FABRICATION AND EVALUATION OF ETHYL CELLULOSE AND CELLULOSE ACETATE COATED CONTROLLED RELEASE MULTIPARTICULATE FORMULATION OF KETOPROFEN BY DRY POWDER LAYERING TECHNOLOGY

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ABSTRACT: Multiparticulate is one of the most widely accepted technologies in the pharmaceutical industries. Present study aim is to prepare controlled release multiparticulate of Ketoprofen by drug powder layering technology using two different release retardant (Ethyl Cellulose & Cellulose Acetate) in five different drug: release retardant concentrations (5%, 10%, 20%, 30% & 40%). The most widely used multiparticulate system in pharmaceutical industries is Dry Powder Layering Technique. Powder layering involves the deposition of successive layers of dry powder(s) and excipients on preformed nuclei or cores with the help of binding liquids. The prepared multiparticles were evaluated for friability, drug content uniformity, density and percentage yield. The release rate was evaluated by dissolution studies. To establish drug polymer compatibility DSC and FT IR was done. Study concluded that Dry Powder Layering of Ketoprofen can be effectively used for drug loading on non-pareil seeds. It was also found that formulation having Ethyl Cellulose have more retarding capacity than the Cellulose Acetate in both formulations and drug release follows Zero order kinetics. DSC and FT IR study concluded that there is no interaction between EC and CA. From dissolution parameter of the prepared multiparticles it is concluded that formulation EC3 (20%) and CA4 (30%) posses the required characteristics of oral controlled release formulation. It is assumed that above 90% of the drug will be released within 24 hours. Hence this formulation can be used as once daily dosage regimen for the controlled release of Ketoprofen.

Key words: Ketoprofen, Multiparticulate, Ethyl Cellulose, Cellulose Acetate, Dry Powder layering.

INTRODUCTION:

Multiparticualte systems offer various advantages over single-unit systems. These include no risk of dose dumping, flexibility of blending units with different release patterns, and reproducible and short gastric residence time (Gothoskar & Joshi, 2004). Multiparticulates may be prepared by several methods. Different methods require different processing conditions and produce multiparticulates of distinct qualities. Some of these methods may be broadly classified as pelletization, granulation, spray drying, and spray congealing (Elaine et al. 2005). The layering process comprises the deposition of successive layers of drug entities from solution, suspension or dry powder on nuclei which may be crystals or granules of the same material or inert starter seeds. In solution/suspension layering, drug particles are dissolved or suspended in the binding liquid (Gamlen, 1985, Jackson et al. 1989). In powder drug layering, a binder solution is first sprayed onto the previously prepared inert seeds, followed by the addition of powder (Ghebre-Sellassie et al, 1985, Gajdos, 1983, Niskanen et al, 1990, Muhammed, 1991). Sugar spheres were poured into the coating pan, then intermittently treated with a nebulized binder solution applied by spray guns and with a finely dispersed drug powder applied by a specially designed powder feeding unit (Claudio et al, 2000). Drug particles may be entrapped within the multiparticulates or layered around them. Subsequently, these multiparticulates may be modified in many ways to achieve the desired drug-release profile. The factors affecting the coating and drug-release characteristics from multiparticles are important because control of these factors ensures consistency of drug release between the batches. Factors may be classified into four groups: characteristics of cores, characteristics of SR coats, coating equipment, and coating process conditions (Elaine, 2005).

Ketoprofen is (RS)2-(3-benzoylphenyl)-propionic acid (chemical formula $C_{16}H_{14}O_3$) is one of the propionic acid derivatives of non-steroidal anti-inflammatory drug (NSAID) with analgesic and antipyretic effects (Kantor, 1986). It acts by inhibiting the body's production of prostaglandin. Ketoprofen undergoes metabolism in the liver via conjugation with glucoronic acid, CYP3A4 and CYP2C9 hydroxylation of the benzoyl ring, and reduction of its keto function (Lemke et al, 2008).

Present study is aim to prepare controlled release multiparticulate of Ketoprofen by drug powder layering technology using two different release retardant(Ethyl Cellulose & Cellulose Acetate) in five different drug : release retardant concentrations(5%, 10%, 20%, 30%& 40%). Cellulose acetate core effectively controlled the drug release for a period of 11 hr at ph 7.5 (Shivkumar et al, 2006). Talc being an important component of the coating dispersion is known to reduce the porosity of the acrylic film coatings and lower their water permeability. The particles of talc are reported to form a lattice structure, which are easily embedded in the polymer layers thereby significantly reducing the sticking during the film forming process (Lehmann et al, 1994). Finally prepared formulation of Ketoprofen subjected for various physical characteristics studies to characterize the influence of release retardants on the release profile of Ketoprofen from multiparticulate formulation.

