC

Stock solutions were prepared by dissolving 100 µg/ml lornoxicam (internal standard) in chloroform. These stock solutions were further diluted suitably to get final solutions of 5, 10, 15, 20 and 25 µl/ml. 1 ml solution from each diluted stock solutions was then added with 0.2 ml of plasma and the tubes were vortex-mixed. This mixed

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Table 1: Compositions of Lornoxicam Fast Dissolving Tablet

Ingredients	Formula Code								
	A	B	C	E	F	G	H	I	J
LC-Kollidon VA64 SD (Avicel PH 101) (mg)	Eq.wt 10 mg			-	-	-	-	-	-
LC-Kollidon VA64 SD (Avicel PH 102) (mg)	-	-	-	Eq.wt 10 mg			-	-	-
LC-Kollidon VA64 SD(NFC) (mg)	-	-	-	-	-	-	Eq.wt 10 mg		
NeucilinUS2(mg)	20	20	20	20	20	20	20	20	20
Ac-Di-Sol (mg)	30	30	30	30	30	30	30	30	30
Mannitol (mg)	Upto130 mg								
Mg Stearate (mg)	6	6	6	6	6	6	6	6	6

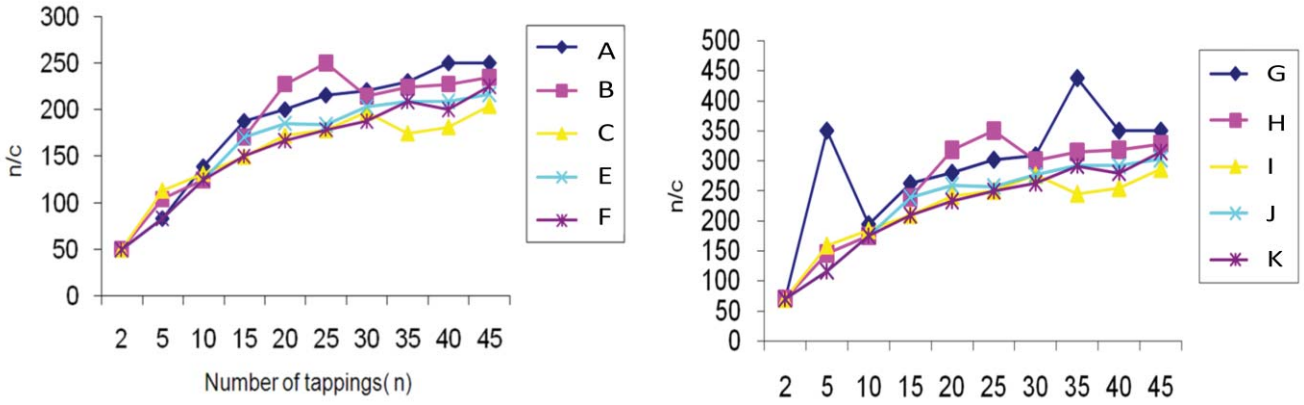

Figure 1: Kawakita plots explaining the flowability of solid dispersion of LC-Kollidon va-64

solution was then filtered and the filtrate was evaporated to get dry residue of lornoxicam, which was then reconstituted by adding 1 ml of mobile phase. 20 µl of solution from this reconstituted solution was injected into HPLC column for determination of lornoxicam concentration. [40-42]

RESULTS AND DISCUSSION

Nanofibrillar Cellulose

The nanofibrillar cellulose was produced and kindly donated by UPM-Kymmene Corporation, Finland. The aim of this study was to evaluate the usability of spray-dried NCF as novel tabletting material for immediate release formulations. For the purpose, NCF material was compared to two commercially available grades of MCC: Avicel PH 101 and Avicel PH 102. MCC was chosen for comparison due to its similarity to CNF in chemical structure. Determination of powders main physical characteristics was done as well as examination of their precompression behavior.

