

Design and Evaluation of Controlled Release of Piroxicam from the Pellets of Microcrystalline Cellulose and Hydroxypropylmethyl Cellulose Blends

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ABSTRACT: The aim of the present study was to minimize the local gastrointestinal irritation which is one of the major side effects of Piroxicam (PR) after oral ingestion by kinetic control of drug release. PR was incorporated into the biocompatible blends of micro crystalline cellulose (MCC) and Hydroxymethyl cellulose (HPMC) matrix pellets using pelletization technique using PVP as binder. The prepared pellets were subjected to Micromeritic properties, SEM, DSC, FTIR and stability studies. Solid, free flowing matrix pellets and yields up to 97.3 %. More than 98 % of the isolated pellets were of particle size range 1.35 to 1.44 mm. The obtained matrix pellets having smooth surfaces, with free flowing and good packing properties. Scanning electron microscope (SEM) confirmed their spherical structures. Drug loaded MCC/HPMC pellets was stable and compatible as confirmed by DSC and FTIR studies. The release of drug from the blends was controlled up to 20 h. Intestinal drug release from pellets was studied.

Keywords: Pelletization, Piroxicam, Eudragit, Binder, 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]. 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 facilitate accurate delivery of small quantity of potent drugs and reduce the drug concentrations at sites other than the target organ. Multiparticulate dosage forms disperse freely in gastrointestinal tract and invariably maximize drug absorption, reduce peak plasma fluctuation and minimize potential side effects without

lowering drug bioavailability. They are less susceptible to dose dumping than reservoir type single unit formulations like tablets. Pelletization involves the process of conversion of fine powders or granules of bulk drugs and excipient into small, free flowing, spherical units in size between 0.5-1.5 mm. Pellets are increasingly being used as multiple unit dosage forms. Pellets possess many pharmacological advantages as they disperse freely in the gastrointestinal tract, maximize drug absorption, reduce peak plasma fluctuations and minimize potential side effects without appreciably lowering the bioavailability [3-5]. They avoid high local concentrations of bioactive agents, which may inherently be irritative or anesthetic to stomach [6]. Additionally they reduce intra and inter subject variability of plasma profiles by reducing variations in gastric emptying rates and overall transit times. Extrusion-spheronization is the most commonly used method for pellet production [7]. Use of suitable excipients and fillers can be made to produce pellets of desirable quality [8]. Different excipients from a variety of sources have been evaluated for the

formation of spherical pellets [9,10]. Spherical pellets possess many advantages, including a low surface area to volume ratio, good flow properties and uniformity in packing [11]. The force required and the characterization of the extrudates produced is dependant on the rheological properties, design of the die and rate at which the material is forced through die. In spheronizer, a plate (diameter 10-1000 cm) rotates within the confines of a cylinder. The extruded, cylindrically shaped particles are broken into uniform lengths almost instantaneously and are gradually transformed into spherical shapes. A sphere has several geometric advantages over other forms such as lowest surface-to-volume ratio and because of its shape [12-14]. Microcrystalline cellulose (MCC) is the most commonly used excipient in extrusion-spheronization. It leads to the formation of round spheres with desirable characteristics. It is generally regarded as a nontoxic and nonirritant material. It is not absorbed systemically following oral administration. In pharmaceuticals, it is widely used primarily as a diluent in oral tablet and capsule formulations where it is used in both wet granulation and direct compression processes. In addition to its use as a diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting. MCC during spheronization, the moisture entrapped in the MCC microfibrils adds plasticity to the extrudates and helps to round the short extrudates into spherical pellets [15-17]. Hydroxypropyl methyl cellulose is well known water soluble polymer used as carrier for solid dispersions [18-20]. Piroxicam is a non-steroidal anti-inflammatory drug (NSAID) used to relieve symptoms of rheumatoid and osteoarthritis, primary dysmenorrhoea, postoperative pain and act as an analgesic, especially where there is an inflammatory component [21]. It is also used in veterinary medicine to treat certain neoplasias expressing cyclooxygenase (COX) receptors, such as bladder, colon and prostate cancers [22,23]. One of the major side effects associated with the use of NSAID is gastrointestinal irritation [24]. Irritation can vary from minor gastric discomfort to ulceration and bleeding of the mucosa [25] and is not only caused by the inhibition of prostaglandin synthesis, but is probably also due to direct contact of the drug with the mucosa [26] and to enterohepatic recirculation [27,28]. Assuming that the local effects are relatively important, the development of a suitable drug delivery system may reduce the contact time of the drug with the gastric mucosa, while the application of an enteric coating may offer additional protection [29]. The objectives of the present study was to formulate, characterize, *in vitro* drug release from blend of MCC/HPMC pellets loaded with Piroxicam and to achieve the controlled drug release system.