MATERIALS AND METHODS:

Materials

Non-pariel seeds were obtained from Tagorf Pure Chemical. Ketoprofen was obtained from Torrent Pharmaceutical ltd, Ahmedabad. Potassium dihydrogen ortho phosphate, sodium hydroxide was of analytical grade purchased from S.D.Fine chem. Ltd, Mumbai. Ethyl Cellulose, cellulose acetate and polyvinyl pyrolidone obtained from Loba Chemie, Mumbai.

Method

Spectrophotometric method development of Ketoprofen:

An accurately weighted amount of Ketoprofen equivalent to 100mg was transferred into 100ml volumetric flask. To this 50ml of Phosphate buffer pH 7.2 was added, sonicated for 10 min, shaken thoroughly for 15 min and then made the volume with Phosphate buffer pH 7.2. The solution was filtered and further dilutions were made with phosphate buffer pH 7.2. A series of standard solution containing 5-30 µg/ml of Ketoprofen were prepared in phosphate buffer pH 7.2 and absorbance was measured at 260 nm against solvent blank using U.V.Spectrophotometer (Shimadzu–UV 1700). The sample was stored at room temperature and again absorbance was measured after 48 hours for the verification of stability and reproducibility of the drug in the buffer.

Preparation of Ketoprofen loaded Multiparticulate formulation by Dry Powder Layering Technology (Claudio et al, 2000) :

Accurately weighted 100 gm of non-pareil seed of 30 mesh size (600) were dried at 35°C to remove any moisture present. These dried non-pareil seeds were charged into the coating pan, which has the bed temperature of 35°C. 5 % binder solution of PVP-K30 in 70:30 of IPA:H_20 was sprayed with a help of a spray gun (Type 64 Pilot Spray gun attached with compressor) till the bed become wet. Immediately require amount of drug powder was layered on the wet bed of multiparticles at 1:1 Non-pareil : Drug ratio. Pan rotation was continued until the drug powder adheres onto the wetted multiparticles properly. Drying bed temperature and blowing air temperature maintained properly to avoid over heating of drug loaded multiparticles (DLM), which may cause the separation of drug from the multiparticles after several pan rotations. After layering the Drug Loaded Multiparticles (DLM) were kept in an oven for 2 hr at 35 °C. (Table 1)

Table 1: Coating Specification

Coating Specification	
Pan Diameter	12 inch
Heating temperature	40°C
Diameter of blower	40 mm
Air flow	10 CFM (cubic feet per minute)
Pan rotation	20 rpm
Bed temperature	35°C
Pressure from Air Compressor	15 kg/cm²
Powder drug application rate	20 gm/min
Spray gun position to the bed	90° to the bed
Spray nozzle Diameter	1.2 mm
Rolling time	15 min

Coating of DLM with Ethyl Cellulose (EC) and Cellulose Acetate (CA):

Actually dried and weighted DLM were charged in to coating pan at 35^{0}C. Ethyl Cellulose and Cellulose Acetate of 5%, 10%, 20%, 30% and 40% were prepared in 40:60 ratio of Acetone : Isopropyl alcohol and 50:50 ratio of Dichlormethane : Ethanol respectively. A measured quantity of polymer mixed with their respective solvent by using a magnetic stirrer for 20 mins. 5 % Talc as an anti sticking agent was added to each solution based on the solid dry weight of EC and CA and mixed for 30 minutes. Coating was done until the multiparticulate achieve 10 to 12 % TWG (Theoretical Weight Gain). % TWG is relative to the weight of the coated multiparticles and calculated using the following formulae:

TWG (%) = (X/Y-1) X 100

X = Weight of uncoated multiparticles.

Y = Weight of coated multiparticles.