Solid Dispersions of Lornoxicam

We produced porous structured solid dispersion powder with NFC as a material and drug incorporated within a porous fiber network. The solid dispersion was produced by spray drying the suspension prepared by mixing drug solution in a suitable dispersion of NFC and Avicels. Since NFC creates highly viscous gel-like dispersions in concentrations over 1.5%, the concentration of feeding suspension for the spray drying had to be kept low (total solid content of 0.5%). This factor combined with a high affinity of NFC to water and short retention time of drying material in the drying chamber required a high temperature for successful drying. Thus, drugs with suitable thermal stability and melting point were chosen as model active pharmaceutical ingredients (APIs). During the spraying process, a problem of adherence of non-completely dried particles was encountered, which resulted in low yields of the production process.

Spray dried NFC particles were characterized in terms of their main physical properties relevant for the potential application as a novel filler in tablet production. Its main characteristics were then compared to those of two commercially available grades of microcrystalline cellulose (MCC); Avicel PH 101 and Avicel PH 102. The commercially available MCCs show broad particle size distributions with main diameters of 50 µm for Avicel PH 101 and 100 µm for Avicel PH 102.

Formulation of Immediate Release Tablet

An interactive mixture consisting of close to identical ordered units, the drug dissolution rate is affected by the particle size of both drug and carrier as well as by the physicochemical properties of the carrier. The compositions of the tablets used in this study were discussed (Table 1).

Evaluation of Powder Blend

Mannitol was selected as the basic excipients because of proven safety. Due to their excellent compactability, they are often used in tablet formulations to prevent capping. Furthermore, Ac-Di-Sol was also used as a superdisintegrant because it swells to a large extent when it comes into contact with water. Since the powder material was free flowing, tablets were obtained of uniform weight variations as per Pharmacopeial specifications. Bulk

Table 2: Precompression Characterization of Ordered Powder Mass

Code	Angle of Repose (θ)	Bulk Density (gm/cm³)	Tapped Density (gm/cm³)	% Porosity	Carr's Index (%)	Hausner' Ratio
A	33.37 ±0.81	0.69 ±0.01	0.73±0.02	0.057 ±0.007	5.7 ±0.007	1.05
B	31.20 ±1.15	0.62 ±0.02	0.80±0.02	0.150 ±0.010	15.0 ±0.010	1.30
C	32.34 ±0.38	0.60 ±0.02	0.73±0.02	0.165 ±0.005	16.5 ±0.005	1.21
E	33.13 ±0.35	0.60 ±0.01	0.66±0.02	0.110 ±0.010	11.0 ±0.010	1.09
F	31.01 ±0.17	0.71 ±0.01	0.80±0.02	0.117 ±0.005	11.7 ±0.005	1.13
G	31.00 ±0.26	0.56 ±0.03	0.68±0.03	0.120 ±0.010	12.0 ±0.010	1.22
H	30.14 ±0.65	0.70 ±0.01	0.83±0.02	0.126 ±0.006	12.6 ±0.006	1.18
I	30.57 ±0.99	0.55 ±0.01	0.61±0.05	0.062 ±0.045	6.2 ±0.045	1.11
J	33.70 ±0.53	0.57 ±0.02	0.64±0.05	0.110 ±0.011	11.0 ±0.011	1.12
K (PM)	28.87 ±0.65	0.72 ±0.02	0.68±0.02	0.116 ±0.005	11.6 ±0.005	0.95

n=3 ±S.D.

