

Improved Dissolution Rate of Oxcarbazepine by Centrifugal Spinning: In-Vitro and In-Vivo Implications [†]

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Abstract: Low dissolution rates of poorly soluble drugs are the factor afflicting their bioavailability. The aim of this study is to prepare a 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 a centrifugal melt spinning technique using a cotton candy machine. The prepared microfibers were characterized using Scanning electron microscopy (SEM), PXRD, Differential Scanning Calorimetry (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 rapidly produced dissolving microfibers (diameter are <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 polyvinylpyrrolidone (PVP) in the formulations. The dissolution studies have revealed >90% of the drug was dissolved in just 2 min as compared with drug alone that shows only 15% dissolution at this time interval. XRD and DSC analyses have shown the amorphous state of the drug in the fibers while the FTIR analysis showed chemical stability of oxcarbazepine in the fibers. In vivo studies have revealed a 2 h reduction in t_{max} of drug in the rabbits treated with microfibers as compared with controlled group which was given pure oxcarbazepine. The study concludes the potential of the 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 intention of attracting pediatric patients.

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1. Introduction

The majority of newly developed active pharmaceutical ingredients (APIs) are poorly soluble owing to their lipophilic natures [1]. This leads to the low dissolution rates and in turn poor bioavailability of these drugs [2]. The majority of these drugs belong to BCS class II [3]. Thus, for this class of APIs dissolution is the rate limiting step in drug absorption and hence in bioavailability [4]. The Noyes–Whitney equation states that the rate of dissolution is directly proportional to the surface area and solubility of APIs [5]. Thus, manipulations based on enhancement of surface area or solubility could be opted

for to enhance the dissolution rates of poorly soluble drugs. One such useful approach is to make fibrous solid dispersions of a hydrophobic drug in a hydrophilic carrier [6,7]. The enormous surface area is the main contributing factor to the high dissolution rates of these microfibers [8]. This fabrication of solid dispersions into microfibers with increased surface areas is a developing drift in the pharma industry.

Several fiber generation techniques are mentioned in the literature such as melt blowing [9], phase separation, bicomponent fiber spinning, template synthesis, electrospinning [10], self-assembly and hydrogel formation [11]. Low production rates, 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 rates and low costs [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 environmentally friendly. Fibers for the enhancement of dissolution rate were previously produced by electrospinning and used to load drugs such as diclofenac sodium, tetracycline hydrochloride [14] ibuprofen [15], meloxicam [16], indomethacin, and itraconazole [17] paracetamol/caffeine [18].

There are many recent studies which have focused on the development of drug loaded microfibers using the CS/CMS technique for the development of quick release formulation—e.g., the 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 (OXC) is a BCS class II, antiepileptic drug. 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 does not only act 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; additionally, in vivo studies of these formulation were carried out.

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) of analytical/pharmaceutical grade were used, as were HPLC grade methanol and acetonitrile trifluoro acetic acid (Duksan Pure Chemicals LTD.CO, Korea). Approval from an ethical committee to conduct in vivo studies in rabbits was also obtained.

2.2. Method

2.2.1. Preparation of Microfiber

A physical mixture of OXC and excipients (sucrose and PVP) in the ratio as given in Table 1 were prepared by mixing for 5 min using mortar and pestle. This mixture (~5 g) was transferred to the spinneret head of the 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 (stored for 3 months at 30 °C and 65 ± 5% humidity) were 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), the 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 the above criteria, PVP-K30 was selected as a polymer and sucrose as base to make OXC loaded nanofibers for this study.

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

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 the following equation and calculation was 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 a 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 a 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 the equation below.

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

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 a stopwatch.

Note: based on the 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 a 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 OXC, alone and in fibers (DSP20, fresh and aged), was assessed using a D8 Discover, (Bruker, Germany) diffractometer [23].

2.7. ATR-FTIR Spectroscopy

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

2.8. Thermal Characterization Using Differential Scanning Calorimetry

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

2.9. In Vitro Dissolution Studies

The dissolution rate of OXC alone and in its fibrous formulations and 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 the dissolution medium. Percentage of OXC released at each time interval (0.5, 1, 2, 4, 6, 10 min) was calculated using absorbance values from the UV spectrophotometer (Figure 1). All measurements were carried out in triplicate ($n = 3$) and the average values were reported.