EXPERIMENTAL

MATERIALS

Piroxicam (PR) is obtained from M/s Astral Pharmaceuticals, Mumbai, India, as gift sample. It is a white to off-white crystalline powder with bitter taste, readily soluble in organic solvents, sparingly soluble in water. Hydroxypropyl methylcellulose (HPMC) was obtained from M/s Sisco research laboratories, Mumbai, is a tasteless and odorless, white to slightly off white, fibrous or granular powder. soluble in cold water, glacial acetic acid, ethanol, insoluble in hot water, commonly used as a drug carrier, a coating agent, a tableting agent, an emulsifier in ointments, a thickener in suspensions, a non-ionic surfactant, a binder, and a film forming agent.

Polyvinyl pyrrolidone (PVP K-30) was obtained from M/s Indo Pharma, Mumbai, India. It is white to creamy-white colored, odorless or almost odorless, hygroscopic powder dissolves in water, alcohol, isopropanol but it is insoluble in acetone and diethyl ether. It is mainly used as binder for tablet, dissolving assistant for injection, flow assistant for capsule, dispersant for liquid medicine and pigment, stablizer for enzyme and heat sensitive drug. Micro crystalline cellulose pH 101 (MCC) was procured from Signet Chemicals, Mumbai, India. It is a white colourless, odorless, tasteless and crystalline powder. MCC is widely used as a diluent in oral tablet and capsule formulations where it is used in wet granulation and direct compression process. It also has some lubricant and disintegrant properties that make it useful in tableting. All other chemicals used were of analytical grade.

Preparation of MCC/HPMC based matrix pellets by extrusion- spheronization method

The pellets were prepared by using extrusion / spheronization pelletization technique. Required amount of PR, MCC and HPMC were passed through sieve No. 40 prior to pelletization and mixed uniformly in a planetary mixer. Isopropyl alcohol is used to bind the mass along with polyvinyl pyrrolidone solution was added drop wise to the mixture to obtain dough mass, which was extruded using a piston extruder (1 mm orifice, Kalweka, India). The extrudates were immediately spheronized for 4 min at a rotational speed of 1400 rpm and an air velocity of 1 kg/cm². The pellets were dried at 40 °C for 2 h in a fluid bed dryer (Kothari, India).

Characterization and evaluation of pellets**Particle size analysis**

The particle size of drug loaded formulations was measured 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 40x was used for this purpose. The instrument was calibrated at 1 unit of eyepiece micrometer was equal to 1/30mm (33.33 μ m).

Measurement of micromeritic properties, granule density and friability of pellets

The flow properties were investigated by measuring the angle of repose of drug loaded pellets using fixed base cone method. Pellets 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. Angle of repose (θ) was assessed to know the flowability of matrix pellets, by a fixed funnel method.

$$\tan(\theta) = \text{height} / \text{radius} \dots\dots\dots(1)$$

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

$$\text{Carr's index (I, \%)} =$$

$$\frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \dots\dots\dots(2)$$

Tapped density ...