Table 3(A): Physical Properties of Tablets

Formulation Code	Weight Variation (mg)	Content Uniformity (%)	Thickness (mm)	Crushing Strength (N)	Friability (%)
A	128.00 ±0.20	96.10 ±0.60	2.90 ±0.01	3.1±0.31	0.85 ±0.05
B	129.13 ±0.12	97.25 ±0.25	2.95 ±0.01	2.9±0.10	0.92 ±0.03
C	129.43 ±0.40	99.07 ±0.25	2.83 ±0.03	4.4±0.25	1.03 ±0.06
E	129.13 ± 0.12	98.20 ±0.20	2.95 ±0.03	2.9±0.08	0.88 ±0.03
F	129.80 ±0.10	98.87 ±0.15	2.98 ±0.03	4.1±0.03	0.75 ±0.04
G	129.83 ±0.46	99.10 ±0.50	2.95 ±0.05	5.2±0.42	0.63 ±0.02
H	128.77 ±0.25	96.20 ±0.20	2.98 ±0.08	3.6±0.38	0.65 ±0.05
I	128.97 ±0.12	98.93 ±0.45	2.78 ±0.03	2.1±0.21	0.56 ±0.04
J	130.00 ±0.20	99.27 ±0.27	3.08 ±0.08	5.5±0.42	0.58 ±0.02
K (PM)	129.23 ±0.25	96.30 ±0.30	2.90 ±0.06	2.9±0.10	0.80 ±0.02

n=3 ±S.D.

Table 3(B): Physical properties of Tablets

Formulation code	Disintegration Time (Sec)	Wetting Time (sec)	*In-Vitro* Dispersion Time (sec)	Tablet Porosity	Tablet Tensile Strength
A	32±3.0	43 ±5.7	38 ±1.5	0.9654±0.0566	19.2±0.003
B	36±2.0	35 ±2.5	28 ±2.0	0.9980±0.0006	11.3±0.002
C	46±4.0	32 ±5.3	37 ±2.1	0.9828±0.0241	27.5±0.002
E	39±2.0	38 ±3.0	50 ±1.5	0.9961±0.0021	17.2±0.003
F	50±5.56	47 ±5.0	46 ±1.0	0.9981±0.0008	15.7±0.004
G	35±4.0	70 ±4.5	48 ±1.5	0.9950±0.0035	16.6±0.003
H	28±3.61	47 ±3.1	35 ±2.5	0.9978±0.0007	21.9±0.002
I	47±5.51	124 ±4.6	64 ±2.1	0.9979±0.0009	23.3±0.002
J	63±1.53	109 ±4.2	49 ±1.0	0.9957±0.0021	26.7±0.002
K (PM)	48±2.08	42 ±6.0	53 ±1.5	0.9966±0.0014	34.7±0.003

n=3 ±S.D.

density was found to be between 0.52±0.01 to 0.72 ±0.02 gm/cm³ and tapped density between 0.59±0.44 to 0.83±0.02 gm/cm³ for all formulations (Table 2). From density data % compressibility was calculated and was found to be between 5.7 ±0.007 to 18.0 ±0.010 percent. Angle of repose was found to be in the range of 28.87 ±0.65 to 33.70 ±0.53.

A Hausner ratio value of less than 1.20 is indicative of good flowability of the material, whereas a value of 1.5 or higher suggests a poor flow display by the material exceptionally few formulation crosses the limits of hausner ratio. The Carr index is also called "percent compressibility." A value between 5 and 15, 12 and 16, 18 and 21 and 23 and 28 indicates excellent, good, fair and poor flow properties of the material, respectively. The Hausner ratio and Carr's index for products used in this study suggest that they all possess good flow properties. The Hausner ratio and the Carr index are measures of interparticle friction and the potential powder arch or bridge strength and stability, respectively and widely used to estimate the flow properties of powders. All the formulation shows the fair to good flow properties for compression and hence tablets were prepared.

In Kawakita plot 'a' is properties of consolidation as close packing and 'b' is packing velocity. The constant 'a' is equal to the minimum porosity of the bed prior to compression while 'b' which is termed as the coefficient of compression, is related to the plasticity of the material (Figure 1). The grater the value of b indicates good compactibility and if packing velocity is high means yield pressure are breaking strength is less. All the formulations indicate the good flowability.

