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آموزش مهارت های کاربردی در تدوین و چاپ مقاله
Formulation and evaluation of olanzapine matrix pellets for controlled release

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Received 29 March 2011; Revised 14 Aug 2011; Accepted 15 Aug 2011

**ABSTRACT**

**Background and the purpose of the study:** Olanzapine is an antipsychotic used in treatment of schizophrenia. This research was carried out to design oral controlled release matrix pellets of water insoluble drug Olanzapine (OZ), using blend of Sodium Alginate (SA) and Glyceryl Palmito-Stearate (GPS) as matrix polymers, micro crystalline cellulose (MCC) as spheronizer enhancer and Sodium Lauryl Sulphate (SLS) as pore forming agent.

**Methods:** OZ formulations were developed by the pelletization technique by drug loaded pellets and characterized with regard to the drug content, size distribution, Scanning Electron Microscopy (SEM), Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR) and X-ray Diffraction study (XRD). Stability studies were carried out on the optimized formulation for a period of 90 days at 40 ± 2 °C and 75 ± 5% relative humidity.

**Results and major conclusion:** The drug content was in the range of 93.34-98.12 %. The mean particle size of the drug loaded pellets was in the range 1024 to 1087µm. SEM photographs and calculated sphericity factor confirmed that the prepared formulations were spherical in nature. The compatibility between drug and polymers in the drug loaded pellets was confirmed by DSC and FTIR studies. Stability studies indicated that pellets are stable. XRD patterns revealed the crystalline nature of the pure OZ. Loose surface crystal study indicated that crystalline OZ is present in all formulations and more clear in formulation F5. Drug release was controlled for more than 24 hrs and mechanism of the drug release followed by Fickian diffusion. It may be concluded that F5 is an ideal formulation for once a day administration.

**Keywords:** Pelletization, Microporous membrane, Release kinetics, SEM.

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**INTRODUCTION**

In recent years a wide variety of newer oral drug delivery systems like controlled/sustained release dosage forms are designed and evaluated to overcome the limitations of conventional therapy. These products are able to maintain steady drug plasma levels for extended periods of time and as a result the variations of the drug levels in the blood are prevented and drug related side effects are minimized. Olanzapine (2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine) is a potential and most commonly used typical antipsychotic, for treatment of schizophrenia, acute mania in bipolar disorder, agitation associated with schizophrenia, and bipolar disorder (1, 2). The starting dose of OZ is a single evening dose of 10 mg and the usual maximum dose is 20 mg. It is practically insoluble in water and has only 60% oral bioavailability. Based upon individual patient characteristics dosage adjustments may be required (3).

OZ should be given in at least two doses along with an additional maintenance dose per day. Due to its low therapeutic index, the frequency of adverse effects may be dose related. A controlled release dosage form is preferable than the conventional one, because there is a considerable savings in nurses’ and pharmacists’ time. As demonstrated by pharmacokinetic studies on OZ, the ingestion of a single controlled release formulation is effective even when administered once a day. Some schizophrenic patients hide a conventional tablet under their tongues to avoid its daily dose for an atypical antipsychotic. Also schizophrenic patients with dysphagia are not able to swallow conventional OZ tablet (4). To overcome this problem an attempt was made to formulate and evaluate controlled release dosage forms of OZ by making matrix pellets to improve the solubility of OZ which in turn would lead to enhancement of the dissolution of OZ.

Evidences have shown in the recent years that hydrophilic and hydrophobic carriers materials have the physical properties suitable to prepare
gastro-resistant, biocompatible, biodegradable matrix pellets to release the entrapped drug in the intestinal lumen (5). In the present study, a novel extrusion/spheronization method was employed using inert hydrophilic and hydrophobic carrier materials and non-toxic solvents to load the drug into pellets. SA is a natural polymer that is very promising and has been widely exploited in pharmaceutical industry, because of its tailor made to suit the demands of applications (6). SA has the advantages of being non-toxic orally, high biocompatibility, and inability to reswell in acidic environment, whereas they easily reswell in an alkaline environment. So acid sensitive drugs incorporated into the beads would be protected from gastric juice. The chief characteristic of sodium alginate is impermeability to gastric juices and susceptibility to intestinal juices (7). Dispersion of finely divided poorly water soluble drug in hydrophilic and lipidic carriers is an interesting technique for the production of matrix pellets (8). Different methods have been applied for the preparation of lipidic matrix based pellets by extrusion/spheronization (9). The interest in pellets as dosage forms (filled into hard gelatin capsules or compressed into disintegrating tablets) has increased continuously.

