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Fabrication and characterization of rizatriptan loaded pullulan nanofibers as oral fast-dissolving drug system

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Abstract

Fast drug-dissolving systems have been introduced to mediate the drugs which are difficult to swallow or having poor water solubility. Rizatriptan benzoate is a drug recommended for the patients of migraine which effect one out of every 5 women and 15 men globally. But least bioavailability (40%–50%) and reduced on set action always increases the demand of a drug carrier in order to overcome these limitations. Here in pullulan mediated fast drug-dissolving systems was developed by using rizatriptan benzoate as a model drug. While rizatriptan loaded pullulan nanofiber mat was prepared via electrospinning. Physiochemical outcomes (SEM, FTIR, and XRD) revealed good compatibility of pullulan nanofibers and rizatriptan thoroughly distributed on electrospun NFs matrix. Wetting time (1 s) and dissolutions time (3 s) suggests burst release of the drug from the polymers matrix as dissolution time is directly proportional with release profile. Further, this was confirmed by UV-release profile studies and maximum release was found within 30 s. In vitro release kinetics were analyzed by fitting the results with higuchi and korsmeyer models.

Introduction

The demand for fast-dissolving drug delivery systems is growing to introduce new methods of rehabilitations [1, 2]. Difficulty in swallowing medicines by patients can lead to in-effective cure. In this case, FDD’S can be helpful remedy because not only FDD’s are easy to swallow but also additional benefits such as easy solubility of drug, feature of taking medicine without water, and extended half-life of existing drug makes them an ideal choice [3, 4].

As traditional pills must be porous in their physical structure in order for them to get wet easily and soak quickly in water, many techniques have already been introduced to combat this, i.e., spray drying, compaction, lyophilization, three-dimensional printing, sublimation, moisture treatment, ultrafast rapid-freezing and sintering etc [5–7]. Though considering the widespread use of FDD’s in the medical field, it is always desired to develop new strategies.

Migraine is a moderate severe headache which affects one out of every 5 women and 15 men worldwide [8]. The common symptoms of migraine are headache, feeling sick, being sick, fatigue and sensitivity to light and sound which can cause physical and mental disorder of patients [9]. Nonsteroidal anti-inflammatory have been reported to have potential to decrease pain, drop fever, and inhibits blood clots, however the pills of triptan clan have been frequently advised to treat severe and chronic migraine patients [10]. Rizatriptan benzoate of triptan...
family belongs to the class of drugs called Serotonin 5-HT-Receptor Agonists; Antimigraine Agents which is frequently prescribed for migraine therapy [11] because it has utmost efficiency and unveils shortest $T_{\text{max}}$, resulting quick relief to the migraine patients. The prescribed amount of rizatriptan for adults is 5 to 10 mg [11]. However, monoamine oxidase A isoenzyme (MOA-S) speeds up the metabolism of Rb which results a limited bioavailability of the drug up to 40%–50% only. Furthermore, if Rb is taken with conventional pills, it slows down their onset of action [12]. Therefore, an appropriate drug-carrier will always be required to overcome the limitations of Rb treatment.

Nanotechnology and electrospun nanofibers have gained a new approach in controlled drug delivery systems including fast [13, 14], sustained release [15], biphasic release [16], and multiple-pulsatile release [17] that form most diseases owing to their high flexibility, porosity, and superficial and good mechanical features [18, 19]. Electrospinning is a viable top-down method to prepare a wide range of micro and Nano structured nonwoven polymeric mats [20]. Ultra-low fiber diameter owned high surface area, which can be suitable for controlled drug delivery systems with required features. The drug must be well mixed with the electrospun polymeric solution in such a way that the drug does not lose its properties [21]. In recent years, electrospun nanofibers are well known for controlled anticancer drugs delivery due to feasible binding characteristics between polymer and drug. The US Food and Drug Administration (FDA) and other drug agencies have approved numerous nano structural therapies that contain the drug. Therefore, a good market is estimated with the increased demand of these developments [22]. There are numerous electrospinning systems has been introduced including single-fluid [23], side by side [24], coaxial [25], triaxial [26], and other complicated blending systems [27]. Fibers with single-fluid structures are a good suggestion to solve the FDD’s problem [28]. The single-fluid electrospinning is a simple, cost effective and single-step technique that allows fibers with controlled fibrous morphology for safe drug release.

