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Controlled Release Behaviour of Nifedipine from the Pellets of Gelucire/Microcrystalline Cellulose Blends

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ABSTRACT: The aim of the present study was to prepare matrix pellets loaded nifedipine (NF) as model drug by pellitization technique by using blend of gelucire 50/13 (GL) and glyceryl palmito stearate (GPS) as hydrophilic and hydrophobic carriers in different concentrations. This system was able to prolong the drug release, minimizing the drug related adverse effects and improve bioavailability in different GI-tract conditions. The prepared formulations was subjected to micromeritic properties, SEM, DSC, FTIR and stability studies. The obtained microspheres having smooth surfaces, with free flowing and good packing properties, angle of repose, % Carr's index and tapped density values were within the limit. The drug loaded in microspheres was stable and compatible, as confirmed by DSC and FTIR studies. *In-vitro* drug release profile of NF from pellets was studied in simulated gastric fluid pH1.2 for initial 2h and in simulated gastric fluid pH 7.4 upto 22 h and compared with oral formulation Adalat CR® 20 capsule. The release of drug from the pellets showed negligible drug release in pH1.2. Under intestinal conditions resulting optimum level of drug released in a controlled manner and exhibited fickian diffusion.

Keywords:, Pelletization, nifedipine, hydrophillic and hydrophobic carrier, release kinetics.

INTRODUCTION

Development of controlled release drug delivery systems provide a uniform concentration or amount of drug at absorption site, maintained plasma concentration within a therapeutic range, minimizes the side effects and reduces the frequency of drug administration [1]. In the last decade, a considerable attention has been focused on the development of novel drug delivery systems because of their obvious advantages such as ease of administration, controlled releases of drug at slower predetermined rate, effectiveness in the treatment at chronic conditions and better patient convenience due to simplified dosing schedule. A number of design options are available for the preparation of controlled release formulations to modify oral absorption by matrix pellet [2].Pellets are defined as spherical, free-flowing granules with a narrow size distribution, typically varying between 500 and 1500 µm for pharmaceutical applications. The interest in pellets as dosage forms (filled into hard gelatin capsules or compressed into disintegrating tablets) has been increasing continuously, since their multiparticulate nature offers some important pharmacological as well as technological advantages over conventional single-unit solid dosage forms. Smaller sized pellets rapidly emptied from the stomach regardless of the feeding state of the patient and influence the gastric emptying rate on the upper gastro-intestinal transit time. Multi particulate unit dosage forms such as pellets, reduces the intra and inter-subject variability in gastric emptying times and exhibited easy distribution of the contents at gastrointestinal tract, compared to single-unit dosage forms. The uniform dispersion of a drug into pellets reduces the risk of high drug concentration, dose dumping and irritating effect on gastric mucosa.

Furthermore, drug absorption is maximised and peak plasma fluctuations are reduced. Pellet offers the possibility of combining several active components, incompatible drugs or drugs with different release profiles in the same dosage unit and easy to coat. Spherical shape of the pellets exhibited a good flow property which ensures narrow size distribution and good content uniformity [3].

Extrusion-spheronization is the more specific term usually associated with spherical units formed by size enlargement process, that includes a spheronization step, where extrudates or agglomerates are rounded as they tumble on rotating frictional base plate. Due to spheronization, spherical particles have optimal mean size, uniform size distribution, and spherical shape when compared with granules. The spherical pellets has good flowability [4], which allows accurate capsule filling with minimal unit dose variation, minimal friction avoids the dust formation, ability to withstand mechanical stress and desired drug release can be achieved from pellets. Many polymers are showed to be suitable as matrix forming agents, such as ethyl cellulose, poly (vinyl acetate) (PVAc), poly (acrylic acid) (PAA), partially hydrolyzed gelatin, polyvinyl pyrolidine (PVP), polyethylene glycol (PEG) and hydroxypropyl methyl cellulose (HPMC) which are providing desired drug release kinetics [5]. Pellets prepared by extrusion-spheronization using combination of glycerol monostearate (GM) and microcrystallinewax (MW), glycerolmonostearate and microcrystalline cellulose based pellets controlled the solubility of drug [6,7]. Lipids such as various grades of gelucires, waxes and maltodextrins offer great potential as matrix pellet formers [8]. The physicochemical nature of the polymer matrix determines the underlying drug release mechanisms. Various technologies were used to prepare lipidic matrix pellets [9-11]. NF is a calcium antagonist, widely used as a coronary dilator in hypertension and has a narrow margin of safety. It is necessary to prolong the plasma concentrations so as to control and regulate the therapeutic effects of Nifedipine over a longer duration. The drug is weakly basic (pKa = 3.93), photosensitive and poorly water soluble (5.6µg/ml in water at pH 7.0 in 37 °C). Low and irregular bioavailability following oral administration of nifedipine was reported and it has a short biological half-life of about 2-5 h [12]. Types and nature of the lipid was found strongly affect the drug release mechanisms [13,14]. Moreover, the drug administered thrice a day in a conventional dosage regime which consumes valuable time as far as the physician, patient and pharmacist concerned. When finely divided drug particles dispersed in lipid carriers, responsible for crystallization upon storage under humid condition was resulting in changes in drug dissolution and bioavailability [15]. Dispersion of finely devided poorly water soluble drug in lipidic carriers is an interesting technique for the production of matrix pellets. Different methods were applied for the preparation of lipidic matrix based pellets by extrusion – spheronization [16, 17]. A thorough literature search revealed a lack of information on combination of hydrophilic gelucire 50/13 and hydrophobic glyceryl palmito stearate based pellets for controlled drug release, using spheronizer enhancer MCC and tween 80 (0.5 % w/w) as leachable pore forming and wetting agent. Gelucire 50/13 is manufactured from vegetable and petrochemical origin, used as a excipient for hard gelatin capsule, bioavailability enhancer, increase the solubility and bioavailability of poorly soluble drugs, controls the drug release, protects the drug against oxidation and hydrolysis and suitable to handle toxic or low dose drugs [18]. Glyceryl palmito stearate act as an inert matrix and drug released very slowly as compared to hydrodispersible and hydrophilic matrix gelucire 50/13. Glyceryl palmito stearate 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 [19]. 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 [20, 21]. The objectives of the present study, was to develop controlled release oral product pellets of NF loaded with blend of GL, GPS and MCC with tween 80. Further, examines influences of various process parameters on physicochemical properties and drug release potential. In the proposed method pelletization by extrusion-spheronization, mixture of drug and polymer dispersion into aqueous solution, dough mass occurs instantaneously resulting to the formation of spherical sized pellets, with narrow particle size, high yield, low porosity and optimum controlled release in various physiological gastrointestinal conditions [22,23].