A thorough literature search revealed a lack of information on combination of hydrophilic SA and hydrophobic (GPS) based pellets for controlled drug release, using spheronizer enhancer MCC and SLS (0.1% w/v) as a leachable pore forming and wetting agent. GPS act as an inert matrix and drug is released very slowly as compared to hydrodispersible, hydrophilic matrix gelucire 50/13 (10). GPS has been reported as a solidifier which controls the drug release, protects the hygroscopic substances and facilitates the incorporation of liposoluble active ingredients and preservative for lipids, oils, waxes and solvents (11). MCC has been incorporated in most formulations via extrusion-spheronisation, because it enhances the rheological properties of the wetted mass, resulting in good sphericity, low friability, high density and smooth surface for successful extrusion-spheronization (12). In the present study controlled release pellets were developed by extrusion-spheronization of OZ/SA/ GPS by addition of MCC with SLS to tailor drug release. The aim was to develop OZ suitable for once daily formulation and examine the influences of various process parameters on physicochemical properties of the pellets and drug release potential.

**MATERIAL AND METHODS**

**Materials**

Olanzapine was a gift sample from Microlabs, India. Sodium Alginate was a gift sample from F.M.C. International biopolymers, Ireland. GPS, SLS and microcrystalline cellulose were procured from Loba Chemie, India. Solvents and other chemicals were of analytical grade.

**Methods**

**Preparation of pellets**

The pellets were prepared by pelletization technique using extrusion/spheronization. OZ, SA, GPS and MCC were passed through sieve No. 40 prior to pelletization and mixed uniformly in a planetary mixer. The bubble free SLS (0.1% w/v) solution was added dropwise to the mixture and mixed for 30 min. The obtained dough mass was extruded using a screw extruder (1 mm orifice, Kalweka, India). The extrudates were immediately spheronized for 6 min at a rotational speed of 400 rpm and an air velocity of 1 kg/cm². The pellets were dried overnight at room temperature and cured at 40 °C for 24 hrs in a tray dryer (Kothari, India) (13).

**Micromeritic properties (13)**

Angle of repose (θ) was assessed to know the flowability of matrix pellets, by a fixed funnel method. Tap density and bulk density of the pellets was determined using tap density tester (TDT, Electrolab, India). Granule density of the pellets was determined by displacement method using petroleum ether. For the friability test, pellets of known mass were placed in a Roche Friability tester (Electro lab Friability tester, EF -2, India) and subjected to testing at 25 rpm for 4 min.

**Particle size analysis**

The particle sizes of drug loaded formulations were measured by an optical microscope (Olympus model, SZX-12) having resolution of 40X.

**Scanning electron microscopy analysis (SEM)**

The shape and surface characteristics were determined by scanning electron microscopy (model-LV 5600, Jeol, USA).

**Pellet Sphericity**

Photomicrographs were taken with a digital camera (Sony, DSC T-4010.Cyber shot, Japan) and were processed by the image analysis software (Digimizer, USA) to characterize each individual pellet by two-dimensional shape factor (eR)

\[ \varepsilon_R = \frac{2\pi r}{Pm-(b/l)^2} \]  

where \( r \) is the radius, \( Pm \) is the perimeter, \( l \) is the length and \( b \) is the width of the pellet (13).

**Internal pore structure**

To determine the internal pore structure, computed tomography CT scanner (Phoenixn nanotom-M,
GE-India) was used.

**Differential scanning calorimetry (DSC)**
The DSC scans of the samples were recorded using Du Pont thermal analyzer with 2010 DSC module in nitrogen atmosphere at a heating rate of 10 °C/min.

**Fourier transform- infrared spectroscopic analysis (FT-IR)**
Spectra were obtained by powder diffuse reflectance on a FTIR spectrophotometer (Shimadzu, Model 8400S, Japan) in the wave number region of 400-4000 cm⁻¹ using KBr pellet method.