Many water-soluble natural and synthetistic polymeric mats, prepared via electrospinning, have long been used as FDD’s. The polymers used in biomedical applications should be bio-compatible and bio-degradable. Polysaccharides have been extensively used as a bio-material due to its promising properties of stability, biocompatibility, biodegradability, abundance, and Non-noxiousness [29]. Pullulan is an extracellular and microbial polysaccharide having a basic structure of linear glucan which are made up of three glucose units in a-[1, 4] maltotriose linked in a-[1, 6] manner [30]. Exceptional properties of high water-solubility, biocompatibility, biodegradability, thermal stability and non-toxicity makes pullulan an ideal carrier for FDDs. Inspired to its unique properties, herein, drug-loading capacity and fast drug-dissolving potential of pullulan electrospun nanofiber mats was assessed. Rizatriptan- an anti-migraine drug was loaded as a model drug which is extensively used against migraine attacks and due to its lesser bioavailability (30 to 40%) and lower on set action it is always advisable to over-come the limitations of said drug by using suitable drug-carriers.

**Experimental section**

**Materials**

Pullulan ($M_w = 200,000$) was supplied by Tianjin Beiyaang bacc the biological Co. Ltd China, Rizatriptan benzoate (saturated solubility 42 mg ml$^{-1}$) was kindly supplied by Heibei Ausun Gaobo, Pharmaceutical Co. Ltd (Heibeii, China) and PBS buffer was purchased from Sino pharm Group of chemical reagents, China. Ultra-pure water was used during all experiments.

**Fabrication of rizatriptan loaded pullulan nanofibers**

The fabrication of rizatriptan load pullulan nanofibers was carried out by electrospinning method as illustrated in figure 1. A 20% (w/w) of pullulan polymer was dissolved in ultra-pure water and stirred at room temperature for about 24 h. After solution appears homogeneous, a 20% rizatriptan (on polymer weight) was loaded to assess the drug release behavior with pullulan. The solution was kept stirrer further 4 h for well homogenized. For electrospinning, the obtained solutions were then poured into 10 ml syringe and keep flowrate of 0.8 ml h$^{-1}$. A 23 kV power supply was applied on metallic tip of syringe and 15 cm tip to collector distance was maintained. The nanofibers were collected on aluminum foil rapped on a rotary collector drum. An average 30 $\mu$m thickness pullulan/rizatriptan nanofibers were obtained for each further experiment.

**Assessment of Pullulan NFs aptitude as a carrier for FDDs**

Soaking time and disintegration test

A previously suggested method was followed to examine disintegration behavior of nanofibers [31]. Briefly, two layers of porous paper were moisturized with ultra-pure water and ensure papers were completely wetted. Later, neat pullulan and rizatriptan loaded pullulan nanofibers were retained on above wetted papers and disintegration behavior of samples was recorded at 40 frames per second with the help of a digital camera.
In vitro drug release profile

Drug release behavior of rizatriptan loaded samples was determined in order to examine its potential to categorize pullulan NFs as a suitable carrier for FDD’s. For this, a particular amount (25 mg) of rizatriptan loaded pullulan NFs were peeled from aluminum foil and immersed in DI water (40 ml) at a temperature of 37 °C and stirred at 250 rpm. After dissolution, the concentration of rizatriptan in the NFs was assessed by taking UV absorption peaks with the help of a UV-VIS photo spectrometer (Shimadzu UV2450, Japan) at an optical wavelength of 276 nm for different time scales (0 s, 10 s, 20 s to 100 sec) after being rinsed in DI water.