Physical Characterization of Immediate Release Tablet

The materials and compositions used are presented in Table 1. The physical characterizations of the materials are shown in Table 3 (A) and (B).

1. General Appearance, Thickness, Diameter and Volume of Tablet

The comparison of physical properties of the immediate release tablets is shown in Table 3 (A) and (B). Drug uniformity results were found to be good among different batches of tablets and the percentage of drug content was more than 98%. The results also showed acceptable and homogenous distribution of drug in tablets.

The weight and thickness of the formulations ranged from 127 to 130 mg and from 2.78 to 3.08 mm, respectively. All tablets prepared in this study meet the USP requirements for weight variation of all formulae was less than 2% (USP 31). In all the formulations, the hardness test indicated good mechanical strength. Tablet hardness is not an absolute indicator of strength. Another measure of a tablet's strength is friability. In the present study, the percentage friability for all the formulations was below 1%, indicating that the friability is within the compendial limits (USP 31) and had a good mechanical resistance.

2. *In-vitro* Disintegration Study

In principle, the tablets should disintegrate rapidly, to instantly generate many ordered units consisting of lornoxicam SD, superdisintegrant, basic excipients and respectively other ingredients. The disintegration time of the all batches of tablets containing lornoxicam SD was 28-63 sec (Table 3B). The higher value was probably caused by adhesion of the tablets to the discs (because of the addition of bioadhesive), which fudged the endpoint. It seems reasonable from these results that the tablet will adhere to the mucosa in the mouth. The *in-vitro* data obtained with discs probably better reflects the disintegration time *in-vivo* into ordered units. However, the movements that occur in the mouth may contribute to the disintegration of the tablets.

The most important parameter that needs to be optimized in the development of immediate release tablets is the disintegration time of tablets. In the present study, all the tablets disintegrated in the range varied from 28±3.61 to 63±1.53 sec (Table 3B). In the USP disintegration test for immediate release tablets, the disintegration apparatus for oral tablets is used without the covering plastic discs and 2 min is specified as the acceptable time limit for tablet disintegration fulfilling the official requirements (<2 min) for sublingual tablets (USP 31). So all of our formulations meet the requirement for disintegration. The rapid and desired disintegration of tablets is due to the presence and good proportion of Mannitol and Ac-Di-Sol and can be explained with following reasons.

MCC (Avicel) has good wicking and absorbing capacities. Tablets of NFC disintegrated rapidly due to the rapid passage of water into the tablets resulting in the instantaneous rupture of the hydrogen bonds. The ratio of NFC in tablet formulations changes between 10% and 20% and verifies the findings that the optimum concentration of NFC may be less than 15%. NFC accelerates water penetration into tablets can cause easily swelling of Ac-Di-Sol and this reveals readily superdisintegrant property of Ac-Di-Sol. But here, there is another important point that must be taken into consideration that the ratio of Ac-Di-Sol in immediate release tablet formulation is very important because it was reported that disintegration time increased with increase in the level of Ac-Di-Sol in the tablets. It was shown that the increase in the level of Ac-Di-Sol had a negative effect on the disintegration of the tablets. At higher levels, formation of a viscous gel layer by Ac-Di-Sol might have formed a thick barrier to the further penetration of the disintegration medium and hindered the disintegration or leakage of tablet contents. Thus, tablet disintegration is retarded to some extent with tablets containing Ac-Di-Sol. So it can be concluded that the use of Ac-Di-Sol in immediate release tablet formulations in 10 mg gives the tablet desired disintegration time. On the other hand, mannitol has a highly water soluble property and this may leave pores in the tablet matrix after rapid dissolution of it. These pores can accelerate capillary action that may be responsible for penetration of surrounding fluid in the tablet matrix and there after rapid disintegration.

3. Water Absorption, Porosity and Wetting Time

Water uptake increased with increased mannitol content and caused a great deal of swelling. During the manufacture of MCC, accessible amorphous regions of cellulose molecules are hydrolyzed away, so that MCC shows relatively high crystallinity. It can absorb only small amounts of water and reaches equilibrium rapidly.

