Development and evaluation of indomethacin matrix pellets for controlled release

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ABSTRACT
This research work was done to design oral controlled release matrix pellets of water insoluble drug Indomethacin (IM), using blend of Hydroxypropyl cellulose (HPC) and glyceryl palmito stearate (GPS) as matrix polymer, methyl crystalline cellulose (MCC) as spheronomizer enhancer, sodium lauryl sulphate (SLS) as pore forming agent. Drug loaded pellets were characterized with regard to the drug content, size distribution, and pellets were further characterize by 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 forulation for a period of 90 d 40 ± 2 °C and 75 ± 5% relative humidity. It was found that drug content was in the range of 92.11 to 97.45 %. The mean particle size of drug loaded pellets was in the range 1032 to 1176 μm. SEM photographs and calculated sphericity factor confirms that the prepared formulations were spherical in nature. The drug loaded pellets were stable, compatible, as confirmed by DSC and FTIR studies. XRD patterns revealed the crystalline nature of pure IM. The higher amount of IM released was observed from formulation A5 (97.12 %) and Microcid SR – 75mg capsule (98.43%) as compared to all other formulations and mechanism of drug release followed Fickian diffusion. It can be conclude that formulation A5 is an ideal formulation for once a day administration.

Introduction
In recent years, considerable attention has been focused on the development of novel drug delivery system (NDDS). The reason for this paradigm shift is that low development cost and time required for introducing a NDDS, as compared to new chemical entity. Among the various NDDS available in the market, oral controlled release system hold a major position because of ease of administration and better patient compliance

Indomethacin (IM) is a non-steroidal, anti-inflammatory agent with anti pyretic, analgesic properties. Now a days IM is widely used in the treatment of active stages of moderate to severe stages of rheumatoid arthritis.

Due to its narrow therapeutic index, the frequency of adverse effects is dose related. Considering the long therapeutic regimen of osteoarthritis therapy, the administration of IM may induce adverse side effects on gastro intestinal tract (GIT) as well as central nervous system (CNS), renal and cardiac systems. The occurrence of these adverse effects can be reduced by the use of controlled release formulations

In the present study, a novel extrusion/spheronization method was employed using inert hydrophilic and hydrophobic carrier’s material and non-toxic solvents to load the drug into pellets. Hydroxypropyl cellulose (HPC) is a derivative of cellulose with both water solubility and organic solubility. It is also used in formulations containing water-insoluble drugs. HPC exhibits controlled surface erosion that provides a constant delivery of poorly soluble drugs via multi-unit erosion matrix and drug release was found to be proportional to matrix erosion. Hence matrix erosion could be used to predict drug release.

GPS act as an inert matrix and drug released very slowly as compared to hydrodispersible, hydrophilic matrix gelucire 50/13. GPS reported as a solidifier, controls the drug release, protects the hygroscopic substances and facilitates the incorporation of liposolable active ingredients and preservative for lipids, oils, waxes and solvents.

MCC was incorporated in most formulations via extrusion-spheronisation, because it enhanced the rheological properties of the wetted mass, resulted good sphericity, low friability, high density and smooth surface for successful extrusion-spheronisation.

A thorough literature search revealed a lack of information on combination of hydrophilic HPC and hydrophobic glyceryl palmito stearate (GPS) based pellets for controlled drug release, using spheronizer enhancer MCC. Sodium lauryl sulphate (SLS) was used as a leachable pore forming and wetting agent. In the present study, we made an attempt to develop matrix pellets by extrusion-spheronization containing IM/HPC/GPS with addition of MCC with SLS to tailor drug release.

The aim was to develop matrix pellet formulation loaded with IM suitable for once daily and examine the influences of various process parameters on physicochemical properties of the pellets and drug release potential.
Material and methods

Materials

Indomethacin (IM) was a gift sample from Microlabs, India. Hydroxypropyl cellulose (HPC) fine particle sized Klucel® Pharm Hydroxypropylcellulose (HPC) grades EF (D50 typically 100 – 150 μm with a molecular weight of 50). Glyceryl palmito stearate (GPS- Precirol ATO 5), Sodium lauryl sulphate (SLS) and micro crystalline cellulose (MCC) were procured from Loba Chemie, Mumbai, India. Solvents and chemicals were of analytical grade.