EXPERIMENTAL

MATERIALS

Nifedipine (NF) obtained as gift sample from Cadila Laboratory, Ahmedabad, India. Blocks of gelucire 50/13, glyceryl palmito stearate (GPS- Precirol ATO 5) and micro crystalline cellulose (MCC) were procured from Loba Chemie, Mumbai, India. Tween 80, other solvents and chemicals were of analytical grade.

Preparation of gelucire based matrix pellets by extrusion- spheronization method

The pellets were prepared by pelletization technique using extrusion / spheronization. NF, GL, GPS and MCC were passed through sieve No. 40 prior to pelletization and mixed uniformly in a planetary mixer. The buble free tween 80 (0.5 %) 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 750 rpm and an air velocity of 1 kg/cm^2. The pellets were dried over night at room temperature and cured at 40 ^{o}C for 24 h in a fluid bed dryer (Kothari, India).

Characterization and evaluation of pellets

Particle size analysis

The particle sizes of drug loaded formulations were measured [24] by an optical microscope fitted with an ocular and stage micrometer and particle size distribution was calculated. The Olympus model (SZX-12) having resolution of 40 x was used for this purpose. The instrument was calibrated at 1 unit of eyepiece micrometer was equal to 1/30mm (33.33µm). In all measurements at least 20 particles in five different fields were studied. Each experiment was carried out in triplicate.

Measurement of micromeritic properties, granule density and friability of pellets

The flow properties were investigated by measuring the angle of repose of drug loaded microbeads using fixed base cone method. Microbeads were allowed to fall freely through a funnel fixed at 1cm above the horizontal flat surface until the apex of the conical pile just touches to the tip of the funnel. The height and diameter of the cone was measured and angle of repose was calculated by using the following formula. Each experiment was carried out in triplicate[n=3].

Angle of repose (θ) was assessed to know the flowability of matrix pellets, by a fixed funnel method.

Tan (θ) = height / radius ……(1)

Tap density and bulk density of the matrix pellets were determined using tap density tester.The percentage Carr's index (I, %) was calculated using the formula;

Carr's index (I, %) = Tapped density – Bulk density/Tapped density ……(2)

Granule density of the pellets was determined by displacement method using petroleum ether.

Granule density = Weight of pellets/Volume of petroleum ether displaced ……..(3)

The Hausner ratio of the matrix pellets was calculated using the formula;

Hausner ratio = Tapped density / Bulk density …..(4)

The friability test was performed on the pellets to ensure their mechanical strength. Lower friability values indicate good mechanical strength. Pellets of known mass (1000 – 1400 m) were placed in a Roche Friability tester (Electro lab Friability tester, EF -2) and subjected to impact testing at 25 RPM for 5 min. Pass the pellets through a sieve of mesh size 16 (1000µm), weight of pellets retained on the sieve was noted and the friability was calculated [16] using the following equation;

Friability (%) = [1– initial weight / weight retained after 100 rotations] × 100 ……(5)

Scanning electron microscopyanalysis (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. In order to determine the sphericity of the pellets, the tracings of pellets (magnification 45 X) were taken on a block paper using camera lucida (model -Prism type, Rolex, India) and circulatory factor was calculated using the equation;

$S = p^2 / (12.56 \times A)$ ……(6)

where, A is the area (cm^2) and p is the perimeter (cm).

Differential scanning calorimetry (DSC)

. DSC studies were carried out to study the thermal behaviors of drug alone and mixture of drug and polymer using Du Pont thermal analyzer with 2010 DSC module. 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 the temperature range ambient to 220 °C in nitrogen atmosphere at a heating rate of 10 °C /min.

Fourier transform- infrared spectroscopic analysis (FT- IR)

Drug polymer interactions were studied by FT-IR spectrophotometer (JASSCO-4100, Japan) by KBr pellet method.The IR- spectrum of the pellet from 400- 4000cm-1 was recorded.

