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Improved Dissolution Rate of Oxcarbazepine by Centrifugal Spinning: In-Vitro, In-Vivo Implications †

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Abstract: Low dissolution rates of poorly soluble drugs are the problem afflicting their bioavailability. The aim of this study is to prepare centrifugal spinning based formulation of a poorly soluble drug, oxcarbazepine for the improvement of dissolution rate and hence quick action. Sucrose based microfibers of oxcarbazepine were prepared by centrifugal melt spinning technique using a cotton candy machine. The prepared microfibers were characterized using SEM, PXRD, DSC and FTIR. The optimum formulation was molded into tablets and tested for in-vitro drug release and in-vivo pharmacokinetic studies using rabbits as test animals. The results indicated that the centrifugal spinning has produced rapidly dissolving microfibers (diameter ranges <10 μm and dissolve in few seconds). In these fibers ~20% oxcarbazepine was loaded, and both the yield and drug loading efficiency were improved by incorporating PVP in the formulations. The dissolution studies have revealed >90% of drug was dissolved in just 2 min as compared with drug alone that shows only 15% dissolution at this time interval. XRD and DSC analysis have shown amorphous state of drug in the fibers while FTIR study have shown chemical stability of oxcarbazepine in the fibers. In-vivo studies have revealed a 2 h reduction in tmax of drug in the rabbits treated with microfibers as compared with controlled group which was given pure oxcarbazepine. The study concludes the potential of centrifugal spinning technique for the production of drug loaded fibers that can significantly enhance the dissolution rates of poorly soluble drugs and thus produce formulations for quick action of such drugs. Furthermore, the sucrose-based formulation can enhance the palatability with the intend to attract pediatric patients.

Keywords: centrifugal spinning; Microfibrous; dissolution enhancement; quick action formulation

1. Introduction

Majority of newly developed active pharmaceutical ingredient (APIs) are poorly soluble owing to their lipophilic nature [1]. This leads to low dissolution rate and in turn poor bioavailability of these drugs [2]. Majority of these drugs belongs to BCS class II [3]. Thus, for this class of APIs dissolution is the rate limiting step in drug's absorption and hence in bioavailability [4]. Noye's Whitney equation states that the rate of dissolution is directly proportional to the surface area and

solubility of API [5]. Thus, manipulations based on enhancement of surface area or solubility, both could be opted for the enhancement of dissolution rate of poorly soluble drugs. One such useful approach is to make fibrous solid dispersion of hydrophobic drug in a hydrophilic carrier [6,7]. Enormous surface area is the main contributing factor to high dissolution rate of these microfibers [8]. This fabrication of solid dispersions into microfibers with increased surface area is a developing drift in Pharma industry.

Several fiber generations techniques are mentioned in literature like melt blowing [9], phase separation, bicomponent fiber spinning, template synthesis, Electrospinning [10], self-assembly and hydrogel formation [11]. Low production rate, complicated manufacturing equipment, challenging separation and collection methods, limited choice of materials, safety concerns due to current application and gas pressure etc. are the major disadvantages of these techniques [11]. *Centrifugal spinning* or centrifugal melt spinning (CS/CMS) is one of the alternative techniques which has the potential to overcome these problems and produce fibers from the solid dispersions with high production rate and low cost [12]. This technique was initially developed in 1924 by Hooper to produce artificial silk fiber from viscose [13] and it requires simple equipment and is environment friendly. Fibers for the enhancement of dissolution rate were previously produced by electrospinning and used to load drugs like diclofenac sodium, tetracycline hydrochloride [14] ibuprofen [15], meloxicam [16], Indomethacin, Itraconazole [17] paracetamol/caffeine [18].

There are many recent studies which have focused on the development of drug loaded microfibers using CS/CMS technique for the development of quick release formulation e.g., Effect of high humidity was studied on the fibers of olanzapine, Itraconazole and piroxicam and it was concluded that even upon drug recrystallization in the aged samples, high dissolution behavior was retained [6]. Fibrous films were loaded with Ibuprofen, tinidazole, metoprolol tartrate, nifedipine and Indomethacin (IND) using CMS [11]. Centrifugal melt atomization was used to make granules instead of fibers of hydrophobic drugs that exhibit high dissolution rates [19]. All the above studies are based on the process and formulation parameters of microfibers. Bioavailability studies have not yet been conducted [20].