Methods

Preparation of pellets

The pellets were prepared by pelletization technique using extrusion / spheronization. IM/HPC/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 the mixture and mixed for 30 min. The obtained good dough mass was extruded using a piston extruder (1 mm orifice, Kalweca, India). The extrudates were immediately spheronized for 5 min at a rotational speed of 450 rpm and an air velocity of 1 kg/cm². The pellets were dried over night at room temperature and cured at 35°C for 24 h in a fluid bed dryer (Kothari, India).

Particle size analysis

Particle sizes of drug loaded formulations were measurements by laser light diffractometry using a dry feeder (Malvern PS 2600c, Malvern Instruments, Malvern, UK) and calculating the median particle size (D50) and particle size distribution for 10% (D10) and 90% (D90) as well as the specific surface area of the powder. Each experiment was carried out in triplicate.

Micromeritic properties

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 were determined using tap density tester, friability test was performed on the pellets in a Roche Friability tester (Electro lab Friability tester, EF -2, India).

Scanning electron microscopy analysis (SEM)

The shape and surface characteristics were determined by scanning electron microscopy (model-LV 5600, Jeol, USA) and photomicrographs were recorded, by suitable magnification at room temperature.

Pellet Sphericity

Pellet sphericity was determined with a digital camera (Sony, DSC T-4010,Cyber shot, Japan). The obtained images were processed by image analysis software to characterize each individual pellet by mean Feret diameter (FD) (average of 180 calliper measurements with an angle of rotation of 1°). Aspect ratio (AR) (ratio of longest Feret diameter and its longest perpendicular diameter) and two-dimensional shape factor (eR)

\[ R = 2\pi Pm^{-1}(b/l)^2 \]  

where r is the radius, Pm the perimeter, l the length (longest Feret diameter) and b the width (longest perpendicular diameter to the longest Feret diameter) of the pellet.

Internal pore structure

To determine the internal pore structure of the pellets, computed tomography CT scanner (Phoenixx nanotom-M, GE-India) was used. Combining the data of the maximum inscribed diameter (d_max) and the equivalent diameter (d_e) provides information about the structure of the pores.

Differential scanning calorimetry (DSC)

DSC studies (Du Pont thermal analyzer with 2010 DSC module) were carried out to study the thermal behaviors of drug alone and mixture of drug and polymer. Calorimetric measurements were made with the help of an empty cell (high purity alpha alumina disc) as the reference. The instrument was calibrated using high purity indium metal as standard. The DSC scans of the samples were recorded in nitrogen atmosphere at a heating rate of 10 °C/min.

Fourier transform- infrared spectroscopic analysis (FT- IR)

FTIR spectra of pure drug, empty pellets and drug loaded pellets were obtained using KBr pellet method (applying pressure of 6000 kg/cm²). Spectral measurements were obtained by powder diffuse reflectance on a FTIR spectrophotometer (Shimadzu, Model 8400S, Japan).

X-ray diffractometry (XRD)

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

Determination of drug content

100 mg of drug loaded pellets were dissolved in 100 ml of methanol. The resulting IM concentrations were assayed using a fully validated high performance liquid chromatography with ultra violet detection (HPLC-UV) method⁶. Quantification was achieved by the measurement of the peak area ratio of the IM to the internal standard (metanamic acid). The HPLC system consisted of HPLC-Shimadzu (Tokyo, Japan) LC-6A model, fitted with a μ -Bondapack C18 (4.6 X 250 mm) column of particle size 5μm (Supelco, Bellefonte, PA). The flow rate was maintained at 1 μL/min, and the drug concentration was detected using a UV/visible detector (SPD- 6Av). The mobile phase consisted of 80% methanol and 0.02 M sodium acetate buffer (60:40 v/v). The pH of the acetate buffer was 3.6. The column was heated to 40 °C and wavelength of 320 nm was used. Calibration standards, controls, and samples were processed in batches.

Loose surface crystal study (LSC)

100 mg of drug loaded pellets were suspended in 100 ml of methanol. The samples were shaken vigorously for 15 min in a mechanical shaker. The amount of drug leached out from the surface was analyzed by HPLC-UV method.