Determination of drug entrapment efficiency

NF content in the pellets was estimated by a UV-spectrophotometric method. Accurately weighed 50mg of pellets were dissolved in methanol and suspended in 100ml of phosphate buffer pH 7.42. The resulting solution was kept for 24hrs. Next day it was stirred for 15min. The solution was filtered, after suitable dilution, NF content in the filtrate was analyzed at 338nm using Shimadzu 1601 UV-Visible

spectrophotometer. The obtained absorbance was plotted on the standard curve to get the exact concentration of the entrapped drug. Calculating this concentration with dilution factor we get the percentage of actual drug encapsulated in pellets.

Loose surface crystal study (LSC)

This study was conducted to estimate the amount of drug present on the surface of the pellets which showed immediate release in dissolution media. 100mg of pellets were suspended in 100ml of phosphate buffer (pH 7.4), simulating the dissolution media. The samples were shaken vigorously for 15min in a mechanical shaker.The amount of drug leached out from the surface was analyzed spectrophotometrically at 338nm. Percentage of drug released with respect to entrapped drug in the sample was recorded[26].

In vitro drug release studies

The release profiles of NF from pellets were studied and compared with Adalat ® 20 CR capsule in two different buffer solutions to mimic the various physiological GI-tract. The media of pH 1.2 was represent the gastric condition and and pH 7.4, which is simulated intestinal fluid. The dissolution process was carried out by using USP XXI dissolution apparatus, Type II (Electrolab, TDT 08L, Mumbai, India) rotating basket apparatus. The drug loaded pellets (equivalent to 20mg of NF) filled in empty capsule shells were put into the basket rotated at a constant speed at 100 rpm and maintained temperature 37 ± 0.5°C. The 900ml of the dissolution medium, pH 1.2 and the test was done for 2h. At the end of 2h continued the test with changing the dissolution media with pH 7.4 buffer solution up to the end of 24h. At scheduled time intervals (30 min for first 4 h and at 60 min inetvals for the next 20 h), the sample (10 ml) was withdrawn and replaced with same volume of fresh medium. The withdraw sample were filtered through a 0.45µm membrane filter and after appropriate dilution using guarded sample collectors, then estimated for NF concentration spectrphotometrically. Finally, corresponding drug content in the samples were calculated from the calibration curve of NF to determine the drug release pattern.

Drug release kinetics

In order to understand the mechanism and kinetics of drug release, the drug release data of the *in-vitro* dissolution study was analyzed with various kinetic equations like zero-order (% release v/s time), first- order (Log % retained v/s time) and korsmeyer and peppas equation.

Coefficient of correlation (r) values were calculated for the linear curves obtained by regression analysis of the above plots.

A differential factor (f_1) and similarity factor (f_2) were calculated from dissolution data according to the following equations;

$$f_1 = \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \times 100 \qquad \text{.....(7)}$$

$$f_2 = 50 \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \qquad \text{.....(8)}$$

where, f_1 - differential factor, f_2 - similarity factor, n – number of time point, Rt – 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 -15. 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 - 100.

Stability studies of pellets

After determining the drug content, the optimized drug loaded pellets (formulation F_5) were charged for the accelerated stability studies according ICH guidelines. To assess long term stability, accurately weighed drug loaded pellets equivalent to 20mg of NF were filled into a hard gelatin capsules manually and sealed in a aluminum packaging coated inside with polyethylene. The studies were performed at 40 °C and 75% relative humidity (RH) in the desiccators with saturated salt solution for up to 6 months. A visual inspection, drug content, *in-vitro* drug release was conducted every 15 days for the entire period of stability study.

RESULTS AND DISCUSSION

Evidence have shown in the recent years that lipidic materials have the physical properties and behavior suitable to prepare matrix pellets to release the entrapped drug into gastro intestinal tract [19]. In the present study, blend of GL, GPS and MCC formulated as pellets by different ratio using non toxic solvent, presented in Table 1.The present method is quite different from that reported by Siepman et *al* [9].

Because, none of them succeeded to formulate pellets by blend of GL, GPS and MCC by extrusion–spheronisation technique. In the present study, examines influences of various process parameters on physicochemical properties and drug release potential have been studied. Incorporation of drug into different ratios of gelucire blend affects the physical appearance of the pellets was observed. In the present study the formulation F5 having the optimum drug and gelucire blend ratio (20: 35: 10: 35) suitable to produce solid, discrete, spherical, free flowing pellets and having a sufficient mechanical strength. Resultant pellets did not have any surface irregularities and they are non aggregated. In order to produce solid, spherical, discrete, free flowing pellets, an optimum composition of drug, gelucire,GPS, MCC blend ratio (20: 35:10: 35 w/w) was used. It was found that the higher amount of drug ratio used (30, 40 and 50 % w/w) with gelucire, GPS, MCC blend, aggregate pellets masses were produced during spheronization. This may be due to the increased amount of drug ratio, responsible for reduced the melting point of gelucire, leads to form aggregate mass and resulted pellets were unsuitable for pharmaceutical uses. SEM photographs also indicated the presence of the drug crystals on the surface of the pellets. Because surface accumulated drug resulting in burst release during dissolution and impossible to control the drug release from the pellets.

