SPRAY-DRIED CHITOSAN MICROSPHERES FOR SUSTAINED DELIVERY OF TRIFLUOPERAZINE HYDROCHLORIDE: FORMULATION AND IN VITRO EVALUATION

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ABSTRACT

Objective: Sustained release systems have the potential to enhance the therapeutic responses in the long-term management of psychiatric disorders. In the present study, cross-linked microspheres of the antipsychotic drug Trifluoperazine (TFP) were prepared using biodegradable polymer-chitosan and various in vitro evaluations were performed on the prepared microparticles.

Methods: The spray drying technique was used to prepare TFP-loaded chitosan microspheres. Tripolyphosphate (TPP) was incorporated into the chitosan solutions as a cross-linking agent in varying concentrations. Different evaluations like production yield, encapsulation efficiency, drug-polymer compatibility, Scanning Electron Microscopy (SEM), X-ray diffraction studies (XRD), Differential Scanning Colorimetry (DSC), particle size, zeta potential analysis and in vitro drug release studies were performed on the developed formulations.

Results: The formulated microspheres exhibited production yields ranging from 38.51 to 57.21% and had reasonably good encapsulation efficiencies (54.52-78.35%). The drug excipient compatibility was confirmed by Infrared Spectroscopy. All the microspheres showed positive zeta potential with a mean diameter ranging from 1.45-3.61 µm. SEM images revealed the formation of spherical particles with indentations on the surface. XRD and DSC studies confirmed the presence of an amorphous form of the drug inside the microspheres. The in vitro release profile of TFP from cross-linked chitosan microspheres was influenced considerably by changing the concentration of polymer and crosslinking agent in the formulation. The drug release from (0.5%) chitosan microspheres reduced from 91% to 79%, when TPP concentration was increased from 10% w/w to 30% w/w. All the formulations clearly showed a burst release of the drug in the initial hours and a subsequent sustained release profile.

Conclusion: The results of this study suggest that TPP crosslinked spray-dried chitosan microparticles could be a promising method for developing a long-acting drug delivery system intended to effectively treat schizophrenia.

Keywords: Trifluoperazine hydrochloride, Spray drying, Chitosan, Microparticles

INTRODUCTION

Schizophrenia is a complex, chronic mental health disorder characterized by a wide range of symptoms such as delusions, hallucinations, disorganized speech or behaviour and impaired cognitive function [1]. Antipsychotics or neuroleptics are tranquilizing drugs used primarily to manage psychosis, particularly in schizophrenia and bipolar disorders. Trifluoperazine (TFP) is the first-generation antipsychotic drug which has proved to be a potent phenothiazine derivative. Trifluoperazine has been considered effective and safe since the 1960s, making it one of the first-line drugs for patients in the acute phase of schizophrenia [2]. Even though several new classes of antipsychotics with fewer extrapyramidal side effects have emerged, TFP remains to be an inexpensive and widely used drug in the management of schizophrenia and anxiety. The drug is well absorbed from GIT, but it is reported to undergo extensive first-pass metabolism in the liver. As with most chronic illnesses, the treatment of psychiatric diseases frequently necessitates long-term treatment, and poor adherence to therapy is a major factor leading to sub-optimal treatment outcomes [3]. The psychological attitude of schizophrenic patients is generally negative and reluctant towards drug therapy leading to poor patient compliance. Recent trials demonstrate that new technologies that provide extended-release of drugs have the potential to enhance outcomes for challenging patients that generally require chronic therapy, notably schizophrenia [4]. Sustained release formulations can produce optimum therapeutic responses, prolonged efficacy, and reduced toxicity by generating a predictable and reproducible drug release rate for a prolonged time [5].