In vitro drug release studies

USP XXI dissolution apparatus, type II was employed to study the percentage of drug release from various formulations prepared. Accurately weighed quantities of drug loaded pellets - 75mg equivalent to a commercial preparation – Microcid⁵ - 75mg capsule, of each batch were taken in 900 ml dissolution medium and drug release was studied ( 2 h in pH 1.2, hydrochloric acid buffer and 10 h in pH 7.2, phosphate buffer) at 100 rpm and at a temperature of 37±0.5 °C. 10 ml of samples were withdrawn periodically using guarded sample collectors at regular intervals (30 min for first 4 h and at 60 min intervals for the next 8 h) sample (10 ml) was withdrawn and replaced with same volume of fresh medium. The withdrawn sample was filtered through a 0.45μm membrane filter and after appropriate dilution estimated for IM concentration by HPLC – UV. Drug release data was analysed using PCP dissolution - V2 – 08 and Graph Pad Instat software. To study the drug release from polymeric blend ( HPC, GPS & MCC), drug release data in dissolution media were fitted to well known exponential
equation\(^{(10)}\) (Korsmyer – Peppas equation), which is often used to
describe the drug release behavior from polymeric systems.
\[ \frac{M_t}{M_f} = k t^n \]  
(7)
where, \(M_t / M_f\) is the drug released fraction at time \(t\), \(k\) is a
constant incorporating the structural and geometric
characteristics of the matrix pellets, \(n\) is the release exponent,
indicative of the drug release mechanism. In case of Fickian
release (diffusion controlled-release), the \(n\) has the limiting
values of 0.45 for release from sphericonic particles. A differential
factor \((f_1)\) and similarity factor \((f_2)\) were calculated from
dissolution data according to the following equations:
\[ f_1 = \frac{\sum_{i=1}^{n} (R_i - T_i)^2}{\sum_{i=1}^{n} R_i} \times 100 \]  
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\[ f_2 = 50 \log \left\{ \left[ 1 + \left( \frac{1}{n} \right)^n \sum_{i=1}^{n} (R_i - T_i)^2 \right]^{-0.5} \times 100 \right\} \]  
9
where, \(f_1\) - differential factor, \(f_2\) - similarity factor, \(n\) – number of
time point, \(R_i\) – dissolution value of the reference at time, ‘\(t\)’
and \(T_i\) – dissolution value of test formulation at time ‘\(t\)’.
Differential factor, \(f_1\) was calculated by the percentage
difference between the two curves at each time point and
measured the relative error between the two curves. The
acceptable range for differential factor, \(f_1\) is 0 to 1.5.
The similarity factor, \(f_2\) was logarithmic reciprocal square root
transformation of the sum-squared error and is a measure of the
similarity in the percentage dissolution between the reference
and test products. If dissolution profile to be considered similar,
the values for \(f_2\) should be in the range 50 to 100.

**Stability studies of pellets**

Optimized drug contain pellets were kept for the accelerated
stability studies. Accurately weighed drug contain pellets
equivalent to 75 mg of IM were filled into a hard gelatin
capsules manually. Study was performed at 40 ± 2 °C and 75 ±
5% relative humidity (RH) for up to 90 days (Thermolab, India).
A visual inspection and drug content estimation was conducted
every 15 days for the entire period of stability study. Drug
content was estimated by HPLC – UV.

**Results and Discussion**

In the present study, blend of HPC, GPS & MCC
formulated as pellets by different ratio using non toxic solvent,
presented in Table 1. The present method is quite different from
reported method\(^1\). Present study examines the influences of
various process parameters on physicochemical properties and
drug release potential from pellets has been studied.

Incorporation of drug into different ratios of HPC blend
affects the physical appearance of the pellets was observed. In
the present study the formulation A5 having the optimum drug
and blend ratio (15: 20: 02: 63) were found to be suitable to
produce solid, discrete, spherical, free flowing pellets and
having a sufficient mechanical strength. It was found that the
higher the ratio of drug used (20, 30 and 40 % w/w) in HPC
blend, produced aggregate pellets masses which were unsuitable
for pharmaceutical uses.

In the present study, optimized concentration of 20 % w/w
of HPC was used to produce spherical pellets. It was found that
higher ratio of HPC (> 20 % w/w) or lowered ratio of HPC (< 20
% w/w) produces pellets were not spherical and not easy to
distinguish as individual pellets. To obtain optimal
concentrations of GPS, concentrations ranging from 2 to 10 %
w/w of the total formulations were investigated. In the present
study, optimum concentration of 02 % w/w of GPS was used to
produce better pellets.