In the present study, optimized ratio of 35 % of gelucire was used. It was observed that an increase in the ratio of gelucire (15, 20, 25 and 30 %), the produced pellets were not spherical and impossible to distinguish as individual pellets. In order to avoid the formation of irregular shaped pellets and to increase the solubility of drug, 35 % w/w of gelucire was used. To obtain optimal concentrations of GPS, various concentarions ranging from 2 to 10 % w/w of the total formulations were investigated. In the present study, optimum concentration, 10% w/w of GPS was used as a solidifier to produce good pellets. Incorparation of drug into polymer pellets require the addition of wetting agent at an optimum concentration of aqueous solution of tween 80 to reduce the interfacial tension between gelucire, GPS and MCC. 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. It may due to repulsion resulting between gelucire, GPS and MCC. It was found that hydrophilic and lipo philic balance (HLB) value of tween 80 is 15, found to be more suitable to increase substantial dispersion of drug in gelucire blend. In order to obtain optimal concentrations of wetting agent, various concentarions ranging from 0.1 to 1.0 % w/w of the total formulations were investgated. But 0.1 to 0.4 % of aqueous solution tween 80 failed to produce required cohesiveness to produce reproducible pellets. However more than 0.5 % w/w aqueous solution tween 80 was used, resultant mass was sticky, aggregate, and impossible to produce pellets. In the present study, optimum concentration, 0.5 % w/w of aqueous solution tween 80 was used to produce spherical pellets. It was also noticed that 12 ml of aqueous solution of tween 80 (0. 5% w/v) was used as binding agent, produced pellets were spherical, free flowing, free from surface irregularities with good binding property. As the volume of binding agent increases, irregularly shaped pellets were produced. As the volume of the binding agent was less than 12 ml, requires more pressure for compaction and difficult to separate as an individual pellets. The percent of wetting solution and volume of binding agent has also an effect on the sphericity of the pellets, confirmed by SEM photographs (Fig. 1 a). The important factor that influences the size distribution of pellets was the spheronization speed and residence time. A spheronization speed of 750 rpm and residence time 5 min was used to obtain reproducible and uniform sized pellets. As increase in spheronization speed from 300 to 750 rpm, a change in the shape and size of the pellets were noticed. When the spheronization speed were 300 rpm, 450 rpm and 600 rpm produced rod, egg and semi spherical shaped pellets respectively. Increased spheronization speed from 750 to 900 rpm, a reduction in the average sizes and recovery yield of the pellets was observed. Spheronization speed was lower than 750 rpm, larger and irregular shaped pellets were formed and not suitable for pharmaceutical purpose. It was found that 750 rpm was optimized condition to produce discrete, spherical, hard and free flowing solid pellets. Spheronization time also affects on the pellet shape and size (Table 1). It was also found that an increase in spheronization residence time from 1 to 4 min (at a stirring speed of 750 rpm) resulted in changes in the shape and size of the pellets. From the study, optimized spheronization time was found to be 5 min, suitable to produce spherical, hard and free flowing solid pellets. However, further increases in spheronization time considerably affect the pellet shape and size. To produce reproducible shape and sizes of the pellets, spheronization speed (750 rpm) and spheronization residence time (5 min) were well controlled. Sieve analysis data presented in Table 2, indicate the average pellet diameter was in the range 1135 to1245 μm. 76.3 to 85.6 % of the pellet size was of size fraction of 1245 μm. About 99 % of the pellets obtained were in the desired particle size proving that the adopted process is reproducible. In the present study, MCC posses a good extrusion aid at optimal concentrations of 35 %, influences the mean diameter of the pellets. Due to good binding properties of MCC, it provide cohesiveness to a wetted mass, able to retain