Microspheres are relatively more economical and less complicated technology that are prepared to achieve prolonged or controlled drug delivery, enhance bioavailability or stability and target drugs to specific sites [6]. Chitosan microspheres are among the most extensively studied drug delivery method for controlled drug release. Chitosan is a linear polysaccharide that consists of copolymers of glucosamine and N-acetyl glucosamine [7]. Being biodegradable, biocompatible and non-toxic, chitosan has been widely investigated in the formulation of particulate drug delivery systems to achieve controlled drug delivery [8, 9]. Chitosan microspheres can be prepared by several methods, among which the spray drying technique is widely used in the pharmaceutical industry [10]. Spray drying is a comparatively simple, rapid and reproducible method for microencapsulation [11]. This technique may be used with hydrophilic or hydrophobic polymers as well as with drugs that are either water-soluble or water-insoluble [12, 13]. Chitosan being a hydrophilic polymer undergoes rapid swelling in water and releases the entrapped drug quickly. Therefore the application of non-cross-linked chitosan microspheres in sustained drug release is limited [12, 14]. To increase the mechanical strength and prolong the drug delivery, chitosan needs to be cross-linked. TPF is a multivalent anion and non-toxic ionic cross-linker, which can create crosslinked networks with cationic chitosan [15]. Earlier studies have also reported that chitosan-TPF crosslinking improved drug entrapment efficiency and extended the drug release period [16].

In the present study, TFP-loaded chitosan microparticles were prepared by spray drying, employing TPF as a crosslinking agent. Various parameters of the developed formulations such as drug-excipient compatibility, surface morphology, drug encapsulation efficiency, practical yield, thermal analysis, particle size analysis and in vitro drug release profiles were studied in detail. The potential of the developed chitosan microspheres for sustained delivery of TFP was investigated.
MATERIALS AND METHODS

Materials

Trifluoperazine dihydrochloride was purchased from Tokyo Chemical Industry, Japan. Medium molecular weight chitosan (deacetylation 75-85 %, viscosity 200-800 cps) was procured from Sigma-Aldrich Chemicals, Bangalore, India. Ultrapure water (Direct-Q 3 UV water purification system) was utilized all through the study. All other chemicals and reagents were of analytical grade and used as received.

Methods

Preparation of TFP-loaded chitosan microspheres

The spray drying technique was used to prepare TFP-loaded chitosan microspheres using a laboratory-scale spray dryer with a standard 0.5 mm nozzle. The concentrations of chitosan and the cross-linking agent TPP, were varied as shown in table 1. The required amount of chitosan was dissolved in 1% v/v of glacial acetic acid after overnight swelling followed by magnetic stirring. The drug was dissolved in the chitosan solution at a concentration of 30% w/w of dry polymer weight, with continuous stirring. TPP (1% w/v in water) was added drop wise to the above solution with gentle magnetic stirring at concentrations of 10% w/w, 20% w/w and 30% w/w concerning the dry weight of chitosan. The solution turned opalescent during the addition of TPP due to crosslinking of chitosan.

The stirring was continued for 20 min and the suspension was spray-dried to obtain TFP-loaded cross-linked chitosan microspheres. The spray-drying is suggested as a rapid method for drying compounds which undergo degradation when dried in the slower classic drying processes. Usually, in a well-designed system, the passage of the sprayed particle through the drying zone takes only 15-30 s time. In a spray drier, the drying takes place almost instantaneously and the evaporation is so rapid that the droplet remains cool until the dry state is reached due to the absorption of heat for evaporating the solvent [17]. The optimum spray drying efficiency can be achieved from a balance of the amount of energy input and the amount of energy needed. The inlet temperature used should be higher than the boiling point of water which is 100 °C at standard conditions. It is relevant to mention the findings of He et al. [1996] here. According to their findings, the optimum inlet temperature for the preparation of chitosan microspheres from aqueous solutions was 160 °C. They reported incomplete solvent evaporation from the droplets and adherence of some liquid droplets to the wall of the drying chamber when the inlet temperature was set below 140 °C [18]. In the present study, air inlet temperature, air outlet temperature, and flow rate parameters for spray drying were set to 170 °C, 75 °C, and 3 ml/min, respectively. The prepared microparticles were stored in a desiccator until usage.

Characterization of TFP-chitosan microspheres

Production yield

The practical yield of the spray-dried microparticles was obtained by comparing the weight of microparticles recovered after spray drying with that of the theoretical weight (the sum of the weights of chitosan, trifluoperazine and TPP) in the suspension in a spray dryer.