**X-Ray Diffractometry**
X-ray diffraction patterns were recorded using X-ray diffractometer (Phillips PW 1710, Tokyo, Japan) with a copper target, voltage 40 Kv, current 30 MA at a scanning speed of 0.30 °C/min.

**Determination of drug content**
One hundred milligrams of pellets were dissolved in 100 ml of methanol. The resulting solution was analyzed spectrophotometrically at 274 nm (Shimadzu-1601, Japan) after suitable dilution with phosphate buffer (pH 7.4) (14).

**Loose Surface Crystal Study (LSC)**
One hundred milligrams of pellets was suspended in 100 ml of phosphate buffer (pH 7.4). The amount of drug was analyzed spectrophotometrically at 274 nm (14).

**In vitro drug release studies**
USP XXI dissolution apparatus, type II (Electrolab, TDT-06L, India) was employed to study the drug release. Drug loaded pellets equivalent to 10 mg of OZ, were taken in 900 ml of the dissolution medium (2 hrs in hydrochloric acid buffer (pH 1.2) and 22 hrs in phosphate buffer (pH 7.4)) at 37±0.5 °C and then were centrifuged at 100 rpm. The data, thus obtained was fit into Peppas model.

\[
\frac{M_t}{M_{\infty}} = Kt^n
\]

\[\frac{M_t}{M_{\infty}}\] is the fraction of drug released at time \(t\); \(K\) is the constant comprising structural and geometric characteristics of the formulation; and \(n\), the release exponent is a parameter that depends on the release mechanism.

\[
M_t/M_{\infty} = [1-8/\pi^2]\exp\left(-\pi^2Dt/4\delta^2\right) \text{ for } 0.4<\eta t/M\eta<1
\]

The diffusivity was calculated to measure diffusion of drug molecules from the pellets by using the above equation. \(D\) is the diffusivity and \(\delta\) is the average radius of pellets. A differential factor (\(f_d\)) and similarity factor (\(f_s\)) were calculated according to the following equations:

\[
f_d = \frac{\sum_{t=1}^{n} [R_t - T_t]}{\sum_{t=1}^{n} R_t} \times 100
\]

\[
f_s = 50 \log \left\{ \left[ 1 + \left( \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t) \right)^{0.5} \right] \times 100 \right\}
\]

where, \(n\) is number of point, \(R_t\) is dissolution value and \(T_t\) is time value ‘t’.

**Stability studies of pellets**
Pellets were filled into a hard gelatin capsules and sealed in an aluminum packaging. The studies were performed at 40±2 °C and 75±5% relative humidity (RH) for 90 days (Thermolab, India).

**RESULTS AND DISCUSSION**
The present method of preparation is quite different from that reported by Siepman et al (15) and examines the influence of various process parameters on physicochemical properties and drug release potential from pellets.

In the present study, optimized concentration of 20% w/w of SA, 5% w/w of GPS, 55% w/w of MCC and 0.1% w/v of SLS aqueous solution (as pore forming agent) was used to produce spherical pellets. It was found that when higher or lower concentrations of SA, GPS, MCC and SLS were used, the produced pellets were not spherical and not easy to distinguish as individual pellets (16). A spheronization speed of 400 rpm and residence time of 6 min was used to obtain reproducible and uniform sized pellets (Table 1). Particle size analysis data (Table 2) indicated that the prepared pellets were in the size range of 1024 to 1212 µm and 56.3-63.6% and of size fraction 1212 µm.

The values of angle of repose (\(\theta\)), tapped density, granule density, % Carr’s index and Hausner ratio (1.023 to 1.165) values indicated good flow potential for the prepared pellets. The friability of the OZ pellet formulations was found to be in the range 0.39-0.53%. Additionally, pellets which were cured at 40 °C for 24 hrs had good mechanical strength which may be due to sufficient moisture content (16).

SEM photomicrograph Fig. 1, showed that the pellets were spherical in nature and had a smooth surface when they cured after 24 hrs at 40 °C (17). From the photomicrograph image analysis, calculated Aspect Ratio (AR) and two-dimensional shape factor (eR) was found to be 1.03 and 0.89, respectively. The obtained AR and eR values of the pellets were closer to the value of 1, which confirmed that the prepared pellets were spherical in nature (18).