Oxcarbazepine is a BCS class II, antiepileptic drug. It is it is given as monotherapy in partial seizures and in generalized seizures in pediatric patients in a dose of 8–10 mg/kg/day [21]. Palatability and swallowing are always problematic in oral drug delivery to pediatric patients. Quick release mouth dissolving tablets were made from these OXC loaded microfibers. Sucrose not only acted as base for the formulation but also masked the taste and made it palatable especially for pediatric patients. Other objectives of the study were; screening of best OXC/excipient combination for the production of stable microfibers with high drug loading and yield; also in-vivo studies of these formulation were done.

2. Experiments

2.1. Material

Oxcarbazepine, crystalline sucrose (Fischer Chemicals, Loughborough, UK) Polyvinyl alcohol (Duksan Pure Chemicals LTD.CO, Gyeonggi-do, Korea) Polyvinyl pyrrolidone K-30, HPMC and monopotassium phosphate (DaeJung Chemicals, Siheung-si, Korea) are of analytical/pharmaceutical grade. HPLC grade Methanol, Acetonitrile trifluoro acetic acid, (Duksan Pure Chemicals LTD.CO, Korea). Approval from ethical committee to conduct in-vivo studies in rabbits was also obtained.

2.2. Method

2.2.1. Preparation of Microfiber

Physical mixture of OXC and excipients (sucrose and PVP) in the ratio as given in Table 1 were prepared by mixing for 5 min in mortar and pestle. This mixture (~5 g) was transferred to spinneret head of Centrifugal spinning machine and rotated at 2400 rpm at temperature of 170~200 °C. Distance of spinning axis from collector wall was fixed at 15 cm. Fresh fibers were collected. Both fresh and

aged fibers (storing for 3 months at 30 °C and 65 ± 5% humidity) and characterized. Selection of polymer (either of PVA, PVP or HPMC) was made on the basis of their ability to enhance saturation solubility of oxcarbazepine in phosphate buffer (pH 6.8), closeness of their melting point to sucrose and OXC and percentage yield of the microfibers prepared from each of them. On the basis or results of above criteria PVP-K30 was selected as a polymer and sucrose as bas to make OXC loaded nanofibers for this study.

Table 1. Formulations of OXC loaded fibers with and without polymer, their drug loading.

Formulation	OXC %	Sucrose %	Polymer	%Age Yield	%age OXC Loaded
Blank	0	100	0	92	
DS5	5	95	0	54	53.2
DS10	10	90	0	51	60.6
DS15	15	85	0	44.2	62
DS20	20	80	00	37.8	63.8
DS30	30	70	0	18	34.2
DSP5	20	75	5	74	77.72
DSP10	20	70	10	78	79.17
DSP15	20	65	15	80	84.52
DSP20	20	60	20	88	90.60

2.2.2. Percentage Yield Calculation

Percentage yield of fibers obtained from 5 gm of physical mixtures of different formulations (Table 1) of OXC with and without polymer was calculated using following equation and calculation is considered as an important tool in selecting the best OXC/ excipient combination [6].

$$\text{Yield (\%w/w)} = \frac{\text{weight of fibers obtained (mg)}}{\text{weight of Physical mixture (mg)}} \times 100$$

2.3. Determination of Drug Content and Entrapment Efficiency of Microfibers

Fibers of each formulation with known amount of OXC were dissolved in 50 mL of buffer, pH 6.8 at 37 ± 0.5 °C and absorbance of OXC was measured using UV- spectrophotometer (Schmadzu, Japan) at 256 nm using buffer as blank [22]. Amount of drug in each sample was calculated from the standard calibration curve ($r^2 = 0.998$) and DLE from below equation.

$$\text{Drug loading efficiency DLE(\%)} = \frac{\text{amount of drug determined}}{\text{theoretical amount of drug based upon drug loading}} \times 100$$

2.4. Disintegration Time

Time taken by the 50 mg of fibers to completely disappear in 20 mL of distilled water at 37 ± 1 °C was noted using stop watch.

Note: Based on highest yield, assay and disintegration time the optimized formulation DSP20 (see the results section) was selected for further characterization.

2.5. Morphology

Morphology and size of freshly made and aged nanofibers (DSP20) was studied using Scanning electron microscope (SEM, Evo LS-10, Carl Zeiss, Oberkochen, Germany) at different zooming ranges.

2.6. X-Ray Diffraction Studies

Solid state, crystalline or amorphous, of OXC alone and in fibers (DSP20, fresh and aged) was assessed using D8 Discover, (Bruker Germany) diffractometer [23].

2.7. ATR-FTIR Spectroscopy

Carry- 630 Agilent's FTIR imaging systems (Agilent Technologies, Santa Clara, CA, US) was used to determine FTIR spectra of pure OXC, sugar and drug loaded fresh and aged fibers.