Encapsulation efficiency (EE)

A predetermined quantity of TFP-loaded microspheres was accurately weighed and dissolved in 50 ml of 0.1 N HCl and kept in an ultrasonic bath to ensure complete solubilization. The solution was centrifuged, suitably diluted and the absorbance at 257 nm was determined spectrophotometrically. The EE was determined using the following equation.

\[
EE (%) = \left( \frac{\text{TFP extracted (mg)}}{\text{TFP theoretically present (mg)}} \right) \times 100
\]

Where TFP extracted is the amount of drug recovered from a known weight of drug-loaded microspheres, TFP theoretically present is the drug expected in an equivalent weight of microspheres. The entrapment efficiency was assessed in triplicate, and the findings are reported as mean±SD.

Infrared spectroscopy

Due to the high temperatures involved in the spray drying process even though for a short period, this technique entails a risk of drug degradation. Attenuated total reflection-infrared spectroscopy (ATR-IR) was used to assess the compatibility of TFP with excipients as well as the stability of the drug in the formulations. The IR spectra of neat TFP hydrochloride, chitosan and a physical mixture of drug and chitosan were recorded in the region of 4000-500 cm⁻¹ using Perkin Elmer Spectrum Two FT-IR Spectrometer and the spectra were compared with that of the drug-loaded microspheres.

Table 1: Preparation of TFP-loaded chitosan microspheres

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>TF-1</th>
<th>TF-2</th>
<th>TF-3</th>
<th>TF-4</th>
<th>TF-5</th>
<th>TF-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chitosan</td>
<td>0.5% w/v</td>
<td>200 ml</td>
<td>200 ml</td>
<td>200 ml</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>solution</td>
<td>0.8% w/v</td>
<td>----</td>
<td>----</td>
<td>----</td>
<td>200 ml</td>
<td>200 ml</td>
</tr>
<tr>
<td>Trifluoperazine (% of dry polymer weight)</td>
<td>30% w/w</td>
<td>30% w/w</td>
<td>30% w/w</td>
<td>30% w/w</td>
<td>30% w/w</td>
<td>30% w/w</td>
</tr>
<tr>
<td>TPP solution</td>
<td>10% w/w of chitosan</td>
<td>10% w/w of chitosan</td>
<td>10% w/w of chitosan</td>
<td>10% w/w of chitosan</td>
<td>10% w/w of chitosan</td>
<td>10% w/w of chitosan</td>
</tr>
</tbody>
</table>

Particle size and surface morphology

Using a field emission scanning electron microscope (FESEM), the chitosan TFP microspheres were analysed for shape and surface features [Jeol 6390LA, Japan]. The samples were previously mounted onto metal stubs using double-sided adhesive tape and gold-sputtered under vacuum for making the sample electrically conductive. The images were taken at an accelerating voltage of 20kV using various magnifications. The range of particle sizes of microparticles was identified through analysis of FESEM data.

Effective light scattering (light source: DPSS LASER 532 nm) using a nano particle analyser, Horiba SZ-100, Horiba Ltd, Japan. The TFP-chitosan microspheres were suspended in absolute ethanol to minimize the swelling and aggregation of the particles.

X-ray diffraction studies (XRD)

The physical state of the drug in a dosage form is a major factor that can influence the drug release profile and mechanism of drug release. The crystallinity of TFP in the spray-dried microspheres was analysed by XRD studies. The X-ray powder diffractogram of TFP, chitosan, and TFP-loaded microspheres was recorded using a (Bruker model D8 advance) diffractometer utilizing monochromatic copper K-alpha radiation at 35mA and a voltage of 40 kV. The samples were analysed at room temperature in a 2θ range angle of 2θ=60° with a scan step size set at 0.02°.