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

$$\text{Granule density} =$$

$$\frac{\text{Weight of pellets}}{\text{Volume of petroleum}} \dots\dots\dots(3)$$

ether displaced

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

$$\text{Hausner ratio} =$$

$$\frac{\text{Tapped density}}{\text{Bulk density}} \dots\dots\dots(4)$$

Bulk density

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 (1000 μ m), weight of pellets retained on the sieve was noted and the friability was calculated using the following equation;

$$\text{Friability (\%)} =$$

$$\frac{[1 - \text{initial weight}]}{[\text{weight retained after 100 rotations}]} \times 100 \dots\dots\dots(5)$$

Scanning electron microscopy (SEM)

The shape and surface characteristics of optimized pellets were determined by scanning electron microscopy (SEM (LV 5600, Jeol, USA).

Determination of Sphericity

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

$$S = p^2 / (12.56 \times A) \dots\dots\dots(6)$$

Where, A is the area (cm²) and p is the perimeter (cm).

Differential scanning calorimetry (DSC)

The thermal behavior of pure drug and optimized formulation was measured by using TA thermal analyzer with 2010 DSC module. The DSC scans of the samples were recorded in the temperature range ambient to 250 °C in nitrogen atmosphere at a heating rate of 10 °C /min.

Fourier transform- infrared spectroscopic analysis (FT- IR)

FTIR spectra of the pure drug, optimized formulation were obtained by FTIR spectrophotometer (Jassco - 4100, Japan).

Determination of drug entrapment efficiency

Accurately weighed 50mg of pellets was dissolved in methanol and suspended in 100ml of phosphate buffer pH 7.42. The resulting solution was kept for 24 h. Next day it was stirred for 15 min. The solution was filtered, after suitable dilution, PR 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)

To estimate the amount of drug present on the surface of the pellets showed immediate release in dissolution media. 100 mg of pellets was suspended in 100 ml of phosphate buffer (pH 7.4), simulating the dissolution media. The sample was shaken vigorously for 15 min in a mechanical shaker. The amount of drug leached out from the surface was analyzed spectrophotometrically at 338 nm. Percentage of drug

released with respect to entrapped drug in the sample was recorded.

In vitro drug release studies

The release profiles of PR from prepared pellets capsule in two different buffer solutions to mimic the various physiological gastrointestinal tract. The media of pH 1.2 will represents the gastric condition 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 PR) filled in empty capsule shells were put into the basket rotated at a constant speed of 100 rpm and maintained temperature $37 \pm 0.5^\circ\text{C}$. The 900ml of the dissolution medium, pH 1.2 and the test was carried out for 2 h. At the end of 2 h continued the test with changing the dissolution media with pH 7.4 buffer solution up to the end of 24 h. At regular intervals (30 min for first 4 h and at 60 min intervals for the next 20 h), the sample (10 ml) was withdrawn and replaced with same volume of fresh medium. The withdraw samples were filtered through a $0.45 \mu\text{m}$ membrane filter and after appropriate dilution using guarded sample collectors, PR concentration was estimated spectro photometrically. Finally, corresponding drug content in the samples was calculated from the calibration curve 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 *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;

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

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

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 to 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

The drug loaded pellets equivalent to 20mg of PR were filled into a hard gelatin capsules manually and sealed in aluminum packaging coated inside with polyethylene. The studies were performed at 40°C and 75% relative humidity (RH) in a desiccator with saturated salt solution up to 6 months. A visual inspection, drug content and *In-vitro* drug release were conducted every 15 days for the entire period of stability study.