Wetting is closely related to the inner structure of tablets and to the hydrophilicity of excipients. According to equation developed from Washburn's, the water penetration rate into the powder bed is proportional to the pore radius and is affected by the hydrophilicity of powders which is expressed by contact angle and surface tension. It is obvious that pore size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. Since the hydrophilicity of NFC is lower than Mannitol, wetting time generally decreases with an increased NFC content. When the NFC content exceeded 90%, however, the wetting time showed a reverse tendency. This suggested that the inner structure of these tablets underwent some change at a high NFC concentration. Since NFC particles are of a concave convex shape and their pores are fairly collapsed by compression.

4. Tablet Tensile Strength

It was generally recognized that tensile strength was influenced by the number of contact points between the powder particles and the interparticle binding force, such as the surface molecular interaction and mechanical interlocking. The number of contact points was altered by the porosity of the tablet and by the shape and diameter of constituent particles. NFC was easily compressed, when

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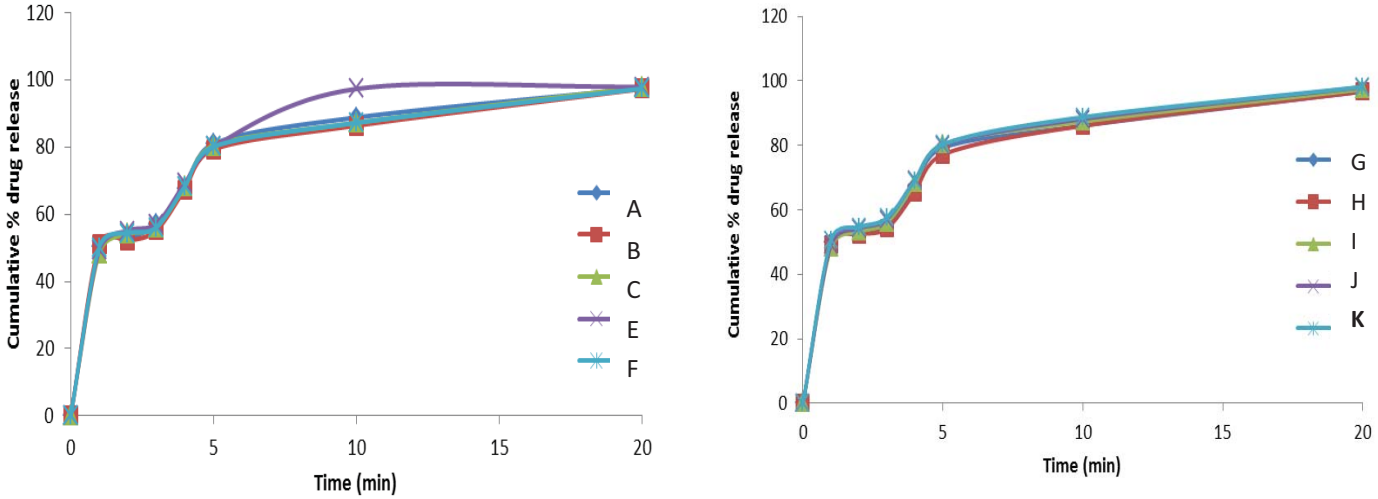

Figure 2: Drug release profile of lornoxicam-SD formulations (A-J)

compressed under the same pressure, tablets containing more NFC showed lower porosity.

Both tablet strength and disintegration times were affected by tablet porosity. The porosity of the tablet may affect the action of the disintegrant. A relatively low porosity was most effective action for the action of a disintegrant. However, no general relationship between porosity and disintegration time was seen and it was concluded that the material properties of the tablet components, such as solubility and bounding ability, would also affect disintegration time. The tablet porosity was approximately 25% for all three batches, which appears adequate considering the results for tablet strength.