Differential scanning calorimetry (DSC)

Next TFP, chitosan and a physical mixture (1:1) of TFP and chitosan were subjected to thermal analysis using differential scanning calorimetry and compared with the DSC data obtained for the
prepared TFP-loaded microparticle formulations (Netzsch DSC 204 F1, Germany). Samples were sealed in aluminium pans and heated from 30 °C to 300 °C at a rate of 10 °C per min under nitrogen purge [19].

Evaluation of in vitro drug release

In vitro drug release studies of TFP-chitosan microparticles in phosphate buffer pH 7.4 were performed by dialysis technique using USP paddle-type dissolution apparatus. Dialysis bags (dialysis membrane-60, Hi-Media Laboratories, India) containing a 1 ml suspension of TFP-chitosan microspheres (equivalent to 10 mg of TFP) was attached horizontally to the paddle of the dissolution apparatus. The drug release study was carried out in 250 ml of dissolution medium maintained at a temperature of 37±2 °C with a paddle rotation speed of 75 rpm. At predetermined times, 5 ml samples were withdrawn from the release medium and replaced with an equal volume of fresh media to maintain sink condition. The samples were suitably diluted and analysed by measuring the absorbance at 257 nm.

RESULTS AND DISCUSSION

Preparation and characterization of TFP-chitosan microspheres

Spray-dried TFP-chitosan microspheres were prepared by using TPP as a cross-linking agent. The concentration of retarding polymer is an important parameter that governs the encapsulation and release of drugs from the particulate systems. In the present study, two different concentrations, 0.5% w/v and 0.8% w/v of chitosan solutions were used for the preparation of TFP-loaded microspheres. TPP is regarded as a safe alternative to aldehyde crosslinkers which may have a cytotoxic effect on cells if their residues are not completely removed [20]. TPP was incorporated as a 1% aqueous solution at three different concentrations (10% w/w, 20% w/w and 30% w/w of the dry weight of chitosan). The incorporation of crosslinking agent is essential as the uncontrolled water uptake and insufficient physical properties of chitosan are reported to limit its application in the development of modified drug release dosage forms [21]. Cross-linked chitosan microspheres are expected to give a more sustained drug release profile. Cross-linking of chitosan with TPP is also reported to improve the mechanical properties and stability of chitosan microspheres [22].

Characterization of TFP-chitosan microspheres

Spray-dried TFP-chitosan microspheres were subjected to various evaluations like production yield, particle size, zeta potential analysis and encapsulation efficiency and the obtained results are presented in table 2. The present study mainly focused to assess the effect of the concentration of chitosan and the crosslinking agent on different characteristics of the TFP microspheres. Hence the drug concentration and spray drying conditions were kept fixed for all the formulations. The production yields of TFP-microspheres produced were determined to be ranging from 38.51 to 57.21%. The spray drying technique often gives a relatively lower practical yield at the lab scale. As reported in the earlier studies, this lower practical yield is due to the low quantity of the feed used, adhering of powder to the cyclone separator wall and due to the formation of light fluffy particles that are not trapped by the aspirator of the machine [23]. The practical yield of microspheres was found to be increasing as the concentration of chitosan solution increased from 0.5% w/v to 0.8% w/v. The droplets with more polymer content upon drying, possibly form a large amount of denser particles which will be trapped by the aspirator of the machine.

The encapsulation efficiency (EE) of the spray-dried TFP-chitosan microspheres was found to be in the range of 54.52 to 78.35%. The results suggest that an increase in the concentration of chitosan solution leads to a slight decrease in EE of TFP microspheres. Even though more amount of polymer was available to entrap the drug, formulations developed with 0.8% chitosan displayed less EE compared to formulations with 0.5% chitosan, which was an unexpected result. This result, to some extent, is related to the high viscosity of the chitosan solution, which might have hindered the TPP crosslinking of the chitosan matrix resulting in the decreased entrapment of the drug within polymer droplets [23]. As the concentration of TPP increased from 10% to 30%, a significant decrease in EE of the spray-dried microspheres was observed. These findings are in concurrence with the previous literature reports on spray-dried chitosan microparticles. This may be due to the ionic interaction of the drug with the added negatively charged TPP leading to a reduction in drug loading with an increase in TPP concentration.