RESULTS AND DISCUSSION

The influences of various process parameters on physicochemical properties and drug release potential have been studied. Different formulation ratios of blend affects the physical appearance of the pellets was observed. In the present investigation, the formulation F5 having the optimum drug and polymer blend ratio 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 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. While incorporating the drug in to the pellets, requires the optimum binder and wetting agent.. As the volume of binding agent increases, irregularly shaped pellets were produced. 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). The important factor that influences the size distribution of pellets was the spheronization speed and residence time. A spheronization speed of 1400 rpm and residence time 5 min was used to obtain reproducible and uniform sized good pellets. As decrease in spheronization speed from 500 to 1100 rpm, a change in the shape and size of the pellets varying from rod shape to dumbbell shape were noticed. Spheronization speed was lower than 1400 rpm, larger and irregular shaped pellets were formed and not suitable for pharmaceutical purpose. It was found that 1400 rpm was optimized condition to produce discrete, spherical, hard and free flowing solid good 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 1400 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. Micromeritic properties data were presented in Table 2. MCC shows good extrusion behaviour at an optimal concentration and influences on 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 and enhancing spheronization by preventing phase separation, during extrusion spheronization. Angle of repose (θ^0) values for the pellets was in the range 23.41 to 24.97 indicating good flow potential for the pellets. The measured tapped density 0.481 to 0.591 g/cm³, granule density 0.545 to 0.493 g/cm³, % Carr's index 9.11 to 9.37 % and Hausner ratio 1.12 to 1.28, were well within the limits, which indicates good flow potential for the prepared pellets. The friability of the pellet formulations was in the range 0.71 to 0.52 % 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 HPMC found to influences the friability. Less moisture content helps to produce pellets with good mechanical strength. As the curing temperature increases (45°C for 24 h), friability of the pellets found to decreases and pellets having shrinkened porosities, due to loss of moisture content. When the pellets cured below 40°C for 2 h, dumbbell shaped pellets were obtained with protruding surfaces as confirmed by SEM, due to presence of more moisture content and these pellets not suitable for pharmaceutical purpose. SEM photomicrograph the pellets (optimized formulation F₅) were spherical in nature and had a smooth surface when they cured at 2 h at 40°C. SEM photomicrograph of the pellets (Fig.1) reveals the uniform distribution of the drug in the pellets. 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 the influence of moisture content on surface morphology of the pellets. The calculated sphericity values of the pellets nearer

to 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 2 h at 40 °C the sphericity values of the pellets nearer to the value 1. FTIR spectra of pure drug displayed broad peaks at about 3048–3718 cm⁻¹, N–H or O–H stretching vibration at 3391 cm⁻¹. N or C=O functions on pyrrolidone moiety with the amide (N–H) group or protonated pyridine N atom of piroxicam were present in both pure and formulations without any change in their positions indicating no chemical interaction between PR and polymers (Fig. 2). DSC thermograms for PR and formulation F₅ is shown in Figure 3. PR exhibits a sharp endothermic peak corresponding to the melting point of crystalline drug was found at 201.95 °C. The DSC curve of F₃ also exhibits endothermic peak at 202.5°C. This results indicates that drug retain its chemical identity in different pellet formulations. 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 17.96 % - 19.23 %. Drug loading was least in formulation F1 and high for formulation F5. The encapsulation efficiency (%) was more in formulation F5 (96.56 %) as compared to formulation F1 (94.30%). It can be concluded that formulation F5 had more encapsulation efficiency. Drug loading increases with increased in pellets size, resulting in increase in encapsulation efficiency. 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 PR in all formulations were investigated by polarized light microscopy. *In vitro* release studies were carried out for the formulations in both acidic and basic media to stimulate *in vivo* conditions. The *in vitro* drug release kinetics 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) 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. Because swollen MCC particles retards the penetration of dissolution media into pellets and thus limiting the release of drug from pellets. The order of drug release from the polymer based pellets is F₅ < F₄ < F₃ < F₂ < F₁. The acceleration of drug release upon curing at 40 °C (2 h) might be due to residual moisture content present in the pellets. This result indicates the

moisture present in the pellets reduces the cohesive force, which facilitates the wetting of pellets and increased the pellets disintegration was visually confirmed. Pellets cured above 45 °C for 2 h, showed the least drug release, due to least amount of residual moisture content present in the pellets which slows down wettability. Surface accumulated drug showed burst release follows slow release of core drug during dissolution studies. It can be seen that (0.1 N HCl versus phosphate buffer pH 7.4) there is no significant influence of the media on drug release kinetics. The rate of drug release followed first order kinetics and numerical data fitted into Peppas's equation.. Formulation F5, which showed optimum drug release