Material characterizations

Scanning electron microscope (JEOL model JSM 6020LA with an accelerating voltage of 30 kv and maximum magnification of 300,000) was used to assess the physical morphology of neat pullulan nanofibers and rizatriptan loaded pullulan nanofibers. Average diameter of samples was observed with the help of Image-J software. Similarly, chemical structure of samples was examined through Fourier Infrared spectroscopy (Thermo Nicolet 5700, Thermo Fisher Scientific Inc. USA). The crystal and amorphous region of samples were observed by examining them on XRD machine (model D/max-IIB, Rigaku).

Results and discussions

Physical and chemical structure

Figure 2 represents SEM images and fiber-diameter distribution of neat pullulan nanofibers and rizatriptan loaded pullulan NFs mats. It can be seen from figures 1(a) and (c) that neat pullulan and rizatriptan loaded pullulan NFs have a smooth and bead free fiber structure. The average diameter of neat pullulan nanofibers was found an average of 129 nm and average diameter was decreased in rizatriptan loaded pullulan NFs to 120 nm. This decrement in average nanofibers diameter is due to drug loaded in similar polymeric solution [32].

Figure 3 shows FT-IR results of samples observed within the range of 500 to 4000 cm−1. Characteristic peaks at 3359 cm−1, 2921 cm−1, 757 cm−1, and 1019 cm−1 were observed in the neat pullulan NFs mats. The stretching peak at 3359 cm−1 shows the presence of Hydroxyl (O−H) abundant groups within the structure of pullulan polymer. While peak between 2921 cm−1 indicates the stretching vibrations of CH2 (Alkenes) present in the structure of pullulan polymer. Whereas peaks at 757 cm−1 and 1019 cm−1 can be ascribed to α-(1,4) glycosidic bonds and α-(1,6) glycosidic bonds within the polymer structure respectively. These characteristics peaks are in well agreement with previously described FTIR spectra of pullulan polymer [33] and which proves that electrospinning doesn’t affect the chemical structure of pullulan polymer. Previous studies have identified that C==C stretching at 1579 cm−1, C=N stretching at 1517 cm−1, C−O stretching at 1233 cm−1, and C−N at 1180 cm−1 for rizatriptan benzoate drug [34] but all these characteristics peaks are missing in rizatriptan loaded pullulan NFs mats, which suggest that drug has not any chemical interaction within the polymers structure. Instead, drug only physically absorbed on the surface of the NF’s mats [35, 36].

The XRD analysis of pure drug (rizatriptan), neat pullulan and rizatriptan loaded pullulan nanofibers are shown in figure 4. The pure rizatriptan exhibited intense sharp peaks at 15.8°, 18.7°, 20.9°, 22.1°, and 24.9°, which is quite support with reported literature [36]. Neat Pullulan nanofibers showed a broad peak at 20.7° and this peak was slightly shifted towards 22.4° in rizatriptan loaded with pullulan nanofibers. This indicates the presence of drug with in nanofibers and both nanofibers confirms the amorphous morphology [28, 37].
Samples disintegration and drug release behavior

As presented in figure 5, the neat pullulan and rizatRIPTan loaded pullulan NFs mats lost their original form and turned in a gel-like nature within few seconds once put on the wet paper. The idea behind using wet paper was to parodist the moisture present in mouth. Hence, this indicates the high solubility of pullulan NFs [33]. And further, it also proposes that drug release profile is directly proportional with the time required for moisture to penetrate the membrane and high porosity of electrospun NFs enables fast diffusion of saliva into the pores in the oral cavity [31, 38].
Similarly, dissolution time of neat and rizatriptan loaded pullulan NFs mats is shown in figure 6. It can be seen that both neat and rizatriptan loaded pullulan NFs mats disappeared quickly and lost their original shape and white color after immersing in ultra-pure water. This sinking and dissolution time was hardly about 1 s and it was difficult to record the whole process with naked eye. Therefore, as drug release is directly dependent with dissolution time, it is anticipated that pullulan can be ascribed as a good carrier for FDDs.
Drug release proficiency
The drug release proficiency of rizatriptan loaded pullulan nanofibers mats is presented in figure 7. It can be seen, that more than 68% of rizatriptan released within first 10 s. After 30 s, it achieved an equilibrium, which means all the rizatriptan present in the pullulan nanofibers released within 30 s in the form of dissolution. The fast drug release profile or dissolution behavior of rizatriptan from the pullulan nanofibers is owing to the high penetrability of nanofibers which increases the rate of drug dissolution and high specific area of the nanofibers which facilitates high drug release [28]. Besides, excellent solubility and dissolution properties of pullulan nanofibers causes fast water molecule penetration within the mat and leads to disintegration of mat and promoting a very fast drug release [29]. However, rizatriptan was loaded during the solution preparation for electrospinning, thus it is anticipated that drug was homogenously distributed within nanofibers mat. Therefore, it is quite rational to accept that drug release rate is dependent of dissolution rate of the nanofibers mats and quick solubility of nanofibers resulted a burst release profile.