In order to obtain optimal concentrations of pore forming
and wetting agent, various concentrations of aqueous solution of
SLS ranging from 0.05 to 0.09 % w/v of the total formulations
were investigated. It was found that 0.05 to 0.09 % of SLS failed
to produce required pores in the pellets. Optimum concentration
of 0.1 % w/v of SLS was used as pore forming agent in the
pellets and resultant pellets contained sufficient numbers of
pores. Incorparation of hydrophillic (HPC) into lipophilic (GPS)
polymer requires the addition of wetting agent at an optimum
concentration of aqueous solution of SLS (0.1 % w/w) to reduce
the interfacial tension between HPC and GPS. An attempt was
made to prepare wet mass without the addition of wetting agent.
But the process was failed and as it resulted, in an aggregate
cake like mass during the pellatization, may be due to repulsion
resulting between HPC and GPS. It was found that hydrophilic
and lipophilic balance (HLB) value of SLS is 40, and was found
to be more suitable to increase substantial dispersion of drug in
HPC/GPS blend. It was also noticed that aqueous solution of
SLS (0.1 % w/v) was used as wetting agent, produced pellets
were spherical, free flowing and free from surface irregularities.

The important factor that influences the size distribution
of pellets was the spherionization speed and residence time. A
spherionization speed of 450 rpm and residence time 6 min was
used to obtain reproducible and uniform sized pellets. As
increase in spherionization speed from 180 to 450 rpm, a change
in the shape and size of the pellets were noticed. When the
spherionization speed was 180, 260, 340, 400 rpm, rod, egg and
semi spherical shaped pellets were produced, respectively. When
the spherionization speed increased from 450 to 500 rpm, a
reduction in the average sizes and recovery yield of the pellets
was observed. Spherionization speed was lower than 450 rpm,
produced larger and irregular shaped pellets were not suitable
for pharmaceutical purpose. It was found that optimized
spherionization speed 450 rpm was suitable to produce discrete,
spherical, hard and free flowing solid pellets. Spherionization
time affects on the pellet shape and size (Table 1).

It was also found that an increase in spherionization
residence time from 2 to 6 min (at a stirring speed of 450 rpm)
resulted in changes in the shape and size of the pellets. From the
study, optimized spherionization time was found to be 6 min,
suitable to produce spherical, free flowing solid pellets having
sufficient mechanical strength. However, further increases in
spherionization time considerably affect the pellet shape and size.
Hence, to produce required shape and sizes of the pellets,
optimum spherionization speed (450 rpm) and spherionization
residence time (6 min) was used.

Sieve analysis data (Table 2) indicates that the prepared
pellets were in the size range of 1032 to176 µm, 92% of the
produced pellets were in the desired size. In the present study,
MCC posses a good extrusion aid at optimal concentration (63
% w/w) influence the mean diameter of the pellets. Due to good
binding properties of MCC, it provides cohesiveness to a wetted
mass, able to retain a large quantity of binding agent which
helps to provide large surface area and high internal porosity.
Hence the optimal concentration, 63 % w/w of MCC improved
the plasticity of wetted mass and enhancing spherionisation by
preventing phase separation, during extrusion spherionisation\(^2\).
Angle of repose ($\theta$) for the pellet was in the range 25.12 – 25.98 indicating good flow potential for the pellets. The measured tapped density (0.765 to 0.802 g/cm$^3$), granule density (1.023 to 1.063 g/cm$^3$), % Carr’s index (7.54 to 8.12%), and Hausner ratio (1.011 to 1.078), were well within the limits, which indicates good flow potential for the prepared pellets. Friability of pellet formulations were in the range of 0.29 - 0.55 % and it was in the expected range (less than 5% as per FDA specification). Friability of the pellets was found to increase as the ratio of MCC & GPS increased with decreased ratio of HPC (Table 2). When the pellets cured at 40°C for 24h, pellets exhibits good mechanical strength, it may be due to sufficient moisture content. As the curing temperature increases (45°C for 24 h), friability of the pellets found to decreases, because drop in residual moisture content in pellets. But pellets cured below 37°C for 24 h., produced pellets were dumbbell shaped with protruding surfaces (confirmed from SEM photomicrographs) and not suitable for pharmaceutical purpose.