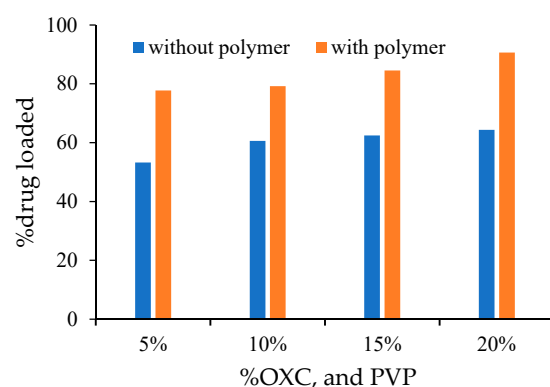


Figure 1. Percentage OXC loaded in different formulations with and without polymer.

2.10. Preparation and Characterization of Suitable Dosage Form

The formulation with optimal results, DSP20, was pressed into round-tablet-shape fibrous mats using a single die press (Carver press, Perkin Elmer, Waltham, MA, USA). These tablets were assayed for their OXC contents using HPLC and evaluated for their in vitro and in vivo dissolution release.

2.11. In Vivo Dissolution Studies (Salivary Method)

The 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 was placed in the oral cavity and they were asked to spit out the disintegrated tablet along with saliva at fixed time intervals (30, 60, 90 s) into calibrated bottles. The concentration of OXC in each saliva sample was 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 were 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 samples from the marginal

ear vein of rabbits were 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 $-20\text{ }^{\circ}\text{C}$ until analysis was carried out. Quantity of OXC in each sample was determined by using HPLC. OXC peak time and AUC were recorded. Calibration curves (r^2 , 0.9998) were constructed using spiked plasma solutions of known concentrations (0–100 $\mu\text{g/mL}$). Pharmacokinetic parameters were calculated from plasma level time curves obtained from HPLC.

2.13. Stability Studies (Aged Sample)

Freshly made microfibers (DSP20) and tablets were stored at $30 \pm 5\text{ }^{\circ}\text{C}$ at $65 \pm 5\%$ RH for 3 months. After this time period, fibers were evaluated again to study the effect of storage on drug release, amorphization, and morphology.

3. Results

3.1. Percentage Yield, Drug Loading and Disintegration Time

A percentage yield of up to 80% and drug loading efficiency up to $90 \pm 5\%$ were obtained with different OXC/excipient combinations (Table 1). Results showed that increasing the content of OXC in fibers without polymer increased the drug loading but decreased the yield. The highest drug loaded fibers were achieved with 20% of the drug. When PVP was added to this formulation, the concentration increased up to 20%, which improved the polymer properties to the desired level. The disintegration time of formulations (DSP5–DSP20) was 5 ± 1 seconds.

3.2. Morphology

SEM images of fresh (Figure 2) and aged fibers from DSP20 showed an intricate pattern of fiber distribution with average diameters 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].

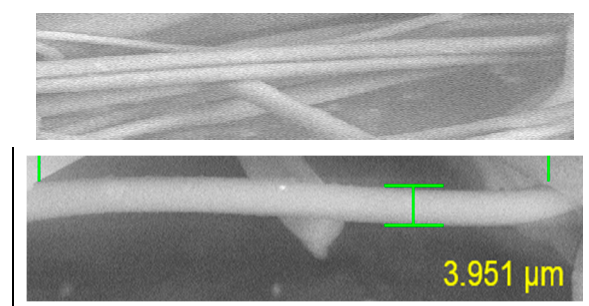


Figure 2. SEM images shows morphology of freshly prepared microfibers (DSP20).

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.

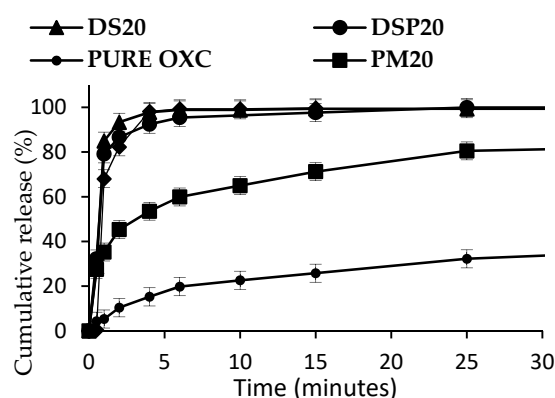


Figure 3. Dissolution profile of OXC, compared to formulations without fiber (DS20) with polymer (DSP20), physical mixture and its corresponding tablet.

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].