5. *In-Vitro* Dissolution Studies

The dissolution rests revealed that lornoxicam was dissolved almost instantly from the tablets. Data for the amount of dissolved lornoxicam as a function of time are presented in Figure 2. In formulated tablets, roughly 50% of the substance was dissolved from the tablet within 1 min and more than 90% within 10 min (Figure 2). The dissolution profiles for all the tablets are comparable with those obtained for ordered mixtures i.e. compaction of the ordered units did not negatively influence the dissolution rate. After initially rapid disintegration, ordered units are quickly exposed to the solvent and drug dissolution starts more or less instantly. In these studies a large amount of dissolution medium (900 ml, pH 6.8) was used. However the volume of fluid used in in vivo was much smaller.

According to the literature, the amount of drug dissolved from immediate release tablets must exceed 85% in 15 min. therefore; the resulted dissolution profile met the above mentioned requirement.

Fast dissolution of the drug from the formulations can be explained with the few comments like; manufacturing method can be one of the most important parameters for the dissolution. As it is known, the tablets prepared by direct compression disintegrate into lornoxicam particles instead of granules that directly come into contact with dissolution fluid and exhibits comparatively faster dissolution. It is well known that the addition of mannitol can improve the flow and bond properties of other excipients during direct compression. In particular, mannitol with higher solubility might also facilitate the dissolution of solid dosage forms. When evaluate all formulations, mannitol ratios can give us the chance of preparing sublingual tablets without changing their basic tablet characteristics especially disintegration and dissolution profiles.

6. Model-Independent Methods to Compare Dissolution Profiles

After studying the effect of spray dried NFC, Avicel PH 101 and Avicel PH 102 on the responses, the optimum response for batch J was determined. The optimum formulation is one that gives high value of hardness and a fast drug in the resultant tablet.

The results revealed that, the amount of SD, NFC, Avicel, Mannitol, Ac-di-sol and Neusulin affected significantly the response. It can be concluded that, immediate release tablets provide several advantages especially when administered to children and elderly patients. Rapid absorption into the systemic circulation within a shorter period o time may be achieved. Dosage forms developed in such a way provide therefore, an interesting field for further research given that the results may be extrapolated to other drugs, for which a rapid onset of effect is a desirable objective.

Optimized formulation was compared with the reference formulation in terms of f1 and f2, throughout the stability (Table 4). Optimized formulations were considered similar to the reference, by f1 and f2 factor. In this case, dissolution profiles were accepted as similar. The assay value was 99.50% and 99.25% for Batch-J and Marketed formulation respectively.

7. Permeation Study

Low and slow release of drug can be attributed to small volume (2 ml) of donor compartment makes tablets swell. Swollen particles have porosity and drug release occurs by diffusion through the openings created by the porosity of matrix as described by Higuchi square root equation. The

Table 4: Comparative of Optimized Formulation with Marketed Formulation

Parameter		Batch-J	Marketed Formulation
Permeation study	Steady state flux J_{ss}	256.43±89.50 (µg/cm²h)	310.43±92.10
	Permeability coefficient Kp	12.82±4.47 (cm/h)	13.20±5.30
Difference factor	f1	0.97	
Similarity factor	f2	52.53	
Dissolution profile	Dissolution profile	Similar	
Qt	$t_{\%}$ release (10 min)	90.20	95.21
Assay	Drug content	99.50	99.25