SEM photomicrographs (Fig.1 a), showed that the pellets (formulation F5) were spherical in nature and had a smooth surface Fine pores were observed (F5) on the surface of the pellets (Fig.1 b).

The porosity and median pore diameter of the porous pellets was found to be 46.3 ± 0.3% and 0.6 ± 0.2µm, respectively. Equivalent diameter (387µm) of the detected one pore structure of a pellet was found to more than the maximum inscribed diameter (112µm). FTIR spectra for IM and formulation F5 is shown in Fig.3. The characteristic IR absorption peaks of IM compared the IR spectra at 3413 (aromatic C-H stretching), 2618 (carboxylic acid stretching), 1693 (C=O stretching), 1604 (aromatic C=C stretching), 1452 (O - CH$_3$ deformation) and 1236 cm$^{-1}$ (O-H deformation) were not alter after successful encapsulation of drug, indicating no chemical interactions between the drug and carriers used.

The X-ray diffractogram of IM loaded matrix pellets (A5) showed broad peaks with low intensity. This may be attributed to the incorporation of IM between parts of the crystal lattice of the HPC, leading to a change in the degree of crystallinity of the IM. X-RD pattern of pure IM showed principal peak at 22.1° and intense peaks at 10.3°, 11.8°, 12.9°, 16.9°, 22.1° 26.5 and IM loaded matrix pellets (A5) showed intense peaks at 10.2°, 11.7°, 12.7°, 16.5°, 22.2°, 26.6° as presented in Fig.4. X-ray diffraction patterns revealed the crystalline nature of pure IM. The X-ray diffractogram of IM showed number of sharp and intense peaks. The diffractogram of IM loaded matrix pellets (A5) showed broad peaks with low intensity. This may be attributed to the incorporation of IM between parts of the crystal lattice of the HPC, leading to a change in the degree of crystallinity of the IM.

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Figure 1. SEM photomicrographs of; (a) IM loaded pellets in spherical shape (F5), (b) IM loaded pellets showing surface pores (F5)

Surface inward dents and shrinkage were observed (collapse of the wall of the pellets ) when the pellets were cured at 24 h for 45°C, might be due to drop in residual moisture content from pellets during curing. Drug crystals were observed on the surface of pellets as a result of migration along with water to the surface during drying. This clearly indicates that influence of moisture content on surface morphology of the pellets.

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 and Feret diameter (FD) was 897µm. The obtained AR and eR values of the pellets nearer to the value 1, confirmed that the prepared pellets were spherical in nature and 92 % of the pellets were in the range of 1032 to1176 µm. Interestingly, pellets cured for 24 h at 40°C, sphericity values of the pellets nearer to the value 1, whereas pellets cured for 24 h at 45 °C, obtained sphericity values ranged between 1.20 -1.26 (pellets were shrunk and elongated form). The removal of residual moisture content from pellets during curing exerts an influence on the morphology of the final product.

Nano CT – scanning of IM loaded matrix pellets (A5) containing pore structure presented in Fig.2.

Figure 2. Nano CT - scan showing internal pore structure of a porous pellet (A5)
Drug content in all the formulations were in the range of 16.03 to 18.21% w/w. Drug content was least in formulation F1 (16.03 % w/w) and high for formulation A5 (18.21 % w/w). Drug encapsulation efficiency was found to be more in formulation A5 (97.54 % w/w) and less in formulation A1 (95.29 % w/w). Interestingly drug content and drug encapsulation efficiency increases with increasing in pellets size (1032 to 1176 µm). This might be due to increased relative surface area of the pellets, leads to more drug content and drug encapsulation efficiency.

**Figure 5. DSC thermograms of IM (peak A), and IM loaded matrix pellets A5 (peak B)**

Loose surface crystal (LSC) study is an important parameter giving indications of the amount of drug on the surface of the pellets. The microscopic study indicated that crystalline IM was observed in all formulation and more clear in formulation A5 (Drug content was 18.21 % w/w).