Density of multiparticles:

Density of multiparticles can be known by liquid displacement method using n-Hexane method. Weight of the specific gravity bottle =W1g
Weight of the specific gravity bottle plus sample =W2g
Weight of sample (W3) = W2-W1
Weight of the specific gravity bottle plus sample plus solvent = W4
Weight of liquid displaced by solid = W4-W2
True density = W2-W1/W4-W2

Drug content Uniformity:

The prepared multiparticles formulations of Ketoprofen were tested for their drug content. Multiparticles of each formulation were taken and triturated properly. Then a quantity of powder equivalent to 100 mg of drug was taken and mixed with 100 ml phosphate buffer p^H 7.2 and shaken properly for 15 minutes. Then it was diluted to analyze for Ketoprofen content at 260 nm using U.V.Spectrophotometer.

Compatibility study by Fourier Transform Infrared Spectroscopy (Chowdary and Girija Sankar 1997) (FTIR) :

The dried powder samples of 1 gm were taken with 100 mg of KBr and grounded together to make it fine. They were pressed under high pressure to a pellet of 10.00 mm diameter and 1-2 mm thick. The pellets were scanned over a wave range of 4000 cm $^{-1}$ to 400 cm^{-1} using FTIR. (Figure 1. and Figure 2.)

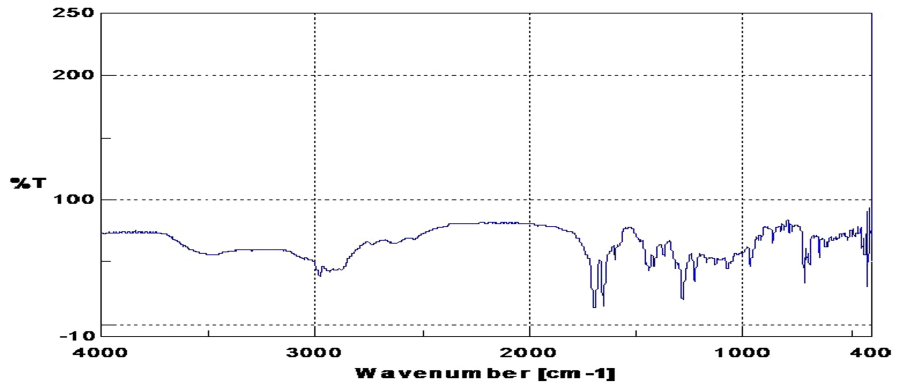

Figure 1.

Figure 1. Characteristic peaks of IR transmission of ketoprofen pure drug.

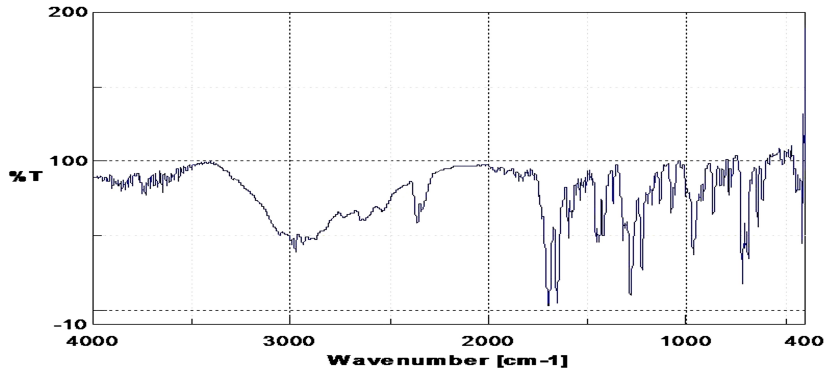

Figure 2.

Figure 2. Characteristic peaks of IR transmission of ketoprofen formulation.

Differential scanning calorimetry (DSC):

Differential scanning calorimetry (DSC) is valuable in studying the beginning of melting of a compound. The temperature at which the suspected melting endothermic peak begins is considered to be the beginning of melting. Thermograms of ketoprofen-pellets were obtained using a Perkin Elmer-Jeda DSC instrument equipped with an intra-cooler. Powder samples were hermetically sealed in perforated aluminum pans and heated at a constant rate. Purge gas-nitrogen at a flow rate 20 ml/min and heating temperature of 100ºC was used to maintain inert atmosphere. (Figure 3. and Figure 4.)