Zeta potential

The Zeta potential of the spray dried chitosan TFP microspheres was found to be in the range of +34.7 to +44.7 mV. All the formulations showed a positive net charge which is characteristic of chitosan microspheres. However, the positive charge on the particles was found to be decreasing as the concentration of TPP was increased, probably due to the adsorption of excess negatively charged TPP on the surface of the particles.

Table 2: The characteristics of TFP-chitosan microparticles

<table>
<thead>
<tr>
<th>Formulation code</th>
<th>Practical yield (%)</th>
<th>EE (%)</th>
<th>Mean particle size (µm)</th>
<th>Zeta potential (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TF-1</td>
<td>38.5±15.2</td>
<td>78.35±3.1</td>
<td>1.59±0.33</td>
<td>44.7±1.6</td>
</tr>
<tr>
<td>TF-2</td>
<td>42.78±3.7</td>
<td>70.26±2.8</td>
<td>1.45±0.13</td>
<td>44.1±0.7</td>
</tr>
<tr>
<td>TF-3</td>
<td>51.65±4.5</td>
<td>64.85±1.6</td>
<td>2.43±1.80</td>
<td>18.2±0.2</td>
</tr>
<tr>
<td>TF-4</td>
<td>44.39±4.9</td>
<td>67.48±2.7</td>
<td>3.45±0.55</td>
<td>44.7±1.5</td>
</tr>
<tr>
<td>TF-5</td>
<td>53.77±3.0</td>
<td>58.17±3.4</td>
<td>2.83±2.29</td>
<td>39.8±0.8</td>
</tr>
<tr>
<td>TF-6</td>
<td>57.21±2.7</td>
<td>54.52±1.8</td>
<td>3.61±2.48</td>
<td>34.7±0.4</td>
</tr>
</tbody>
</table>

*Data displayed as mean±SD (n=3)

Particles size distribution

The SEM images were examined to get an approximation of the particle size range of the spray dried TFP-chitosan microparticles. SEM images reveal the presence of a large amount of nearly spherical shaped particles as fines as 1-2 µ. The largest particle detected in the image was 9.9 µ. These findings were confirmed by size distribution analysis. The results of particle size distribution analysis by dynamic light scattering are given in fig. 1 and the mean particle sizes of the spray dried microspheres are shown in table 2. The concentration of chitosan was found to have an impact on microsphere size. An increase in chitosan concentration from 0.5 to 0.8 %w/v has led to an increase in mean particle diameter from 1 µ to 3 µ. This could be due to the high polymer concentration of the feed which was subjected to spray drying. High feed concentrations can cause an increase in viscosity, which can consequently lead to the formation of larger droplets and the production of larger sized particles during spray-drying. The samples TF-5 and TF-6 prepared with 0.8% chitosan has shown bimodal distribution, giving additional peaks with a mean particle diameter of 6.3 µ and 6.1 µ respectively. This confirms the formation of larger particles with an increase in polymer concentration. The microspheres of most samples were polydispersed, which is in agreement with previous studies on spray-dried chitosan [24].

Infrared spectroscopy

The possible physical or chemical interactions between the drug and polymer were investigated using ATR-FTIR spectroscopy. The IR spectra of TFP, chitosan and prepared TFP-chitosan microspheres TF-1 to TF-6 were recorded and compared for any spectral changes that happened during formulation (fig. 2). The IR spectra of TFP exhibited bands of CF3 symmetric stretching at 1108, 1143 and 1080 cm⁻¹; C-S stretching at 678 and 754 cm⁻¹ and a strong band due to C-N stretching...
at 1250 cm\(^{-1}\). The absorption band at 1316 cm\(^{-1}\) corresponds to C-CF\(_3\) stretching. The bands of aromatic C=C stretching vibrations were found at 1600, 1565 and 1470 cm\(^{-1}\) [25, 26].