a large quantity of binding agent helps to provide large surface area and high internal porosity. MCC also improves the plasticity of wetted mass [22] and enhancing spheronisation by preventing phase separation, during extrusion spheronisation. Generally spherical drug delivery systems are formulated as single dosage forms in the form of capsule or tablet, because such systems posses better and adequate micromeritic properties. The values of angle of repose (θ^0) for the pellet were in the range 26.30 - 27.45 indicating good flow potential for the pellets. The measured tapped density (0.839 to 0.902 g /cm^3), granule density (1.056 to 1.075 g/ cm^3), % Carr's index (8.69 to 9.39 %), and Hausner ratio (1.090 to 1.210), were well within the limits, which indicates good flow potential for the prepared pellets. The friability of the nifedipine pellet formulations was in the range 0.43 - 0.53 % and it lies in the expected range (less than 1% as per FDA specification). Friability is measured to assess the mechanical strength of the pellets in terms of fragmenting or powdering during the filling operation of the capsule shell. From the above result, the amount of MCC and GPS found to influences the friability. Less moisture content helps to produce pellets with good mechanical strength (pellets cured at 40° C for 24 h). As the curing temperature increases (45° C for 24 h), friability of the pellets found to decreases and pellets having shrinked porosities, due to loss of moisture content. When the pellets cured below 40° C for 24 h, produced pellets were dumbbell shapedwere obtained with protruding surfaces (confirmed from SEM photomicrographs) due to presence of more moisture content and these pellets 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 when they cured at 24 h at 40 °C. SEM photomicrographs of the pellets reveal the uniform distribution of the drug in the pellets. Figure 2 b shows the SEM photomicrographs of the surface of the pellets and presence of fine pores (F5) and these pores were formed due to the leaching of tween 80 into dissolution media. The formed fine pores size in microns can be clearly observed. When the pellets were cured at 24 h for\45 °C, surface inward dents and shrinkage were observed (collapse of the wall of the pellets), which might be due to drop in residual moisture content from pellets. The drug crystals observed on the surface were probably formed as a result of their migration along with water to the surface during drying.This result clearly indicates that influence of moisture content on surface morphology of the pellets [23]. The calculated sphericity values of the pellets nearer to the value 1, confirmed the prepared pellets were spherical in nature. The parameters such as spheronization time and speed, optimal concentrations of wetting liquid, concentrations of micro crystalline cellulose and curing temperature affects on the sphericity. 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, sphericity values ranged between 1.2 -1.3 (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 . The IR spectra of the nifedipine and drug-loaded pellets (formulation F5) were found to be identical and presented (Fig. 2). The characterstic IR absorption bands noticed for nifedipine are, 3329 (N-H stretch), 3101 (aromatic C-H stretch), 2961 (C-H stretch for CH3), 1683 (C=O stretch), 1433 (aromatic N-O stretch) and 1226 cm^{-1} (C-O stretch) were present in all formulations. The FTIR spectra of the pure drug and formulation F5 indicated that characteristics bands of nifedipine were not altered without any change in their position after successful encapsulation, indicating no chemical interactions between the drug and carriers used. However, a slight shift in the position of the absorption peaks was noticed. This result showed that a minor physical interaction might have occurred between drug and polymers [24]. DSC scans were recorded for nifedipine and formulation (F5). A representative thermogram of the nifedipine and nifedipine formulation (F5) is shown in Figure 3. The pure nifedipine displayed a single sharp endothermic peak at 175 ^{0}C corresponding to the melting point of the drug and identical peak was observed at 175 ^{0}C in the nifedipine formulation (F5). This result clearly indicated that the drug rtains its identity in the formulation (F5). The additional peak in the formulation (F5) in the DSC thermograms was noticed.This is an agreement with literature findings . Drug loading and encapsulation efficiency of the drug loaded pellets are given in Table 3. Drug loading in all the formulations were in the range of 16.56 % - 19.21 %. Drug loading was least in formulation F1 and high for formulation F5. The encapsulation efficiency (%) was more in formulation F5 (96.32 %) as compared to formulation F1 (84.50 %). It can be concluded that formulation F5 had more encapsulation efficiency. Drug loading increases with increased in pellets size, resulting in inreased in encapsulation efficiency. Drug content increases as increase in pellets size, resulting in increased encapsulation from 84.50 to 96.32 % for pellets size of 1135 -1245 μm. This might be increasing in the relative surface area of the pellets, leads to more drug loading. Loose surface crystal (LSC) study was an important parameter giving an indication of the amount of drug on the surface of the pellets Physical state of NF in all formulations with different drug loading was investigated by polarized

