Available online at www.elixirpublishers.com (Elixir International Journal)

Pharmacy

Elixir Pharmacy 46 (2012) 8248-8254

ISSN: 2229-712X

Development and evaluation of indomethacin matrix pellets for controlled release

A.S.AravindaRam[1], D.V. Gowda[2,*], Mohammed S.Khan[2] and B.Vishwanath[2]

[1]Farooquia College of Pharmacy, Umar Khayyam, Road, Mysore-570015, Karnataka, India.

[2]Department of Pharmaceutics, JSS College of Pharmacy, JSS University, Shri Shivarathreeshwara Nagar, Mysore - 570015, Karnataka, India.

ARTICLE INFO

Article history:

Received: 9 March 2012;

Received in revised form:

15 April 2012;

Accepted: 8 May 2012;

Keywords

Pelletization;

Indomethacin;

Microporous membrane;

Release kinetics.

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 spheronizer 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 calorimetrydsc), 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 d 40 ± 2 ^{o}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 11176 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[1]. Controlled drug delivery systems not only prolong the duration of action, but also result in predictable and reproducible drug release kinetics[2].

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[3]. 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[4]. The occurrence of these adverse effects can be reduced by the use of controlled release formulations[5].

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[6]. 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[7]. GPS reported as a solidifier, controls the drug release, protects the hygroscopic substances and facilitates the incorporation of liposoluble active ingredients and preservative for lipids, oils, waxes and solvents[14].

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 [8].

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.

Tele:

E-mail addresses: dvgowda4@gmail.com

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, Kalweka, India). The extrudates were immediately spheronized for 5 min at a rotational speed of 450 rpm and an air velocity of 1 kg/cm^2. The pellets were dried over night at room temperature and cured at 35^{o}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 (*e*R)

$$R=2\pi r/Pm-(b/l)^2 \quad (6)$$

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 (Phoenixn 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/cm^2). Spectral measurements were obtained by powder diffuse reflectance on a FTIR spectrophotometer (Shimadzu, Model 8400S, Japan).

X-ray diffractometery (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) method[9]. Quantification was achieved by the measurement of the peak area ratio of the IM to the internal standard (mefanamic 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 ^{o} 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 – Microcid®– 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 inetvals 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.

$$Mt / Mf = k\, t^n \quad (7)$$

where, Mt / Mf 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 sperricle particles. A differential factor (f_1) and similarity factor (f_2) were calculated from dissolution data according to the following equations;

$$f_1 = \frac{\sum_{t=1}^{n}(R_t - T_t)^2}{\sum_{t=1}^{n} R_t} \times 100 \quad 8$$

$$f_2 = 50 \log \left\{ \left[1 + \left(\frac{1}{n}\right) \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \quad 9$$

where, f_1 - differential factor, f_2 - similarity factor, n – number of time point, R_t – dissolution value of the reference at time, 't' and T_t - 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 to15. 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 ^oC 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[11]. 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, concentarions 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 concentarions of aqueous solution of SLS ranging from 0.05 to 0.09 % w/v of the total formulations were investgated. 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 spheronization speed and residence time. A spheronization speed of 450 rpm and residence time 6 min was used to obtain reproducible and uniform sized pellets. As increase in spheronization speed from 180 to 450 rpm, a change in the shape and size of the pellets were noticed. When the spheronization speed was 180, 260, 340, 400 rpm, rod, egg and semi spherical shaped pellets were produced, respectively. When the spheronization speed increased from 450 to 500 rpm, a reduction in the average sizes and recovery yield of the pellets was observed. Spheronization speed was lower than 450 rpm, produced larger and irregular shaped pellets were not suitable for pharmaceutical purpose. It was found that optimized spheronization speed 450 rpm was suitable to produce discrete, spherical, hard and free flowing solid pellets. Spheronization time affects on the pellet shape and size (Table 1).

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

Sieve analysis data (Table 2) indicates that the prepared pellets were in the size range of 1032 to1176 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 spheronisation by preventing phase separation, during extrusion spheronisation[12].

Angle of repose (θ^0) 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).

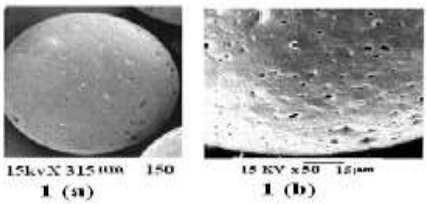

Figure 1. SEM photomicrographs of; (a) IM loaded pellets in spherical shape (F5), (b) IM loaded pellets showing surface pores (F5)

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[13].

From the photomicrograph image analys, calculated aspect ratio (AR) and two-dimensional shape factor (*e*R) was found to be 1.03 and 0.89, respectively and Feret diameter (FD) was 897µm. The obtained AR and *e*R 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 the 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 shrinked and elongated form). The removal of residual moisture content from pellets during curing exerts an influence on the morphology of the final product[14].

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

Figure 2. Nano CT – scan showing internal pore structure of a porous pellet (A5)

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 F_3 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.