Nano CT-scanning of OZ loaded matrix pellets (F5) containing pore structure are presented in figure 2. The porosity and median pore diameter of the porous
pellets was found to be 42.5±0.6% and 0.7±0.3 µm, respectively.

Results of the FTIR studies (Fig. 3) showed peaks at 2932.10 cm⁻¹ due to C-H stretching, at 1586.10 cm⁻¹ due to C=C stretching, at 1559.21 cm⁻¹ due to C=N stretching, at 1225.78 cm⁻¹ due to N-H stretching, at 1033.96 cm⁻¹ due to O-H bending and at 745.88 cm⁻¹ due to C-S bending which are the characteristic bands for important functional group of pure drug and drug-loaded pellets. FTIR spectra showed that after successful encapsulation the characteristics bands of OZ were not altered and their positions had not changed, indicating no chemical interactions between the drug and excipients used.

XRD pattern of pure OZ showed principal peak at 20.87° and intense peaks at 8.48°, 18.22°, 19.69°, 21.39°, 23.84° and OZ loaded matrix pellets (F5) showed intense peaks at 20.95°, 8.58°, 19.85°, 21.45°, 22.21°, 23.89° as presented in figure 4. The diffractogram of OZ loaded matrix pellets (F5) showed broad peaks with low intensity, which may be attributed to the incorporation of OZ between parts of the crystal lattice of the SA, leading to a change in the degree of crystallinity of the OZ (19). OZ exhibited a sharp endothermic peak at 196.26 °C presented in figure 5. There was an endothermic peak of the drug at 193.19 °C in the drug OZ loaded matrix pellets (F5) which indicates that the drug is uniformly distributed in the pellets. Interestingly, drug content and drug encapsulation efficiency as is shown in table 2, increased by increase in pellets size (1024 to1212 µm) which might be due to increase in the relative surface area of the pellets (20).

Table 1. Optimization of process parameters for pelletization.

| Parameters          | Formulation | Parameters | Description of pellets |
|---------------------|-------------|------------|------------------------|
| OZ:SA:GPS:MCC (w/w%) |             |            | Rod shape and brittle  |
|                     | F1          | 20 : 01 : 39 | Egg shape and brittle |
|                     | F2          | 20 : 02 : 43 | Semi spherical and brittle |
|                     | F3          | 20 : 03 : 47 | Spherical and brittle |
|                     | F4          | 20 : 04 : 51 | Spherical and hard |
| Spheronomization speed | F5         | 20 : 05 : 55 | Spherical and hard |
| (rpm)               |             | 150        | Rod shape              |
|                     |             | 200        | Egg shape              |
|                     |             | 300        | Semi spherical         |
|                     |             | 400        | Spherical              |
| Spheronomization speed | F5         | 3          | Rod shape              |
| (time)              |             | 4          | Egg shape              |
|                     |             | 5          | Semi spherical         |
|                     |             | 6          | Spherical              |
| Yield (%)           | F1          | 92.5       | Rod shape and brittle  |
|                     | F2          | 93.1       | Egg shape and brittle  |
|                     | F3          | 94.9       | Spherical and hard     |
|                     | F4          | 95.5       | Spherical and brittle  |
|                     | F5          | 96.3       | Spherical and brittle  |

aOZ=Olanzapine, SA=Sodium alginate, GPS=Glyceryl palmito-stearate, MCC=Microcrystalline cellulose

Table 2. Yield, size distribution, micromeric properties, friability drug loading and encapsulation efficiency of pellets.

| No. | Yield (%) | Average size (µm) | Angle of repose θ | Tapped density (g/cm³) | Granule density (g/cm³) | Carr’s index (%) | Hausner ratio (%) | Friability (%) | Drug loading (mg) | Encapsulation efficiency (%) |
|-----|-----------|-------------------|-------------------|------------------------|-------------------------|-------------------|------------------|---------------|-------------------|-----------------------------|
| F1  | 91.22     | 1024              | 27.23             | 0.821                  | 1.024                   | 8.91              | 1.023            | 0.39          | 16.23             | 95.13                       |
| F2  | 92.80     | 1087              | 26.12             | 0.854                  | 1.056                   | 8.65              | 1.165            | 0.42          | 16.65             | 95.89                       |
| F3  | 93.12     | 1134              | 25.13             | 0.828                  | 1.054                   | 8.45              | 1.145            | 0.45          | 17.43             | 96.32                       |
| F4  | 94.45     | 1189              | 26.43             | 0.873                  | 1.076                   | 8.78              | 1.098            | 0.49          | 17.96             | 96.78                       |
| F5  | 96.76     | 1212              | 26.23             | 0.896                  | 1.032                   | 9.56              | 1.123            | 0.53          | 18.43             | 97.42                       |
The amount of surface drug determined by loose surface crystal study was found to be minimal (1.2-2.8%) (13).