light microscopy. The microscopic study indicated that crystalline NF was observed in all formulations and more clear in formulation F5 (drug content was 19.21 %). *Invitro* release studies were carried out for the formulations in both acidic and basic media to stimulate *invivo* conditions. The *invitro* drug release kinetics of nifedipine from polymer membrane in 0.1N HCl (HCl buffer – simulated gastric fluid – to mimic the acidic conditions prevailing in the stomach - for 2h) and phosphate buffer pH 7.4 (phosphate buffer- to mimic the environment in the small intestine- 22 h) from formulation F1 to F5 were studied [25]. Drug release from 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 NF released was observed for formulation F5 (96.01%) as compared to all other formulations F1 (84.21 %), F2 (85.90 %), F3 (87.51%) and F4 (88.23 %). This result clearly indicates that lowered drug release was noticed for the systems containing higher content of MCC.Because swollen MCC particles retards the penetration of dissolution media into pellets and thus limiting the release of drug from pellets. This typical behavior was commonly observed in diffusion controlled drug delivery systems [26]. The order of drug release from the polymer based pellets is F5 < F4 < F3 < F2 < F1. 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. If pellets containg more proportions of aqueous solution of tween 80 (0.5 %), formed more numbers of pores on the surface of the pellets, resulted easy wettability of pellets with dissolution media, within 7 h, 100 % of the drug release from all the formulations were observed. In this investigation author made an attempt to prepare the pellets with lower levels of gelucire and aqueous tween 80 solution (0.5 %), pellets exhibited initial burst release of drug. This result could be attributed to the dissolution of drug present initially at surface of the matrices and rapid penetrartion of dissolution media into pellets matrix structure. However, the formulations exhibited little burst effect at higher levels of GPS. Further increase in GPS amount, formed thicker gel around the pellets, strongly inhibiting the dissolution media penetration, resulting in significant reduction in the values of rel_{24h} indicating slower drug release. The obtained values of $t_{50\,\%}$ for all pellet formulations lies in the range of 4. 52 – 5.18 h presented in Table 4. The same result was noticed for Adalat CR® 20 capsule (5.12 h). This finding indicated a considerable release retarding potential of the drug from pellets by varying ratios of gelucire / GPS /MCC and pore former. The effect of curing of pellets at different temperature nifedipine release from gelucire / GPS/ MCC pellets was studied. Interestingly pellets cured at 40 ^{0}C for 24 h showed controlled drug release. The acceleration of drug release upon curing at 40 ^{0}C (24 h) might be due to residual moisture content present in the pellets. This result indicates the moisture present in the pelletsreduces 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 which slows down wettability. Melting point of the gelucire was found to be 50.3^0 C and less than the melting point of the gelucire. So the drug loaded gelucire pellets (lipidic nature) 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 gelucire/GPS/MCC pellets depends on curing conditions and moisture content. To better understand the morphology of the pellets and potential changes occur after exposure to the release media was observed by microscopy. Fig.4 shows photographs of NF loaded pellets before and after 2 h exposure to 0.1N HCl and phosphate buffer pH 7.4 respectively. It is evident that the pellets were initially spherical in shape and there was no change occurred up to 30 min exposure (Fig.4 a). But pellets started to looses their edges slowly by disintegration after exposed to 0.1N HCl ((Fig. 4 b) for 2 h. When pellets exposed to phosphate buffer pH 7.4 (after 2h), the edges of the pellets start to disintegrate rapidly and resulting in increasing drug release. For this reason surface accumulated drug showed burst release follows slow release of core drug during dissolution studies. It can be seen that the type of release media (0.1 NHCl versus phosphate buffer pH 7.4) did not significantly affect the resulting NFrelease kinetics. Pellets prepared by using optimal concentrations of aqueous tween 80 solution (12 ml of 0.5 % w/v), 96% of the embedded drug were released over 24 h. It was observed that the pellets prepared by using more or less than the optimal concentration solution (12 ml of 0.5 % aqueous tween 80 solution), fail to release the drug from pellets in a controlled manner. The rate of drug release followed first order kinetics and numerical data fitted into Peppa's equation [18]. Statistically estimated values of n of drug from pellets at 95 % confidence limit,is lie in the range 0.39 – 0.45 and 0.42 for formulation F1-F5 studied and 0.42 for Adalat CR® 20 capsule, indicated that the drug release from the formulations F1 – F5 and Adalat CR® 20 capsule 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. Diffusion is related to transport of drug from the dosage matrix into the *invitro* study fluid depending on the concentrations of the gelucire. As gradient varies, the drug is released, and the distance for diffusion increases. From this it was noticed that drug diffuses at a slower rate as the distance for diffusion increases. This is a good agreement with literature findings [27]. The obtained correlation coefficient, R^2 for the NF pellets lies in the range of 0.927 – 0.991. The same result was noticed for Adalat CR® 20 capsule (0.997). The drug release profiles of the optimized formulation F5 was the same that of release profile of oral formulation Adalat CR® 20. The plot of the cumulative percent drug release as a function of time for formulation F5 and Adalat CR® 20 is shown in Fig 5. From the figure, it is evident that the prepared NF pellets controlls the drug release than the commercially available product. For prepared formulations (F1-F5) and Adalat CR® 20 capsule, the results of drug content were found to be within the limits. Table 4 lists the observed, experimental and percent error values. The experimental value compared with observed values,the percent error varied between 0.06 – 1.28presented in Table 4, reveals that the increased amount of gelucire has a influence on the drug release. Results of drug released was compared between rel_{1h}, rel_{24h} and $t_{50\ \%}$, shows that drug release at 24 h varies slightly linear manner with increase amount of gelucire. This result clearly indicates drug delivery from pellets depends on amount of gelucire. Differential factor (f_1) and similarity (f_2) factor was calculated from dissolution profile and the results were compared to the formulation, F5 and marketed product, Adalat CR® 20 capsule. The differential factor (f_1) and similarity factor (f_2) obtained from dissolution profile indicates that the formulation F5 (9.45, 10.42) and Adalat CR® 20 capsule (78.42, 80.29) were similar. The calculated diffusivity values are given in Table 5. From the table it is noticed that, diffusivity values of trial 1 (without GPS) is quite high, since there is no barrier to control the drug release. The values of F1 and F2 are quite low, due to less amount of gelucire and pore former, resulted in less solubility of drug in aqueous media. On the other hand, the diffusivity values for formulations F3 and F4 was slightly higher. This is due to fact that more ratio of gelucire and pore former resulted more solubility of drug in aqueous media, so the drug diffuses easily into the external environment. Formulation F5, which showed optimum drug release during the *invitro* dissolution studies, exhibited a higher diffusivity, which is an accord with the drug release profile. It also supports the fact that the drug is easily diffusible through the micropores formed in the pellets memrane. The formulation of nifedipine pellets (F5) was subjected for accelerated stability studies. Stability studies were carried out $40^0 \pm 1^0$ C and 75 % ± 5 % relative humidity for a period of 90 d (Table 6). It was observed that, there is no significant change in the drug release at gastric pH and at the end of 24 h, drug release was 95.97 %. It is evident from the table that, formulations F5 exhibited good chemical stability under the investigated period, which indicates the drug in stable form.