2.8. Thermal Characterization Using Differential Scanning Calorimetry

DSC studies of OXC and its formulation (DSP20) (~10 mg) were carried out by using DSC, Q2000 V24.11 Build 124 calorimeter (TA instrument, New Castle, DE, USA).

2.9. In-Vitro Dissolution Studies

Dissolution rate of OXC alone and in its fibrous formulations, physical mixture was determined under sink conditions using USP Type II Paddle apparatus (Galvano Scientific, Lahore, Pakistan) [24]. Phosphate buffer (pH 6.8) was used as dissolution medium. Percentage of OXC released at each time interval (0.5, 1, 2, 4, 6, 10 min) was calculated using absorbance values from UV Spectrophotometer Figure 5. All measurements were carried out in triplicate ($n = 3$) and the average values were reported.

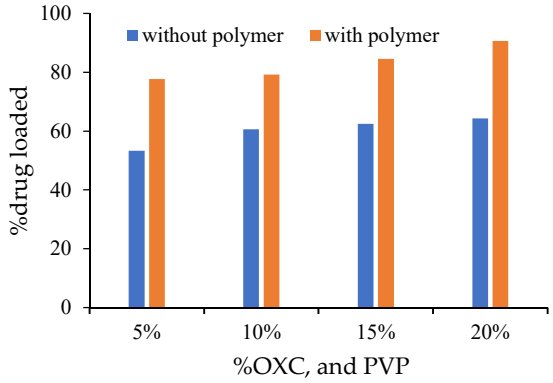

Figure 1. Percentage OXC loaded in different formulations with and without polymer.

2.10. Preparation and Characterization of Suitable Dosage Form

Formulation with optimal results DSP20 was pressed into a round tablet shape fibrous mats using single die press (Carver press, Perkin Elmer, Waltham, MA, USA). These tablets were Assayed for their OXC content using HPLC and evaluated for their In-Vito and In -vivo dissolution release.

2.11. In-Vivo Dissolution Studies (Salivary Method)

Rate at which the tablet was dissolved and released OXC in the human oral cavity was determined by means of 6 healthy adult volunteers. A tablet is placed in the oral cavity and they were asked to spat out the disintegrated tablet along with saliva at fixed time intervals (30, 60, 90 s) into calibrated bottles. Concentration of OXC in each saliva sample is determined using HPLC.

2.12. In-Vivo/Pharmacokinetic Studies

Male albino rabbits (body weight 1.3 ± 0.1 kg) were used for the study. Rabbits are divided into two groups (test and reference) of six rabbits each. Dose equivalent to 10 mg/kg body weight of OXC was administered orally. Blood sample from marginal ear vein of rabbits was collected before and after dosing at set time intervals (0, 0.5, 1, 1.5, 2, 3, 6, 12 h). Plasma was separated and stored at −20 °C until analysis is done. Quantity of OXC in each sample was determined by using HPLC. OXC peak time and AUC is recorded. Calibration curves (r^2, 0.9998) were constructed using spiked plasma solutions of known concentrations (0–100 µg/mL). Pharmacokinetic parameters are calculated from plasma level time curve obtained from HPLC.

2.13. Stability Studies (Aged Sample)

Freshly made microfibers (DSP20) and tablets are stored at 30 ± 5 °C at 65 ± 5% RH for 3 months. After this time period fibers are again evaluated to study the effect of storage on drug release, amorphization, and morphology.

3. Results

3.1. Percentage Yield, Drug Loading and Disintegration Time

Percentage yield of up to 80% and drug loading efficiency up to 90 ± 5% was obtained with different OXC/ excipient combinations (Table 1). Results showed that increasing the content of OXC in fibers without polymer increases the drug loading but decrease the yield. Highest drug loaded fibers are with 20% drug. PVP is added to this formulation in increasing concentration up to 20% which improved the polymer properties to desired level. The disintegration time of formulations (DSP5-DSP20) ranged between 5 ± 1 s.

3.2. Morphology

SEM images of fresh (Figure 2) and aged fibers from DSP20 showed an intricate pattern of fiber distribution with average diameter ranging from 4–8 μm and smooth surface without defects. OXC loaded fibers with PVP showed better structural integrity as compared to without polymer under polaroid microscope. This is because PVP gives the melt plastic properties and increased surface tension and density of molten mix improved its spinning and fiber making properties at room temperature [17].