**Figure 6. Cumulative % release of olanzapine from matrix pellet (A5) (–) and Microcid SR® – 75mg capsule ( – ) in the intestinal environment against time**

*In vitro* release studies were carried out for the formulations in both acidic and basic media to stimulate *in vivo* conditions. Drug release from IM loaded pellets in a biphasic manner, consisting of initial fast release followed by a slow release. This result could be attributed to the dissolution of the drug present initially at the surface of the pellets and rapid penetration of dissolution media from the matrix structure. The higher amount of IM released was observed from formulation A5 (95.89 %) and Microcid SR® – 75mg capsule (97.56) as compared to all other formulations, A1 (86.12 %), A2 (86.68 %), A3 (87.63%) and A4 (88.35 %). This result clearly indicates that lowered drug release was noticed for the systems containing higher content of HPC. Because HPC particles are high water swellable forms leads to higher viscosity, retards the penetration of dissolution media into pellets, thus limiting the drug release from pellets. This typical behavior was commonly observed in diffusion controlled drug delivery systems. The order of drug release from the polymer based pellets was found to be A5 < A4 < A3 < A2 < A1.

Interestingly drug release profile obtained for formulation F5 indicated that it is an ideal formulation for administration for every 24 h, as it released 96 % of the embedded drug in 24 h. The obtained value of $t_{50%}$ for all formulations lies in the range of 4.87 to 5.4s and 5.43 h was noticed for Olanex® – 10 mg tablet.

The effect of curing of pellets at different temperature indomethacin release from HPC/GPS/MCC pellets was studied. Interestingly pellets cured at 40 °C for 24 h showed controlled drug release. Drug release upon curing at 40 °C (24 h) might be due to residual moisture content present in the pellets. This result indicates that the moisture present in the pellets reduces the cohesive force, which facilitates the wetting of pellets and increases the pellets disintegration (confirmed visually). Pellets cured above 45 °C for 24 h, showed the least drug release, due to least amount of residual moisture content present in the pellets responsible for low wettability. Drug contain pellets are softened and produced a denser structure, less permeable for dissolution media, delayed the disintegration of pellets (confirmed by visual observation). This result clearly indicates drug delivery from HPC/GPS/MCC pellets depends on curing conditions and moisture content.

The rate of drug release followed first order kinetics and numerical data fitted into Peppas’ equation. Statistically estimated values of n of drug from pellets at 95 % confidence limit, is in the range 0.32 to 0.40 for formulation F1 to F5 studied and 0.40 for Olanex® – 10 mg tablet, indicated that the drug release from the formulations F1 to F5 and Olanex® – 10 mg tablet was Fickian diffusion. In our experiments the result of ‘n’ clearly indicates that the diffusion is the dominant mechanism of drug release from these formulations. This is a good agreement with literature findings. The obtained correlation coefficient, $R^2$ for the OZ loaded pellets lies in the range of 0.979 – 0.998. The same result was noticed for Olanex® – 10 mg tablet (0.997).

Plot of the cumulative percent drug release as a function of time for formulation F5 and Olanex® – 10 mg tablet is shown in Fig 6. From the figure, it is evident that the drug release was controlled from formulation F5 pellets than the commercially available product Olanex® – 10 mg tablet.

Differential factor ($f_1$) and similarity ($f_2$) factor was calculated from dissolution profile and the results were compared to the formulation, F5 and Olanex® – 10 mg tablet. The differential factor ($f_1$) and similarity factor ($f_2$) 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 obtained in all the formulations were in the range of 0.39 to 0.83 cm²/s. It was observed that, the diffusivity values of trial 1 (without GPS) is quite high (1.28 cm²/s), since there is no barrier to control the drug release. The values of F1 (0.39 cm²/s) and F2 (0.43 cm²/s) are quite low, due to more amount of GPS and HPC and less amount of MCC, resulted in less diffusivity of drug in aqueous media. On the other hand, the diffusivity values for formulations F3 (0.54 cm²/s) and F4 (0.65 cm²/s) was slightly higher. This is due to fact that more ratio of MCC and less ratio of GPS and HPC, so the drug diffuses easily into the external environment. Formulation F5 (0.83 cm²/s), which showed optimum drug release during the *in vitro* dissolution studies, exhibited a higher
diffusivity. It also supports the fact that the drug is easily diffusible through the pores formed in the pellets membrane.