In vitro release studies indicated that higher amount of OZ was released from formulation F5 (96.23%) and Olanex® 10 mg tablet (97.12%) as compared to all other formulations, F1 (85.34%), F2 (86.23%), F3 (87.98%) and F4 (88.78%). This result clearly indicates that lower drug was released for the systems containing higher content of SA. Because SA particles are highly water swellable forms leading to higher viscosity, it retards the penetration of dissolution media into pellets, thus limiting the drug release from pellets (21).

The rate of drug release followed first order kinetics and numerical data fitted into Peppas’ equation. Statistically estimated values of n of the drug from pellets at 95 % confidence limit, was in the range 0.32 to 0.40 for formulations F1-F5 and 0.40 for Olanex®-10 mg tablet, indicating that the drug was Fickian diffusion. The obtained correlation coefficient, R² for the OZ loaded pellets was in the range of 0.979-0.998 and the same result was obtained for Olanex®-10 mg tablet (0.997).

The drug release profiles of the optimized formulation F5 compared with oral formulation Olanex®-10 mg tablet shown in figure 6 indicates that the drug release from formulation F5 pellets is controlled much better than the commercially available product Olanex®-10 mg tablet.

The differential factor (f₁) and similarity factor (f₂) obtained from dissolution profile indicates that the formulation F5 (9.12, 9.56) and Olanex®-10 mg tablet (78.34, 79.13) were similar.
Diffusivity values of all formulations were in the range of 0.39 to 0.83 cm²/s. The diffusivity values of formulations F1 (0.39 cm²/s) and F2 (0.43 cm²/s) were quite low, due to lower amount of GPS, MCC and higher amount of SA, resulting in less diffusivity of drug in aqueous media. On the other hand, the diffusivity values for formulations F3 (0.54 cm²/s), F4 (0.65 cm²/s) and F5 (0.83 cm²/s) were higher due to higher ratios of GPS, MCC and lower ratio of SA which allowed the drug to diffuse easily.

There was no significant change in the drug content (Table 3) from the pellets during stability studies, which indicates that formulation F5 exhibited good stability during investigation period.

**CONCLUSIONS**

The objective of the study was to prepare and evaluate OZ loaded pellets by extrusion/spheronization for controlled release. The method which was employed...
is simple, rapid, economical and did not require the use of toxic solvents. Pellets containing a pore forming agent, aqueous SLS, formed micropores on the surface. The results of micromeritic properties, hausner ratio and friability of the pellets were well within the limit, which indicated good flow potential for the prepared pellets. Drug loaded pellets were spherical in nature as evidenced by SEM photomicrographs and sphericity studies. From the FTIR and DSC studies, it was observed that there was no chemical interaction between the used drug and polymers indicating that drug was in stable form. X-ray diffraction patterns revealed the crystalline nature of pure OZ. The drug content study revealed uniform distribution of the drug in the pellets. The results of in vitro drug release showed the order of formulation F5 > F4 > F3 > F2 > F1. The drug release rate varied among the formulations depending on the compositions of polymers used. The obtained dissolution data indicated that the drug release follows fickian diffusion. Optimized formulation F5 and marketed product Olanex®-10 mg tablet showed similarity in drug release profile. Formulation F5 is an ideal formulation for once daily administration. From the present work, it may be concluded that the prepared matrix pellets demonstrate the potential use of SA/GPS/MCC blend for the development of controlled drug delivery systems for many water insoluble drugs.

| Sampling time (days) | Drug content (\\% ) |
|----------------------|----------------------|
| 00                   | 97.42±0.56           |
| 15                   | 97.41±0.52           |
| 45                   | 97.38±0.68           |
| 90                   | 97.37±0.69           |

*mean±standard deviation, n=3

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آموزش مهارت های کاربردی در تدوین و چاپ مقاله