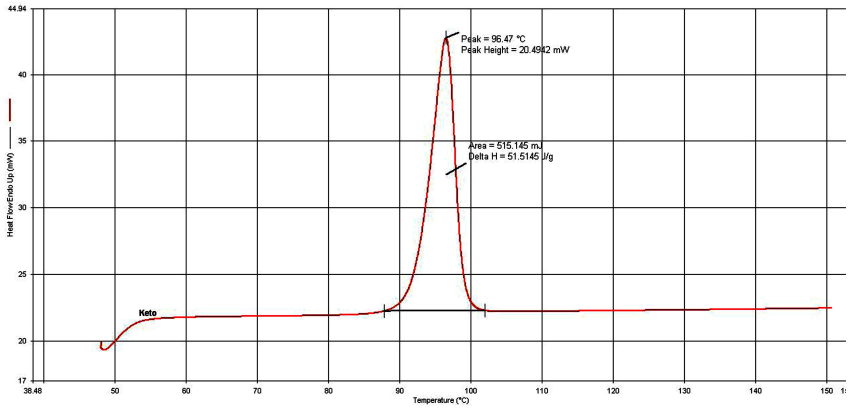

Figure 3.

Figure 3. DSC Thermogram of Secnidazole Formulation

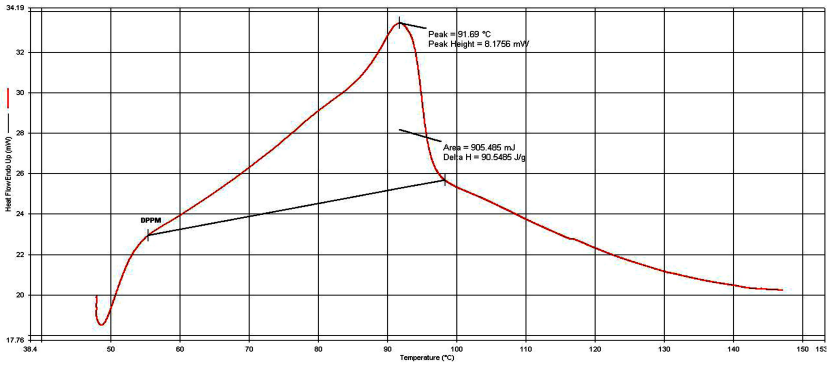

Figure 4.

Figure 4. DSC Thermogram of secnidazole pure drug

Scanning Electron Microscopic Study (SEM) (Alvarez et al, 2003):

Scanning electron microscopy was carried out using Jeol scanning electron microscope (Model- jsm 5200) in 76, 300, 350 magnifications. Before taking the SEM photograph the pellets were subjected to sputter coated with gold. (Figure 5 and Figure 6.)