The optimized formulation F5 was subjected for accelerated stability studies as shown in Table 3. It was observed that, no significant change in the drug content from the pellets was observed. It is evident from the table that, formulations F5 exhibited good stability during investigation period, which indicates the drug was in stable form.

Conclusions

Objective of the study was to prepare and evaluate OZ loaded pellets by extrusion/spheronization for controlled release. Method employed was simple, rapid, economical and does not imply the use of toxic solvents. Pellets containing a pore forming agent, aqueous SLS, which forms micropores on the surface of the pellets. The results of micromeritic properties, hausner ratio and friability of the pellets were well within the limits, which indicates good flow potential for the prepared pellets. Drug loaded pellets exhibited 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 drug and polymers used indicating that the 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 drug release rates were found vary among the formulations depending on the compositions of polymers used. The obtained dissolution data indicated that the drug release through the microporous polymeric membrane 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 can 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.

References

Table 1. Formulation chart & description of process parameters for pelletization

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<tr>
<th>Formulation &amp; Parameters</th>
<th>Parameters</th>
<th>Description</th>
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<tbody>
<tr>
<td>A2 [IM:HPC:GPS:MCC w/w%]</td>
<td>15 : 26 : 08 : 51</td>
<td>Rod shape</td>
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<tr>
<td>A3 [IM:HPC:GPS:MCC w/w%]</td>
<td>15 : 24 : 06 : 55</td>
<td>Egg shape</td>
</tr>
<tr>
<td>A5 [IM:HPC:GPS:MCC w/w%]</td>
<td>15 : 20 : 02 : 63</td>
<td>Spherical</td>
</tr>
</tbody>
</table>

A5 & Spheronization speed (rpm)
- 180: Cylindrical shape
- 260: Rod shape
- 340: Egg shape
- 400: Semi spherical
- 450: Spherical

A5 & Spheronization time (min)
- 2: Cylindrical shape
- 3: Rod shape
- 4: Egg shape
- 5: Semi spherical
- 6: Spherical

<table>
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<tr>
<th>Formulation &amp; Parameters</th>
<th>Parameters</th>
<th>Description</th>
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<tr>
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<td>90.43</td>
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<td>A2</td>
<td>92.76</td>
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<td>A3</td>
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<td>A5</td>
<td>96.32</td>
<td>Spherical</td>
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Table 2. Yield, size distribution, micromeristic properties and friability of pellets

<table>
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<th>Formulation</th>
<th>Yield (%)</th>
<th>Average size (μm)</th>
<th>Angle of repose (°)</th>
<th>Tapped density (g/cm³)</th>
<th>Granule density (g/cm³)</th>
<th>Carr’s index (%)</th>
<th>Hausner ratio (%)</th>
<th>Friability (%)</th>
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<tbody>
<tr>
<td>F1</td>
<td>92.11</td>
<td>1032</td>
<td>25.12</td>
<td>0.765</td>
<td>1.023</td>
<td>7.54</td>
<td>1.011</td>
<td>0.29</td>
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<tr>
<td>F2</td>
<td>93.23</td>
<td>1078</td>
<td>25.32</td>
<td>0.732</td>
<td>1.043</td>
<td>7.65</td>
<td>1.065</td>
<td>0.36</td>
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<tr>
<td>F3</td>
<td>93.89</td>
<td>1108</td>
<td>25.45</td>
<td>0.798</td>
<td>1.048</td>
<td>7.45</td>
<td>1.034</td>
<td>0.41</td>
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<tr>
<td>F4</td>
<td>95.12</td>
<td>1154</td>
<td>25.87</td>
<td>0.803</td>
<td>1.056</td>
<td>7.98</td>
<td>1.045</td>
<td>0.47</td>
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<td>F5</td>
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<td>1176</td>
<td>25.98</td>
<td>0.802</td>
<td>1.063</td>
<td>8.12</td>
<td>1.078</td>
<td>0.55</td>
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</table>

*mean±standard deviation, n = 3

Table 3. Analytical results of pellets (F5) stability studies stored at 40°C and 75% RH

<table>
<thead>
<tr>
<th>Sampling time (days)</th>
<th>Drug content (%)</th>
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<tr>
<td>15</td>
<td>97.41</td>
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<td>45</td>
<td>97.38</td>
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<td>90</td>
<td>97.37</td>
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*mean±standard deviation, n = 3