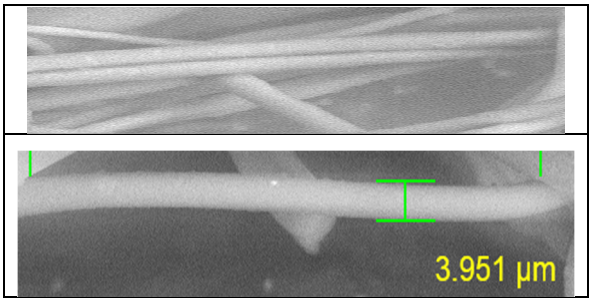

Figure 2. SEM images shows morphology of freshly prepared microfibers (DSP20).

3.3. In-Vitro Dissolution Rate Studies

Dissolution profile of pure OXC was compared to nanofibers (DSP20 and DS20), its physical mixture Figure 3. Enhanced dissolution of OXC physical mix then pure drug might be due to trituration of physical mix increase in saturation solubility by addition of polymer. Enhanced dissolution rate was due to loss of crystal structure [25] and enhanced surface area.

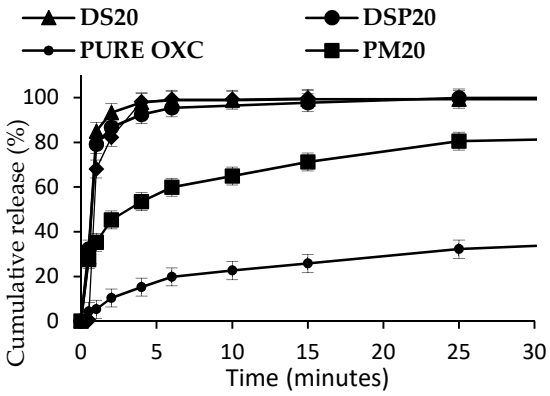

Figure 3. Dissolution profile of OXC, compared to formulations without fiber (DS20) with polymer (DSP20), physical mixture and its corresponding tablet.

3.4. X-Ray Diffraction

Pure OXC diffraction spectrum exhibited several discrete high intensity peaks indicating high crystalline state Figure 4. Whereas, spectra of fresh and aged fibers showed no prominent peaks in the same region displaying complete loss of crystal structure of drug and its amorphization [6]

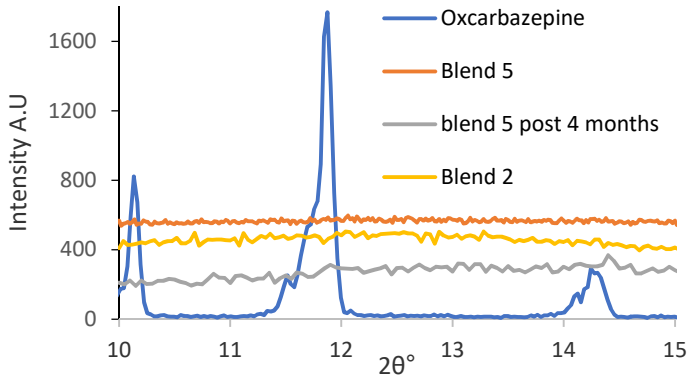

Figure 4. PXRD diffractograms of OXC and microfibers of fresh fibers DSP20, DS20 and aged fibers DSP20.

3.5. ATR-FTIR Spectrophotometry

Characteristic bands for OXC were absent in IR spectrum of nanofibers showing formation of new bonds between excipients and drug.

3.6. Differential Scanning Calorimetry (DSC)

Thermogram showed amorphous forms of OXC microfibers. Melting temperature and destructive temperatures were also determined from it.

3.7. Characterization of Tablet Dosage Form

Tablets molded out of fibrous mats have a diameter of 12 ± 0.1 mm and thickness of 2 ± 0.2 mm with sharp well-defined edges, weighing 500 ± 1 mg. They showed rapid disintegration within 60 ± 10 s in the USP basket rack assembly. Dissolution studies showed <80% of drug released within 2 ± 0.5 min. Assay of the tablets by HPLC showed at drug content of 93 ± 2%.

3.8. In-Vivo Studies

Plasma level time curve obtained from HPLC analysis of rabbit plasma showed an early Tmax and Cmax as compared to pure drug Figure 5. From the pharmacokinetic analysis, it can be concluded that the in vivo studies mimic the in vitro results.