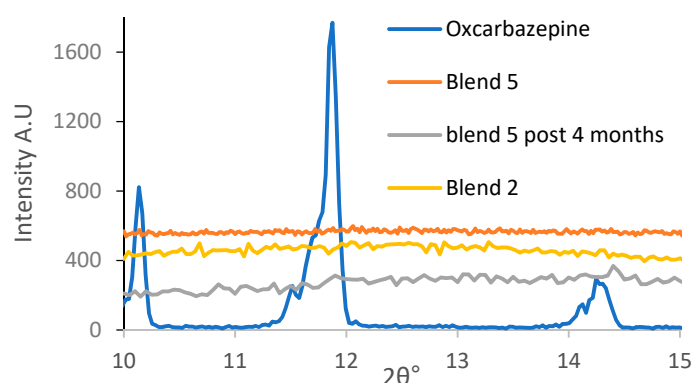


Figure 4. PXRD diffractograms of OXC and microfibers of fresh fibers DSP20, DS20 and aged fibers DSP20.

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 this.

3.7. Characterization of Tablet Dosage Form

Tablets molded out of fibrous mats had diameters of 12 ± 0.1 mm and thicknesses 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 $93 \pm 2\%$.

3.8. In Vivo Studies

Plasma level time curve obtained from HPLC analysis of rabbit plasma showed an early T_{max} and C_{max} 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.

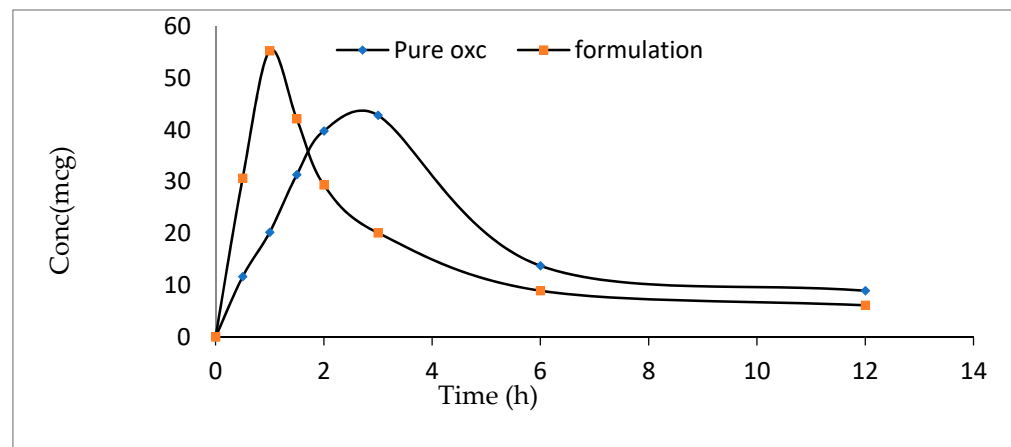


Figure 5. Plasma level time curve of rabbit plasma showing T_{max} and C_{max} after administration of OXC and OXC loaded fibers.

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 fibers lost their structures quickly. This instability of sucrose fibers was overcome by adding PVP which raised the T_g of physical mix [26]. The increase in yield after adding PVP in formulations DSP5-DSP20 was attributed to its plasticizing properties [27]. Increased drug loading was because PVP act as binder and provides an 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, the temperature was reduced to 180 °C to prevent burning. A slightly longer disintegration time in the oral cavity as compared to in vitro test was due to the lower volume and higher viscosity of saliva, which affected the wettability. No remarkable difference in the dissolution properties of the fibers, with and without polymer, was observed. This established the fact that a large surface area is responsible for enhanced dissolution. Amorphization is also a key feature which improved dissolution rate. A somewhat slow release from polymer incorporated fibers is attributed to new bonds between a drug and excipients as shown by FTIR spectra. In vivo studies strengthen the in vitro release studies by showing a remarkable difference of 2 ± 0.1 h in the T_{max} of fibers as compared to pure drug, thus proving the efficiency of these fibers in improving.

5. Conclusions

CMS proved to be a one-step, simple, and 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 the 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 maintains the ideal melt viscosity without burning the content was achieved.

Author Contributions: The idea was conceived by A.H.; experiments were conducted by S.N. and F.H.; data analysis was conducted by A.H., N.I.B., and N.A.; first draft was prepared by A.H., S.N., M.S.A. and N.A.; final review was conducted by J.M., A.A. and S.L. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: Permission from Bioethical committee, University of the Punjab to conduct in-vivo studies in humans and animals was obtained vide letter no. D/1674-A/UZ and D/1690-A/UZ, respectively.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy and publication of extended data afterwards.

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Conflicts of Interest: The authors declare no conflict of interest.

Abbreviations

OXC	Oxcarbazepine
BCS	Biopharmaceutical classification system
API	Active pharmaceutical ingredient
UV	Ultraviolet
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
t _{max}	Time to reach maximum concentration
C _{max}	Maximum concentration
AUC	Area under curve
CMS	Centrifugal melt spinning

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