during the *in vitro* dissolution studies, exhibited a higher diffusivity, which is in accord with the drug release profile. It also supports the fact that the drug is easily diffusible through the micropores formed in the pellets membrane. The formulation of (F₅) pellets was subjected for accelerated stability studies. Stability studies were carried out 40⁰ ± 1⁰ C and 75 % ± 5 % relative humidity for a period of 90 days (Table 4). It was observed that, there was 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 Formulations and process parameters of MCC/HPMC pellets with drug.

Parameters	Formulation code	Parametric values	Description of pellets
Drug:MCC:HPMC (w/w)	F ₁	20:30:50	Rod shape and brittle
	F ₂	20:40:40	Rod shape and brittle
	F ₃	20:50:30	Spherical and brittle
	F ₄	20:60:20	Spherical and brittle
	F ₅	20:70:10	Spherical and hard
Spheronization Speed (rpm)	F ₅	500	Rod shape
		800	Rod shape
		1100	Dumbbell shape
		1400	Spherical
Spheronization Speed (time in minutes)	F ₅	2	Rod shape
		3	Rod shape
		4	Spherical
		6	Spherical
Yield (%)	F ₁	92.5	Rod shape and brittle
	F ₂	92.8	Egg shape and brittle
	F ₃	93.7	Spherical and hard
	F ₄	94.4	Spherical and brittle
	F ₅	97.3	Spherical and brittle

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

Formulation	Yield (%) [*]	Average size (mm) [*]	Angle of repose θ ^{0*}	Tapped density (g/cm ³) [*]	Granule density (g/cm ³) [*]	Carr's index (%) [*]	Hausner ratio (%) [*]	Friability (%) [*]
F ₁	92.5	1.35	23.41	0.481	0.545	9.11	1.12	0.71
F ₂	92.8	1.38	23.71	0.493	0.486	8.76	1.10	0.68
F ₃	93.7	1.40	23.96	0.498	0.479	8.64	1.09	0.57
F ₄	94.4	1.41	24.42	0.521	0.482	8.95	1.21	0.47
F ₅	97.3	1.44	24.97	0.591	0.493	9.37	1.28	0.52

^{*} Standard deviation n = 3

Table:3 Drug loading and encapsulation efficiency of the pellets

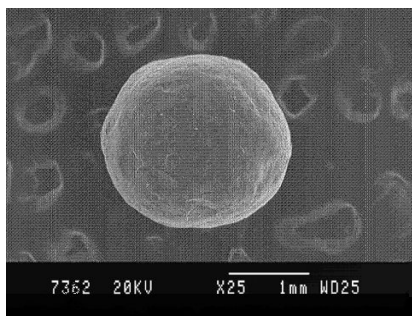
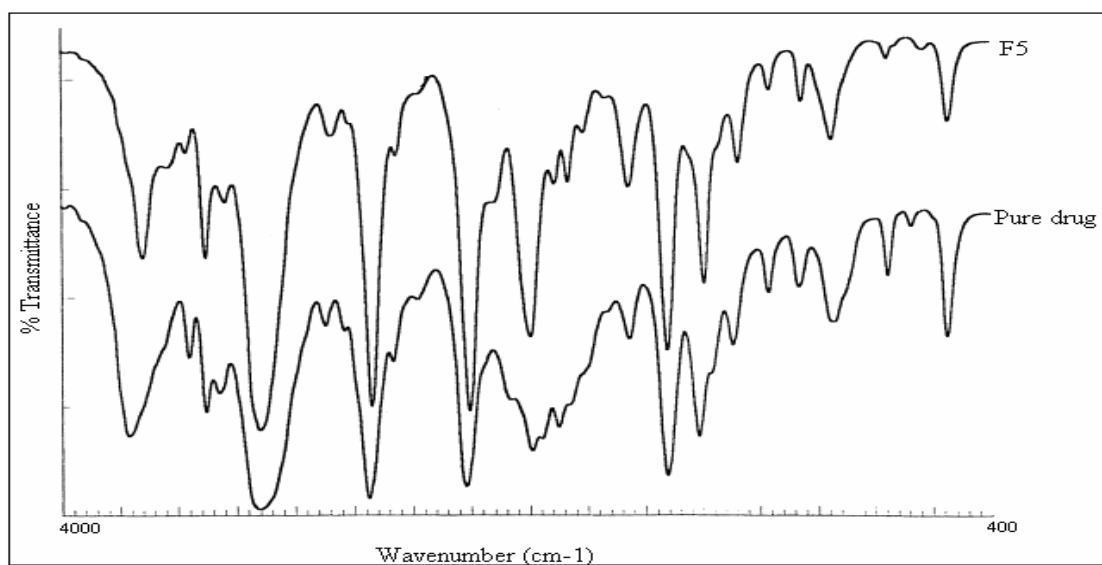
Formulation	Drug loading* (%)	Encapsulation Efficiency (%)*
F ₁	17.96	94.30
F ₂	17.99	95.16
F ₃	18.22	95.78
F ₄	18.71	95.99
F ₅	19.23	96.56