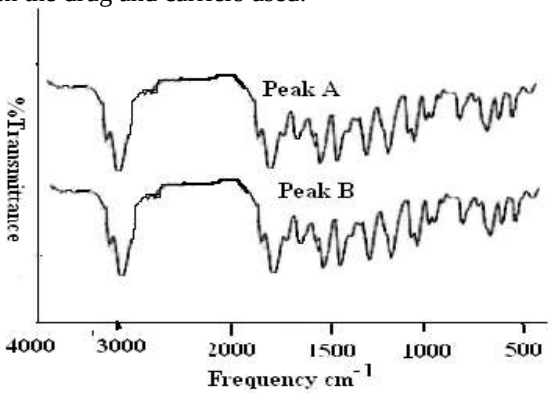

Figure 3. FTIR spectra of IM (peak A) and IM loaded matrix pellet (peak B – A5)

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[15].

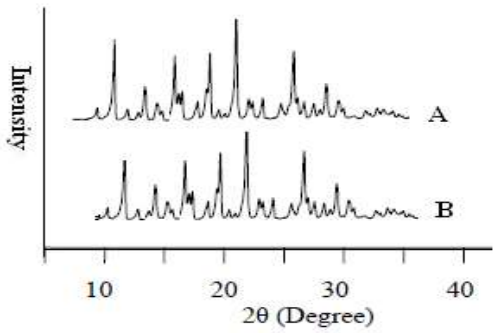

Figure 4. X-ray powder diffraction patterns of Pure drug IM (peak A) & IM loaded matrix pellet A5 (peak B).

DSC studies were performed on pure drug, empty and IM loaded matrix pellets (A5). IM exhibits a sharp endothermic peak at 161.7 ° C presented in Fig.5. It was observed that presence of a endothermic peak of the drug at 162.3° C in the drug IM loaded matrix pellets (A5) indicates, that the drug is uniformly distributed in the pellets. The peak intensity corresponding to the melting of IM decreased in the thermograms of IM loaded matrix pellets (A5). These results indicate that only a small fraction of the drug substance existed in the crystalline state.

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). Interstingly 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.

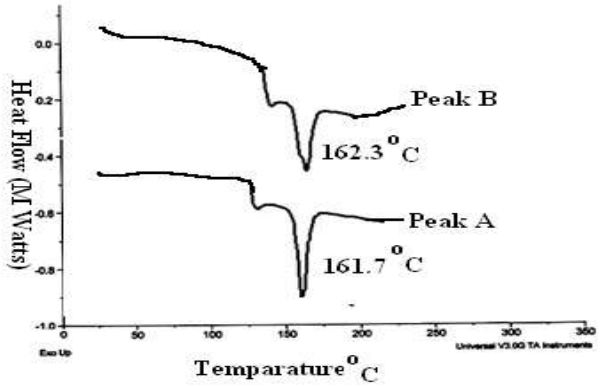

Figure 5. DSC thermograms of IM (peak A), and IM loaded matrix pellets A5 (peak B)

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) .

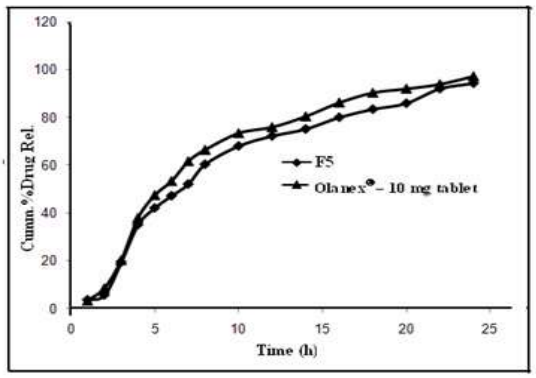

Figure 6. Cummulative % release of olanzapine from matrix pellet (A5) (—♦—) and Microcid SR®– 75mg capsule (▲) in the intestinal environment against time

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[16]. 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 5.54 h 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 ^{0}C for 24 h showed controlled drug release. Drug release upon curing at 40 ^{0}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 increased the pellets disintegration (confirmed visually). Pellets cured above 45 ^{0}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 [17]. 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 0.83cm^2/s. It was observed that, the diffusivity values of trial 1 (without GPS) is quite high (1.28cm^2/s), since there is no barrier to control the drug release. The values of F1 (0.39cm^2/s) and F2 (0.43cm^2/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 (0.54cm^2/s) and F4 (0.65cm^2/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 (0.83cm^2/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 ineraction between the drug and polymers used 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 drug release rate was 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 developoment of controlled drug delivery systems for many water insoluble drugs.