Table 1. Optimization of process parameters for pelletization

Parameters	Formulation	Parameters [a]	Description of pellets
Drug:Gelucire:GPS: MCC (w/w)	F1	20: 15: 02:63	Rod shape and brittle
	F2	20 : 20 : 04 : 56	Egg shape and brittle
	F3	20 : 25 : 06 : 49	Semi spherical and brittle
	F4	20 : 30 : 08 : 42	Spherical and brittle
	F5	20 : 35 : 10 : 35	Spherical and hard
Spheronization Speed (rpm)	F5	300	Rod shape
		450	Egg shape
		600	Semi spherical
		700	Spherical
Spheronization speed (time)	F5	2	Rod shape
		3	Egg shape
		4	Semi spherical
		5	Spherical
Yield (%)	F1	91.2	Rod shape and brittle
	F2	92.5	Egg shape and brittle
	F3	92.7	Spherical and hard
	F4	94.3	Spherical and brittle
	F5	96.5	Spherical and brittle

[a] Standard deviation n = 3

Table 2. Yield, size distribution, micromeritic properties and friabilityof pellets

Formulation	Yield (%)	Average size (μm)	Angle of repose θ^0	Tapped density (g/cm^3)	Granule density (g/cm^3)	Carr's index (%)	Hausner ratio (%)	Friability (%)
F1	89.3	1135	26.54	0.841	1.063	9.12	1.197	0.53
F2	92.6	1189	25.42	0.865	1.075	8.79	1.178	0.52
F3	92.9	1229	25.98	0.839	1.072	8.69	1.090	0.49
F4	93.9	1239	26.30	0.893	1.058	8.93	1.210	0.47
F5	96.5	1245	27.45	0.902	1.056	9.39	1.156	0.43

[a] Standard deviation n = 3

Table 3. Drug loading and encapsulation efficiency of pellets

Formulation	Drug loading [a] (%)	Encapsulation efficiency [a] (%)
F1	16.56	94.50
F2	16.97	95.69
F3	18.32	95.89
F4	18.61	95.98
F5	19.21	96.32

[a] Standard deviation n = 3

Table 4. Formulations experimented and predicted values

Formulation	Release values[a]	Experimental values[a]	Observed values[a]	Percentage error
	rel_{1h}	3.99	4.04	1.25
	rel_{24h}	84.21	84.34	0.15
F1	$t_{50\ \%}$	4.52	4.49	0.66
F2	$rel_{1\ h}$	3.94	3.92	0.51
	$rel_{24\ h}$	85.90	85.79	1.28
	$t_{50\ \%}$	4.55	4.50	1.10
F3	$rel_{1\ h}$	3.84	3.82	0.01
	$rel_{24\ h}$	87.51	87.40	0.13
	$t_{50\ \%}$	4.59	4.56	0.61
F4	$rel_{1\ h}$	3.83	3.78	1.31
	$rel_{24\ h}$	88.23	88.51	0.31
	$t_{50\ \%}$	5.08	5.06	0.39
F5	$rel_{1\ h}$	3.75	3.73	0.53
	$rel_{24\ h}$	96.01	96.07	0.62
	$t_{50\ \%}$	5.18	5.16	0.39
AdalatCR® 20	$rel_{1\ h}$	3.80	3.78	0.53
	$rel_{24\ h}$	98.36	98.42	0.06
	$t_{50\ \%}$	5.12	5.27	0.06

[a] Standard deviation n = 3, $rel_{1\ h}$ = Release in 1 h, $rel_{24\ h}$ = Release in 24 h, $t_{50\ \%}$ =Time to release 50% drug release

Table 5. Diffusivity data for gelucire/ glyceryl GPS,and MCC

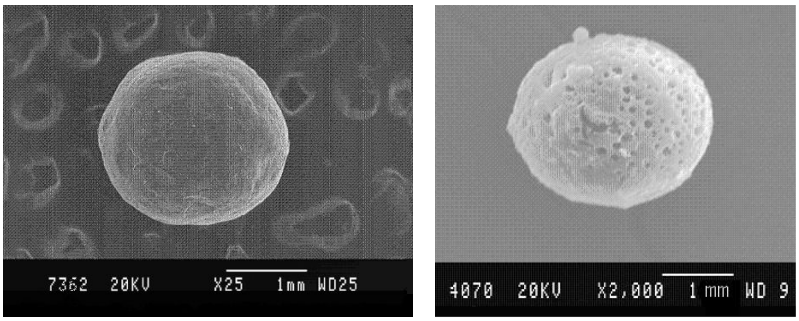
Formulation	D_1 [a] x 10^9 (cm^2/s)	D_2 [a] x 10^9 (cm^2/s)
Trial 1	1.38	1.27
F1	0.42	0.35
F2	0.51	0.49
F3	0.61	0.58
F4	0.72	0.67
F5	0.92	0.89

[a] Standard deviation n = 3, Trial 1= without GPS

Table 6. Drug content and drug release from optimized formulation F5 during the stability study

Sampling time [a] (d)	Drug content [a] (%)	Drug release [a] (%)
15	96.00	96.01
45	95.98	95.99
90	95.97	95.97

[a] Standard deviation n = 3



I (a) **I(b)**

Fig. 1. SEM photomicrographs of; (a) NF loaded pellets in spherical shape (F5), (b) NF pellets showing surface inward dents with pores (F5)