The characteristic absorption peaks of chitosan were found in the region of 3270 and 3365 cm\(^{-1}\) that corresponds to N-H and O-H stretching vibration, as well as the intramolecular hydrogen bonds. The spectra also show absorption bands corresponding to residual N-acetyl groups at 1643, 1315, 1570 cm\(^{-1}\). C-H asymmetric stretching vibration at 2873 cm\(^{-1}\) and asymmetric stretching vibrations of the C-O-C bridge at 1151 cm\(^{-1}\). Skeletal vibrations of C-O stretching were observed at 1063 and 1028 cm\(^{-1}\) [27, 28].

On comparing the IR spectra of TFP and chitosan with that of the TFP-chitosan microspheres, we could find that the characteristic peaks of TFP are present in drug-loaded microspheres also with only minor variations implying effective loading of drug into the microspheres. The peaks of the chitosan were also evident in the spectrum of drug-loaded microparticles indicating that the drug was only physically encapsulated in chitosan microspheres. In the spectra of TFP-chitosan microspheres, no new bands were observed, confirming that no new chemical bonds between TFP and chitosan were formed during spray drying.

**Scanning electron microscopy**

SEM images of spray-dried TFP-chitosan microspheres are presented in fig. 3. All the microspheres appear as polydisperse particles with almost spherical shape and a smooth but slightly wrinkled surface. Deep indentations were produced probably due to the rapid drying of droplets during the spray-drying process. No pores or drug crystals were visible on the surface of the particles, suggesting effective entrapment of the drug within the chitosan matrix.

**X-ray diffraction studies**

X-ray diffraction patterns of the neat TFP, chitosan, physical mixture of drug with chitosan and TFP-chitosan microparticles were analysed to investigate the physical state of the drug in the polymeric matrix. The crystallinity of the encapsulated drug is an important factor that influences the drug release kinetics from the dosage form.
As given in fig. 4, the pure drug TFP is highly crystalline and shows sharp intense peaks in the diffraction pattern. The characteristic deflections of the crystal form of TFP were observed at(2θ) 15.4°, 15.7°, 20.5°, 20.7°, 21.7°, 22°, 23.6°, 26.2°, 27.7° and 32.5° [29]. A physical mixture of TFP, chitosan and TPP was also analysed which shows an XRD pattern with more intense reflections from the drug and TPP, though with less intensity. However, the characteristic reflections of TFP were completely absent in the diffraction pattern of TFP-chitosan microspheres, indicating that TFP formed a molecular dispersion in the chitosan matrix after spray drying. This result was in good agreement with previous reports on formulations based on drug-encapsulated chitosan microparticles entrapping drug as a molecular dispersion [30, 31].

**Differential scanning calorimetry**

 Thermal properties of the drug when incorporated into the formulation were studied by analysing the DSC thermograms of TFP, chitosan, physical mixture (TFP: chitosan 1:1) and spray-dried TFP-chitosan microspheres (TF-1 to TF-6).
chitosan microspheres. The graphs are shown in fig. 5. From the obtained thermogram of neat TFP, it is evident that the melting of TFP starts at approx. 240 °C giving a sharp endothermic peak at 250 °C [29, 32]. Chitosan being an amorphous polymer did not show any crystalline peak but a broad endothermic peak was present in the region of 100 °C. This peak may be due to the loss of water linked to chitosan during the heating process, as the chitosan polysaccharide has a strong affinity for residual water. The melting peak of TFP was observed in the physical mixtures also, indicating that the drug remains crystalline in the mixture. However, the endothermic peak of crystalline TFP disappeared in the DSC thermograms of spray-dried microspheres and only a broad peak near 100 °C due to water loss of chitosan was recognized. This result suggests that the drug has formed a molecular dispersion in the chitosan matrix and this observation was consistent with the XRD results where the characteristic deflections of the TFP disappeared in the diffractogram of spray-dried formulations. The powders produced from spray-drying are generally known to be amorphous in nature [28] and there are previous reports on different formulations based on chitosan where drugs were presented in molecular dispersions inside the polymer matrix [23].