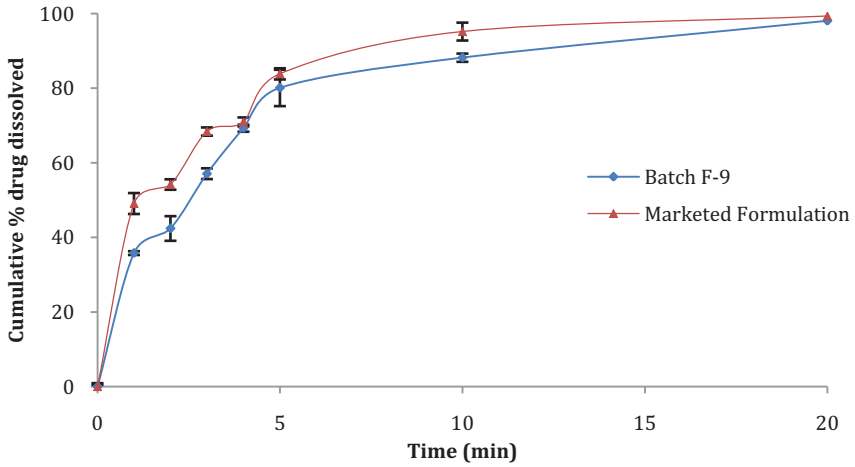

Figure 3: *In-vitro* drug release of optimized formulation

observed value of permeability coefficient and Steady state flux was 12.82 ±4.4 cm/h and 256.43 ±89.50 µg/cm²h respectively. Ac-di-sol and mannitol exhibited more drug release and higher steady state flux and permeability coefficients values. Higher swelling index ratio may cause to extend diffusion pathway of drug in the swollen matrix and this may decrease the drug release (Table 4 and Figure 3).

In-vitro drug release data were fitted to kinetic models such as zero-order, first-order. The regression analysis was performed. No important changes in appearance were recorded throughout the stability study under both aging conditions. There were no visual signs of capping, lamination etc. after formulation during the stability study.

Accelerated Stability

The concentration of lornoxicam measured in the assay was remained within 90% of the initial value throughout the stability study (Table 5), which indicates that the analyzed formulations are chemically stable during the study period at room temperature and accelerated storage temperature. Formulation showed a fast dissolution rate. Linearization of the LX tablet dissolution profiles using the release kinetics equation would better characterize the differences between the both formulations. Consideration of determination coefficients (R^2) can indicate that the release kinetics of the LX tablet. This study examined the effect of accelerated-aging conditions on the performance of LX tablet; they did not have a significant effect on LX chemical stability. Formulated lornoxicam tablet fulfilled the requirements of the assay, uniformity of dosage units and stability of pH values.

Visually, all samples remained stable and did not exhibit signs of any breakage throughout the period. The analyzed tablet was chemically stable throughout the period of storage under both aging conditions. Formulation also had acceptable stability when stored at room temperature throughout their storage periods.

Pharmacokinetics

After single dose administration, plasma concentrations of lornoxicam were obtained within 10 min, with no second peak corresponding to possible gastrointestinal absorption. It therefore appears that the Mannitol promoted the retention of the ordered units under the tongue without hindering the release and local absorption of lornoxicam. It appears that the fraction of the lornoxicam dose that was swallowed was smaller compared to other mucosal delivery systems. This was further supported by calculating the area under the plasma concentration time curves (AUC) and comparing them with pharmacokinetic data obtained from marketed formulation. The formulated immediate release tablet has potential to be a valuable addition to the store of drugs for breakthrough pain.

Pharmacokinetic parameters estimated following the oral administration of lornoxicam and its marketed product. Lornoxicam was found to be absorbed slowly when given orally and a peak serum concentration (C_{max}) of 0.79 µg/ml was observed at 24 hr following administration.