The release profiles of drug were further examined by fitting with Higuchi and Korsmeyer-–Peppas models to analyze the in vitro release kinetics [39]. The equations of Korsmeyer-–Peppas and Higuchi’s models are given as equations (1) and (2), respectively.

\[
\frac{M_t}{M_0} \times 100\% = kt^n
\]  

(1)

\[
\frac{M_t}{M_0} \times 100\% = k_1 t^{1/2}
\]  

(2)

Where, \(M_t\) and \(M_0\) are the masses of the drug releases at time \(t\), and at infinity time, respectively. \(K\) is constant, which defines the characteristics of the delivery system and the drug. \(n\) is the dissolution exponent, which provides release of drug from polymer matrices as a function of time, and further it defines the transport mechanism of the drug, and it is dependent on type of transport, geometry, and polydispersity. Similarly, \(K_1\) is the diffusion rate constant. The drug release was modeled on the mechanism of matrix dissolution. The data from the models fitted to Korsmeyer-–Peppas model and Higuchi’s model are presented in table 1. The regression rate of Korsmeyer-–Peppas is higher than the Higuchi’s model. The value of \(N\) is between 0.45 and 0.869 which indicates that the release mechanism is non-–fiction or anomalous transport. The overall release of the drug from
pullulan polymer is burst (30 s), but it follows the controlled manner, which can avoid the sudden release of drug into system, wastage and ineffectiveness of drug that may have therapeutic and economic effects.

**Conclusion**

This study belongs to assess the proficiency of electrospun pullulan nanofibers as a fast-dissolving drug delivery system. Rizatriptan (Anti-migraine drug) was loaded as a model drug. Physical morphology observed through SEM images suggests a bead free and smooth structure with an average fiber diameter 129 nm for neat pullulan nanofibers mats and average diameter of rizatriptan loaded pullulan NFs decreased to 93 nm which is due to drug loaded in similar polymeric solution. FTIR spectroscopy results concluded that the drug had no chemical interaction with the polymer but instead, drug physically absorbed on the surface of electrospun nanofibers. Further, XRD results revealed that the drug changed to amorphous form instead of maintaining its crystalline structure after loading with Pullulan Nanofibers. Disintegration, wetting potential and drug release profile later proved that pullulan is a promising material that can be used for fast drug delivery systems. 100 % drug releasing proficiency within 20 s encourages its need as a fast drug dissolving system. Further, whole mechanism of drug release was observed by fitting with higuchi and korsmeyer model to assess the in vitro release kinetics.

**Data availability statement**

All data that support the findings of this study are included within the article (and any supplementary files).

**Note**

The authors declare no competing financial interests.

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**Table 1.** Characteristic summary of kinetic models.

| Korsmeyer-Peppas’s kinetic model | Higuchi’s kinetic model |
|---------------------------------|------------------------|
| $N = 0.55$                      | $K_i = 0.26$           |
| $K = 1.23$                      | $R^2 = 0.983$          |
| $R^2 = 0.987$                   |                        |
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