**In vitro drug release studies**

The cumulative release curves of TFP from spray-dried chitosan microspheres (TF-1 to TF-6) are presented in Figure 6. The drug release study was carried out for 8h in pH 7.4 phosphate buffer. It was found that formulations TF-1 to TF-3 released 65.98, 60.71 and 41.55% of the loaded drug respectively, after 2h whereas TF-4 to TF-6 released 42.79, 36.36 and 31.66% of the drug respectively. The data clearly shows an apparent burst release of drug from all the formulations in the initial hours followed by a steady release of drug. Many previous reports suggest a bimodal drug release pattern with an initial burst release followed by sustained drug release from spray-dried chitosan microspheres [23, 33]. The influence of the chitosan concentration on the drug release was evident from the obtained graph. Comparing microspheres with 0.5% chitosan, formulations prepared with 0.8% chitosan clearly showed a more sustained release of TFP throughout the study. The batch TF-1(0.5% chitosan, 10%TPP) was found that formulations TF-1 to TF-3 released 65.98, 60.71 and 41.55% of the loaded drug respectively, after 2h whereas TF-4 to TF-6 released 42.79, 36.36 and 31.66% of the drug respectively. The data clearly shows an apparent burst release of drug from all the formulations in the initial hours followed by a steady release of drug. Many previous reports suggest a bimodal drug release pattern with an initial burst release followed by sustained drug release from spray-dried chitosan microspheres [23, 33]. The influence of the chitosan concentration on the drug release was evident from the obtained graph. Comparing microspheres with 0.5% chitosan, formulations prepared with 0.8% chitosan clearly showed a more sustained release of TFP throughout the study. The batch TF-1(0.5% chitosan, 10%TPP) released 91.64% of the drug in 8h, but when the concentration of chitosan increased to 0.8% (TF-4) with the same 10% cross linker concentration, the drug release was only 70.75% within 8h. This could be due to the formation of a relatively firm and denser polymer matrix upon interaction with TPP when an increased concentration of chitosan solution was used. The less swelling of such a denser polymer matrix would have decreased the drug release from microspheres with a high concentration of chitosan.

The concentration of cross-linking agent incorporated shows a considerable effect on TFP released. The release was slower when a higher concentration of TPP was used for crosslinking. With 0.5% chitosan formulations, the drug release at the end of 8h reduced from 91.64% to 79.5% when TPP concentration was increased from 10% to 30%. Such a decrease in TFP release was observed with microspheres prepared with 0.8% chitosan also. After 8 h, formulations TF-4 to TF-6 released 70.75, 62.98 and 58.49% of the drug respectively. It is evident from these results that increasing the cross linker concentration has a profound retarding effect on drug release from the chitosan matrix. The release of drugs from a microsphere depends on the rigidity of the polymeric matrix. When a high concentration of crosslinking agent has been used, the swelling capacity of the chitosan network decreases slowing down the drug release. As a comparison, a dissolution study of the plain drug enclosed in a dialysis bag was also carried out which released the drug in less than 1h. A close examination of the drug release profile reveals that the initial burst release of the drug has significantly reduced in formulations made with high chitosan concentration when cross-linked with TPP. Formulation TF-5 and TF-6 released only 26% and 24% of the drug in the initial 1 hr. This observation can be related to the previously observed decrease in encapsulation efficiency of microspheres with the increase in chitosan and TPP concentration. Formulations with less concentration of chitosan and TPP encapsulated more amount of the drug, some in the surface layers also, which will be released quickly in the initial hrs. When the concentration of chitosan and cross-linker increases in the formulation, the drug will be trapped inside a denser polymer network from which the drug release will be retarded.

**CONCLUSION**

In this study, sustained release microspheres of the antipsychotic drug TFP were successfully prepared by the spray drying process. The effects of the polymer chitosan and cross linker-TPP, on drug
release was investigated. The prepared formulations showed satisfactory drug loading, drug-excipient compatibility and a sustained drug release. The solid-state characterisation of the microspheres revealed the presence of the drug as a molecular dispersion within the chitosan matrix. The results of the present study demonstrated that the release of TFP from the microspheres could be effectively sustained by varying concentrations of polymer and cross linking agent.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFICT OF INTERESTS

The authors declare no conflict of interest.

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