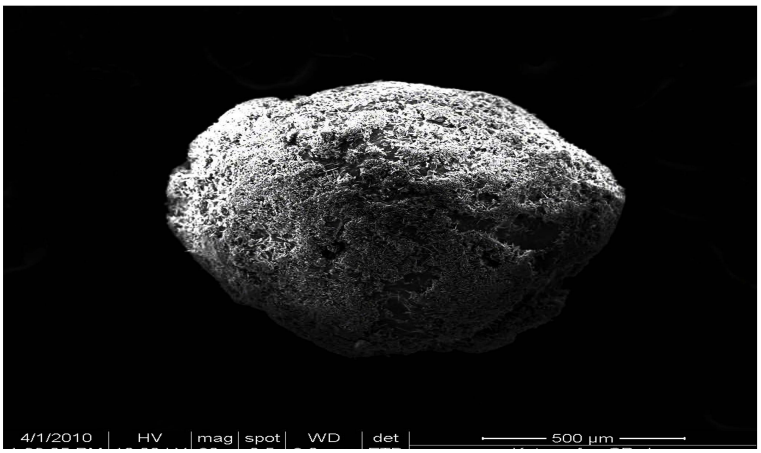

Figure 5. SEM of ketoprofen drug loaded pellet at 80X magnification

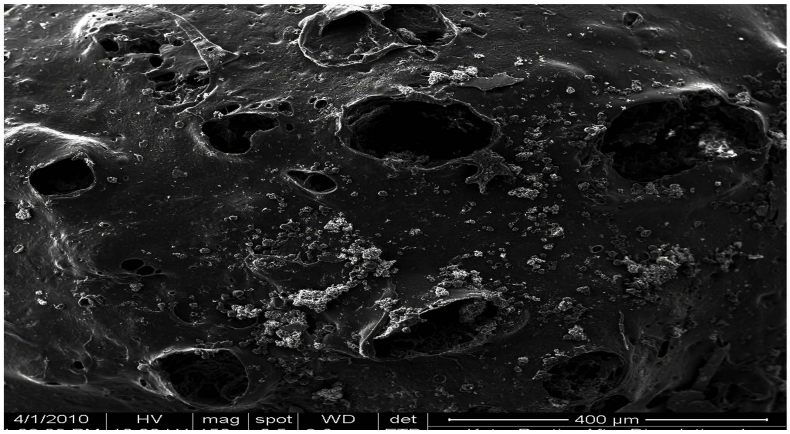

Figure 6. SEM of ketoprofen drug loaded pellet's closed view at 400 X magnification

In Vitro Drug release study:

All the multiparticulate formulations were subjected to in vitro release studies in phosphate buffer p^H 7.2 for 18 hours. Drug release studies were carried out using USP XXI six stage dissolution rate test apparatus (Apparatus 2, 100 RPM, 37^0C) for 18 hrs. 5 ml aliquots were withdrawn at different time intervals and 5ml of fresh 0, 1, 2, 3, 4, 8, 10, 12, 14, 16, 18 hours for all formulations. The absorbance was measured spectrophotometrically at 260 nm and corresponding concentration were determined from respective standard curves. Each experiment was conducted in triplicate.

RESULTS AND DISCUSSION

The Percentage Yield, Drug Content Uniformity and Densities of Ketoprofen multiparticles coated with Ethyl cellulose and Cellulose Acetate is shown in Table 2. The *invitro* dissolution characteristics of Ketoprofen multiparticles with Ethyl Cellulose and Cellulose Acetate showing the order of kinetics is given in Table 3.

Table2. Percentage Yield, Drug Content Uniformity and Densities of Ketoprofen Multiparticles coated with Ethyl cellulose and Cellulose Acetate.

Formulation	% Yield	Drug content %	Density (gm / cm^3)
EC1	69.26±2.41	98.25±2.22	1.895
EC2	72.11±2.42	98.06±3.45	1.983
EC3	69.02±2.69	97.32±3.89	1.981
EC4	75.75±2.01	96.80±2.70	2.102
EC5	77.85±3.98	97.98±2.34	2.186
CA1	84.69±3.26	98.06±3.53	1.843
CA2	81.99±2.67	98.07±3.40	1.701
CA3	84.25±3.56	97.64±2.89	1.832
CA4	81.48±3.22	96.99±3.48	1.784
CA5	79.25±3.09	98.26±2.47	1.889

Table3: In Vitro dissolution characteristics of Ketoprofen Multiparticles with Ethyl Cellulose and Cellulose Acetate:-

Formulation	Zero order release kinetics		First order release kinetics		Higuchi model kinetics	
	K	r	K	r	K	r
CA1	5.2140	0.9941	0.1441	0.9408	25.9117	0.9903
CA2	4.6480	0.9974	0.1270	0.9778	24.5186	0.9946
CA3	4.4896	0.9961	0.1017	0.9951	23.4178	0.9888
CA4	4.2447	0.9962	0.0940	0.9910	20.1793	0.9843
CA5	4.1223	0.9950	0.0890	0.9711	20.7033	0.9897
EC1	4.7420	0.9977	0.0988	0.9824	20.1192	0.9697
EC2	4.4788	0.9934	0.0861	0.9779	22. 4147	0.9719
EC3	4.1599	0.9949	0.0661	0.9727	22.1161	0.9688
EC4	4.2140	0.9987	0.0674	0.9755	21.4459	0.9810
EC5	3.8346	0.9969	0.0507	0.9901	21.7114	0.9747

Study concluded that Dry Powder Layering of Ketoprofen can be effectively used for drug loading on non-pareil seeds and the proposed method is simple and can produce controlled release pellets with uniform size and shape**.** It was also found that formulation with Ethyl Cellulose have more retarding capacity than the Cellulose Acetate in both formulations. From dissolution parameter of the prepared multiparticles it was concluded that formulation EC3 (20%) and CA4 (30%) posses the required characteristics of oral controlled release formulation having r- value 0.9978 and 0.9960 respectively. Drug content of all formulation was found to be above 90 %. The percentage yield of all formulation is between 65-75 %. Hence this formulation can be used as once daily dosage regimen for the controlled release of Ketoprofen.

Conflict of interest*:*

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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