References

1. Berner, B.; Dinh, S. Fundamental concepts in controlled-release. In Treatise on Controlled Drug Delivery, Kydonieus, A., Ed.; Marcel Dekker: New York, 1992; 155-195.
2. Iqbal Z, Babar A, Muhammad A. Controlled-release Naproxen using micronized Ethyl Cellulose by wetgranulation and solid dispersion method. Drug Dev. Ind. Pharm.28 (2002) 129-134.
3. Bogdan M, Pirnau A, Floare C, Bugeal C. Binding interaction of indomethacin with human serum albumin. J Pharm Biomed Anal. 47 (2008) 981– 984.
4. Amir M, Kumar S. Anti-inflammatory and gastro sparing activity of some new indomethacin derivatives. Arch Pharm (Weinheim). 24 (2005) 338 - 344.
5. Tamivanan S, Sa B. Studies on *in vitro* release behavior of indomethacin loaded polystyrene microparticles. Int J Pharm. 201 (2000) 187– 197.
6. Rials TG, Glaser WG. Thermal and dynamic mechanical properties of hydroxy-propylcellulose films. J Appl Polym Sci. 36 (1988)749 -758.
7. Pongajanyakul T, Natalie J, Medlicott G. Ian Tucker. Melted glyceryl palmito stearate pellets for protein delivery. Int .J. Pharm., 271 (2004) 53–62.
8. Kleinebudde P. The crystallite-gel-model for microcrystalline cellulose in wet granulation, extrusion and spheronisation. Pharm. Res, 14 (1997) 804- 809.
9. Gowda D.V, Rajesh N, Afrasin Moin, Shivakumar H.G. Siddaramaiah. Controlled release behaviour of nifedipine from the pellets of gellucire/ microcrystalline cellulose blends. Int. J. Pharm Tech. Res, 2 (2010) 1215-1226.
10. Johnson AG, Roy JE. Improved HPLC method for the determination of indomethacin in plasma.Ther Drug Monit. 14 (1992) 61-65.
11. Koremeyer R, Peppas N, Gurny R. Mechanism of solute release from porous hydrophilic polymers. Int J Pharm. 15 (1983) 25 – 35.
12. Siepmann F, Muschert S, Flament MP, Leterme P, Gayot A, Siepmann A. Gelucire based matrix pellets: Experiment and Theory. Int. J. Pharm., 317 (2006) 136-143.
13. Basist A.W, Newton J.M, Lacey L.F.Formulation of ranitidine pellets by extrusion spheronization with or no microcrystalline cellulose. Pharm. Dev. Tech 2 (1999) 499 – 505.
14. Gowda D.V, GirishB, Shivakumar H.G, Afrasin Moin. Preparation and evaluation of carnaubawax microspheres loaded with aceclofenac for controlled release. Ind. J. Pharm. Educ. Res. 42 (2008) 329 - 336.
15. Sah H. Microencapsulation techniques using ethyl acetate as dispersed solvent effect its extraction rate on the characterstic of plga microspheres. JControl Rel. 7 (1997) 233 – 235.
16. Mahmoud El-Badry1, Gihan Fetih and Mohamed Fathy. Improvement of solubility and dissolution rate of indomethacin by solid dispersions in gelucire 50/13 and PEG 4000. Saudi Pharma J 17 (2009) 219 – 229.
17. Kyeo-Re Lee, Eun-Jung Kim, Sang-Wan Seo and Hoo-Kyun Choi. Effect of poloxamer on the dissolution of felodipine and preparation of controlled release matrix tablets containing felodipine. Arch Pharma Res 31 (2008) 1023-1028.

Table1. Formulation chart & description of process parameters for pelletization

Formulation & Parameters	Parameters	Description
A1 [IM:HPC:GPS:MCC w/w%]	15 : 28 : 10 : 47	Cylindrical shape
A2 [IM:HPC:GPS:MCC w/w%]	15 : 26 : 08 : 51	Rod shape
A3 [IM:HPC:GPS:MCC w/w%]	15 : 24 : 06 : 55	Egg shape
A4 [IM:HPC:GPS:MCC w/w%]	15 : 22 : 04 : 59	Semi spherical
A5 [IM:HPC:GPS:MCC w/w%]	15 : 20 : 02 : 63	Spherical
A5 & Spheronization speed (rpm)	180 260 340 400 450	Cylindrical shape Rod shape Egg shape Semi spherical Spherical
A5 & Spheronization time (min)	2 3 4 5 6	Cylindrical shape Rod shape Egg shape Semi spherical Spherical
Yield (%) A1	90.43	Cylindrical shape
Yield (%) A2	92.76	Rod shape
Yield (%) A3	93.54	Egg shape
Yield (%) A4	94.79	Semi spherical
Yield (%) A5	96.32	Spherical

Table 2. Yield, size distribution, micromeritic properties and friability of pellets

Formulation	Yield [a] (%)	Average size [a] (μm)	Angle of repose [a] θ^0	Tapped density [a] (g/cm^3)	Granule density [a] (g/cm^3)	Carr's index [a] (%)	Hausner ratio [a] (%)	Friability [a] (%)
F1	92.11	1032	25.12	0.765	1.023	7.54	1.011	0.29
F2	93.23	1078	25.32	0.732	1.043	7.65	1.065	0.36
F3	93.89	1108	25.45	0.798	1.048	7.45	1.034	0.41
F4	95.12	1154	25.87	0.803	1.056	7.98	1.045	0.47
F5	97.45	1176	25.98	0.802	1.063	8.12	1.078	0.55

[a] mean±standard deviation, n = 3

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

Sampling time (days)	Drug content [a] (%)
00	97.42
15	97.41
45	97.38
90	97.37

[a] mean±standard deviation, n = 3