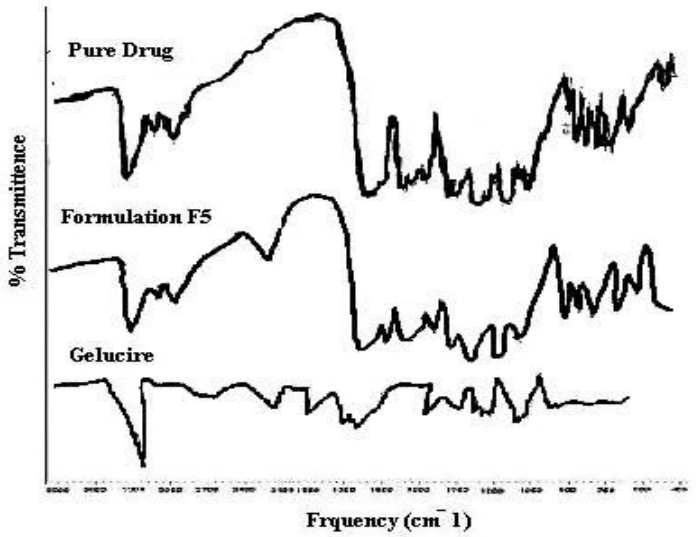


Fig. 2. FTIR spectra of nifedipine, NF loaded matrix pellet (F5) and gelucire 50/13

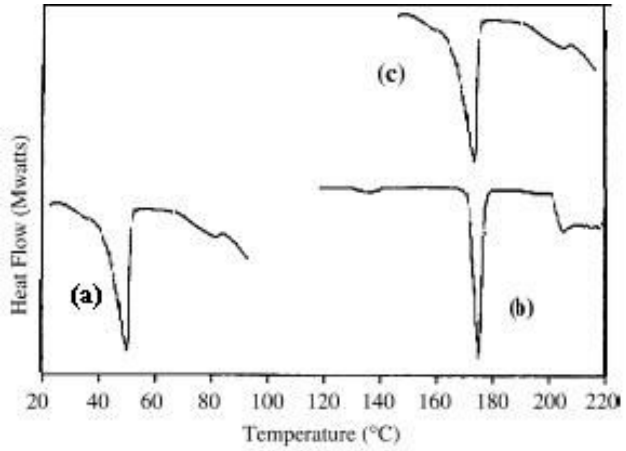


Fig. 3. DSC thermograms of, (a) gelucire, (b) nifedipine (pure drug) and (c) NF loaded matrix pellets (F5)

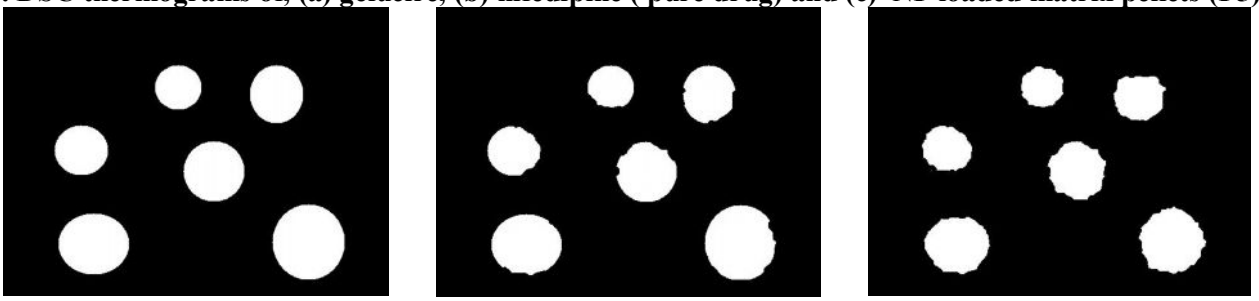


Fig. 4. Microscopic photographs of nifedipine loaded pellets; (a) before exposure, (b) 2 h exposured to 0.1N HCl and (c) 4 h exposured to phosphate buffer 7.2.

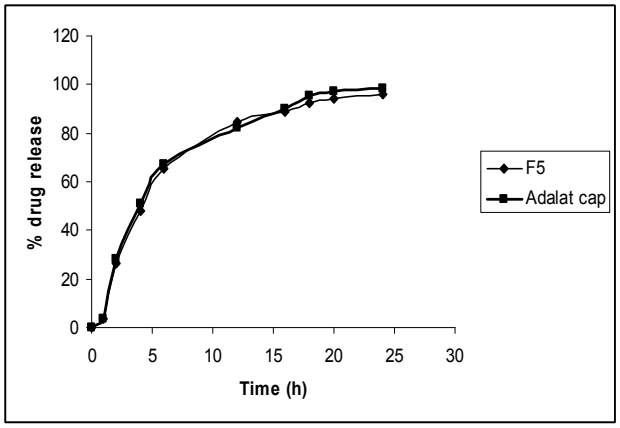


Fig. 5. Percent drug release profiles of NF from formulation F5 and Adalat CR® 20 capsule in the gastric and intestinal environment against the time.
F5 (—♦—) and Adalat CR® 20 and capsule (--■--).

CONCLUSION

Pellets containing a pore forming agent, such as tween 80, 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 mnature 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, indicates that drug is in stable state. The drug content study revealed uniform distribution of the drug in the pellets. The *invitro* drug release results showed that formulation F5 > F4 > F3 > F2 > F1. The drug release rate was found vary among the formulations depending on the compositions and solubility 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 Adalat CR® 20 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 gelucire/GPS/MCC blend for the developoment of controlled drug delivery systems for many water insoluble drugs.

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