All the pharmacokinetic parameters namely C_{max}, T_{max} and AUC to various times and AUC indicated rapid absorption and higher bioavailability of lornoxicam when administered. Higher C_{max} and shorter T_{max} values were

Table 5: Dissolution Comparison Throughout the Accelerated Stability

Storage Time	Parameter	Batch-J	Marketed Formulation
	$t_{90\%}$ release (10 min)	88.78	95.21
	f_1 (0-1 M)		0.97
0 M	f_2 (0-1 M)		52.53
	Dissolution Profile		Similar
	Assay	98.70	98.34
	$t_{90\%}$ release (10 min)	88.54	95.1
	f_1 (1-3 M)		0.82
1 M	f_2 (1-3 M)		52.30
	Dissolution Profile		Similar
	Assay	98.18	98.10
	$t_{90\%}$ release (10 min)	87.21	93
	f_1 (0-3 M)		1.74
3 M	f_2 (0-3 M)		52.82
	Dissolution Profile		Similar
	Assay	97.90	97.80

*Accelerated- 40°C/75% RH

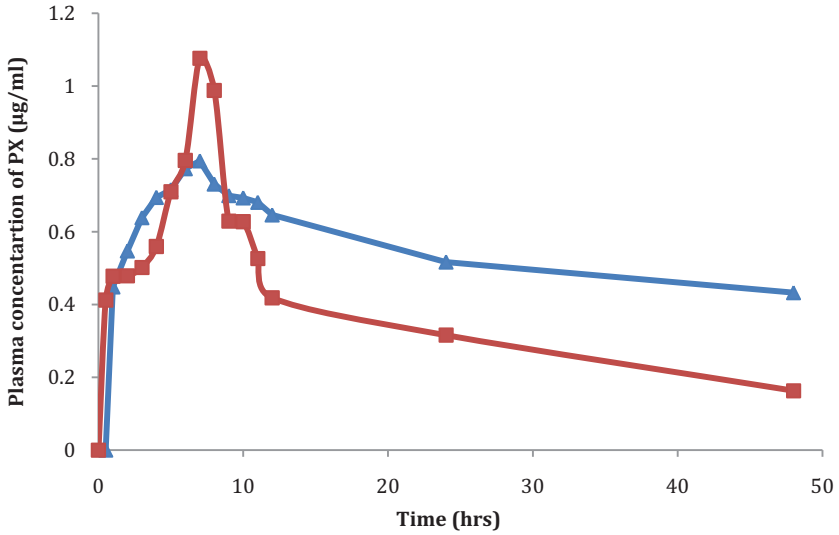

Figure 4: Plasma drug concentration vs. time curves for IR administration of lornoxicam 0.3 mg/kg doses

observed with these products when compared to those of marketed lornoxicam formulation.

AUC (extent of absorption) was also much higher in the case of formulated lornoxicam tablet when compared to marketed formulation. [AUC] 0-24 hr was 22.87µg/ml/hr and 17.82 µg/ml/hr for formulated and marketed tablet. The relative bioavailability of the sublingual tablet was 194. Thus, the results of pharmacokinetic studies indicated rapid and higher oral absorption of lornoxicam with retention in sublingual cavity when administered as tablet.

CONCLUSION

In recent years introduction of combinatorial chemistry and high throughput screening in drug discovery has lead to development of many highly lipophilic drugs and high lipophilicity of these drugs has become a major issue in drug development, research and in formulation development. Nanofibrillar cellulose (NFC) of wood (birch) origin was tested as a novel pharmaceutical excipient. Standard methods for tablet production were used to evaluate the applicability of spray dried NFC as filler/disintegrant for tablet manufacturing. The spray dried NFC powder was characterized in terms of particle size and morphology, density and flowability. The addition of NFC to commercially used microcrystalline cellulose (MCC) improved its flow properties. Tablets made of NFC were successfully prepared either by direct compression method. Compared to MCC, NFC was found to deform less plastically and have more pronounced brittle characteristics. NFC did not affect the drug release from the tablets manufactured with active model compounds. From *in-vivo* pharmacokinetic study, it can be concluded that increased dissolution of lornoxicam by solid dispersion can improve its pharmacokinetic parameters like C_{max}, T_{max}, AUC_{0-24}. This work explores the potential multiple applications of NFC in the manufacture and formulation of pharmaceutical dosage forms and further work is needed to advance its utilization in drug delivery systems.

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