*Standard deviation n = 3

Table:4 Drug content and drug release from optimized formulation F₅ during the stability study

Sampling time in days	Drug content* (%)	Drug release* (%)
15	97.14	96.86
45	96.47	95.19
90	95.96	95.77

*Standard deviation n = 3

**Fig:1 SEM photomicrograph of optimized formulation F₅****Fig:2 FTIR spectra of Pure drug, drug loaded matrix pellet F₅**

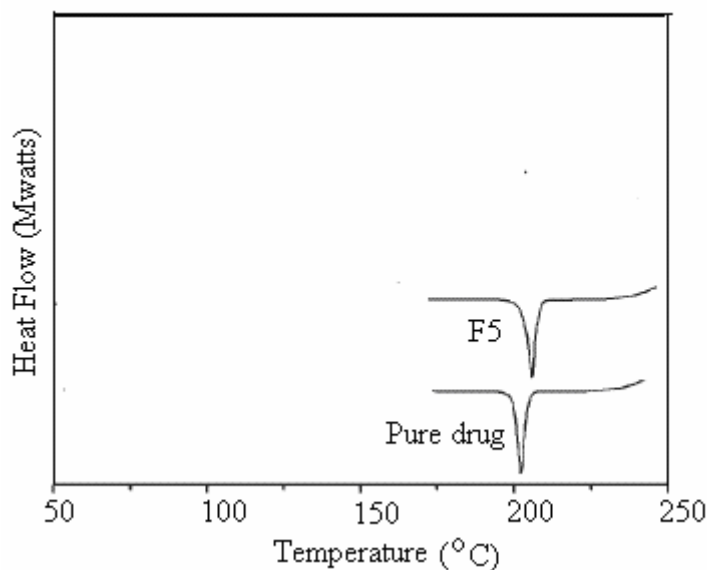


Fig:3 DSC thermograms of pure drug and optimized formulation F₅

CONCLUSIONS

The results of micromeritic properties, Hausner ratio and friability of the MCC/HPMC/PR pellets were well within the limits, which indicate good flow potential for the prepared pellets. Drug loaded pellets exhibited spherical nature as evidenced by SEM photomicrographs and sphericity studies. From FTIR and DSC studies, it was observed that there was no chemical interaction between the drug and polymers used which indicates that drug is in stable state. The drug content study reveals uniform distribution of the drug in the pellets. The *in vitro* drug release was found to be 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

study indicates the drug release through the microporous polymeric membrane follows Fickian diffusion. Optimized formulation pellets F₅. Formulation F₅ is an ideal formulation for once daily administration. From the present study, it can be concluded that the prepared pellets demonstrates the potential use of MCC/HPMC/PR blend for the development of controlled drug delivery systems and improved biocompatibility.

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