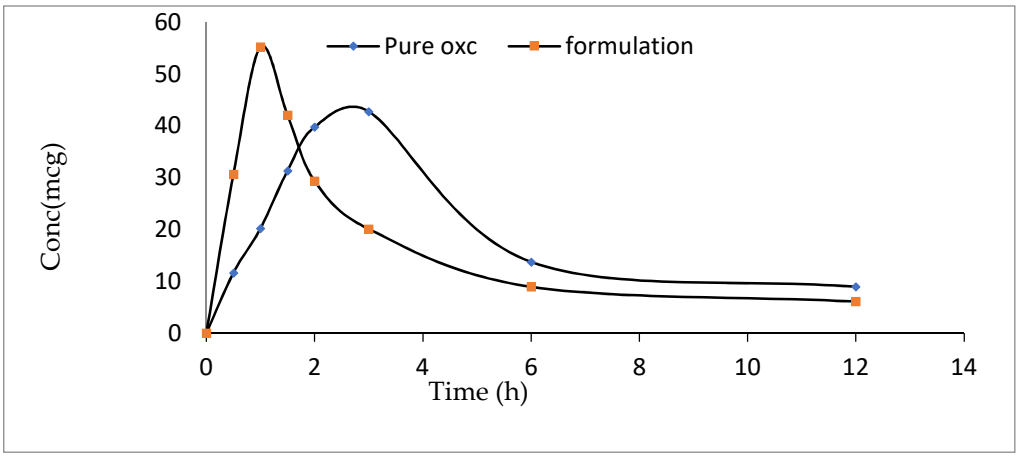

Figure 5. Plasma level time curve of rabbit plasma showing Tmax and Cmax after administration of oxc and oxc loaded fibers.

4. Discussion

Nine different combinations of OXC with sucrose, without and with polymer were spun to make microfibers. Fresh and aged fibers were evaluated. Since oxcarbazepine has no elastic and film forming properties yield decreased with high OXC in sucrose. Drug loaded sucrose fiber lost their structure quickly. This instability of sucrose fibers was overcome by adding PVP which raised the Tg of physical mix [26]. Increase in yield after adding PVP in formulations DSP5-DSP20 was attributed to the its plasticizing properties [27]. Increased drug loading was because PVP act as binder and provides enhanced drug layering effect when melted down in form of solution that results in greater drug loading efficiency [19]. However, PVP content beyond 20% halted the extrusion process because melt viscosity above 20% was high enough to hinder its flowability and fiber generation stopped [28].

Operating temperature control is critical in controlling properties of fibers. Temperature was varied with starting temperature of 200 °C for 2–3 min to speed up initial melting of PM and once fibers start to form temperature was reduced to 180 °C to prevent burning. Slightly longer disintegration time in oral cavity as compared to in-vitro test was due to the less volume and more viscosity of saliva, which effected the wettability. No remarkable difference in the dissolution properties of the fibers, with and without polymer, was observed. This established the fact that large surface area is responsible for enhanced dissolution. Amorphization is also a key feature which improved dissolution rate. Somewhat slow release from polymer incorporated fibers is attributed to new bonds between a drug and excipients as shown by FTIR spectra Figure 7. In- Vivo studies strengthen the in-vitro release studies by showing a remarkable difference of 2 ± 0.1 h in the Tmax of fibers as compared to pure drug. Thus, proving the efficiency of these fibers in improving.

5. Conclusions

CMS proved to be one step, simple, economical method to fabricate microfibers for the enhancement of dissolution rate of poorly soluble drugs. These fibers improved pharmacokinetic properties of the drug and ultimately bioavailability. Finding the best drug/excipient ratio under the set condition of spinning speed, spinneret opening, collector wall distance, and the best operating temperature that maintain the ideal melt viscosity without burning the content was achieved.

Author Contributions: Idea conceived A.H., experiments conducted by S.N. & F.H., data analysis by A.H., N.I.B., N.A. first draft prepared by A.H., S.N., M.S.A. and N.A. finally reviewed J.M., A.A. and S.L. All authors have read and agreed to the published version of the manuscript.

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Abbreviations

OXC	Oxcarbazepine
BCS	Biopharmaceutical classification system
API	Active pharmaceutical ingredient
UV	Ultra violet
USP	United states Pharmacopeia
HPLC	High performance liquid chromatography
DSC	Differential scanning calorimeter
CS	Centrifugal spinning
PVA	Poly vinyl alcohol
PVP	Poly vinyl pyrrolidone
SEM	Scanning electron microscope
DLE	Drug loading efficiency
FTIR	Fourier transform infrared spectroscopy
tmax,	Time to reach maximum concentration
Cmax	Maximum concentration
AUC	Area under curve
CMS	Centrifugal melt spinning

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