Research Article

Development and *In Vitro* Evaluation of Multiparticulate Controlled Drug Delivery System

Gandhi Bipin* **and Baheti Jagdish**

Shri Jagdishprasad Jhabarmal Tibrewala University,
Jhunjhunu, Rajasthan, Jaipur, India.

ABSTRACT

The objective of the present study was to develop and evaluate a multiparticulate system for controlled drug delivery system. The system comprising of Eudragit NE 40D coated pellets, designed for controlled drug delivery of Zolpidem Tartarate. The sugar beads/pellets were loaded with drug (Zolpidem Tartarate) using PVP K30 as a binder and HPMC E5 LV as a coating material. Different coat weights of Eudragit NE 40D were applied to the drug loaded pellets in Fluidized Bed Processor (FBP) to produce the controlled release drug delivery. Scanning electron microscopy revealed that the drug layered pellets were discrete, spherical or oval with a slightly rough surface whereas the coated pellets were covered with a uniform and continuous Eudragit NE 40D film. The friability with glass spheres was below 1.0%, signifying the core pellets produced were sufficiently hard. *In vitro* dissolution studies of the pellets performed which showed that the drug release from the coated pellets depend on the coat weights applied. Since, Zolpidem Tartarate is a drug, which exhibits a high solubility, it would be possible to minimize drug release from coated pellets and effectively release the drug for controlled drug delivery system.

Keywords: Eudragit NE 40D, Zolpidem Tartarate, Multiparticulate System, Fluidised Bed Processor.

INTRODUCTION

Pharmaceutical research and development started focusing on delivery systems which enhance desirable therapeutic objectives while minimizing side effects. Recent trends indicate that multiparticulate drug delivery systems (MDDS) are especially suitable for achieving controlled or delayed release with low risk of dose dumping, flexibility of blending to attain different release patterns as well as reproducible and short gastric residence time. The release of drug from microparticles, pellets depends on a variety of factors including the carrier used to form the multiparticulate system and the amount of drug contained in them. Consequently, multiparticulate drug delivery systems provide tremendous opportunities for designing new controlled and delayed release oral formulations, thus extending the frontier of future for pharmaceutical development. The delayed releases pellets have important properties like high flexibility of doses, dispersed GI tract freely, minimum local irritation and reduce dose dumping.

When compared with single-unit dosage forms, oral multiparticulate drug-delivery systems (e.g. pellets, granules) offer biopharmaceutical advantages in terms of a more even and predictable distribution and transportation through the GI tract, which is fairly independent of the nutritional state. In contrast to single units, coated pellets can be used to mix incompatible drugs or to tailor the overall release of the delivery system by combining pellets with different release patterns. The use of multiparticulate drug delivery systems in preference to single unit dosage forms for colon targeting purposes dates back to 1985 when Hardy and co-workers[1] showed that multiparticulate systems enabled the drug to reach the colon quickly and were retained in the ascending colon for a relatively long period of time. Because of their smaller particle size as compared to single unit dosage forms these systems are capable of passing through the GI tract easily leading to less inter and intra subject variability. Moreover, multiparticulate systems tend to be more uniformly dispersed in the GI tract and also ensure more uniform drug absorption[2-3].

In the field of pharmaceutical development, it is generally agreed that the oral administration of a multiple unit dose formulation possessing a delayed release of the drug substance is beneficial compared to conventional tablet formulations having similar release properties. The benefits of multiple unit dose formulations are primarily that the transport and distribution of the free units in the various segments of the GI tract are more uniform and reproducible than single unit dosage forms. Pellets are used by number of industries to produce variety of agglomerates produced from diverse raw materials using different pieces of manufacturing equipments. Pellets are in the size of 0.5-1.5mm in diameter. A pellet provides high degree of flexibility in the design and development of various oral dosage forms. Pellets can be divided into desired dose strengths to provide different release profiles at the same or different sites in the gastrointestinal tract. Pellets are coated with polymers/drug solution and this are filled in hard gelatin capsules or compressed into a tablet or given in sachets for formulation.

MATERIALS AND METHODS

Zolpidem Tartarate was a gift sample from Aurobindo Pharma, Hyderabad, India. Eudragit® NE 40D was provided by Degussa Evonik, India. Hydroxypropyl methylcellulose E5LV, sodium lauryl sulphate, polyvinyl pyrrolidone K30 (PVP K30) were obtained from Signet Chemical Corporation, Mumbai, India. Sugar pellets (# 25–30, ASTM) were provided by MB Sugars, Malegaon, India. Empty hard gelatin capsules (Size 0) was supplied as a gift from Associated Capsules Pvt. Ltd., Mumbai, India. All other chemicals and reagents used in the study were of analytical grade.

Drug Loading of Pellets

The dry mass consisting of Zolpidem Tartarate was incorporated in a solution of 0.1N HCL containing polyvinyl pyrrolidone (PVP 30K) as a binder and HPMC E5 LV as a coating agent in an isopropyl alcohol with talc as antisticking agent and Sodium Lauryl Sulphate as a solubiliser. This dispersion loaded on 25/30# fraction of the pellets into the fluid bed of FBP.

Eudragit Coating of the Drug-Loaded Pellets

The Eudragit film coating was performed in a FBP. The coating dispersion was prepared by dispersing Eudragit NE 40D (40% w/w) in water to obtain homogeneous solution. A 25/30# fraction of the pellets loaded with Zolpidem Tartarate was charged into the fluid bed of FBP. Four batches of pellets with different coat weights were produced by intermittently applying the coating dispersion on the surface of the drug-loaded pellets. Talc used as a antisticking agent. Eudragit NE 40D can form film without the need of plasticizer and thus diluted with water without the incorporation of a plasticizer. The detailed compositions for film coating are outlined in the Table 1.

Scanning Electron Microscopy (SEM)

Morphology and surface topography of the drug layered and the coated pellets were studied by scanning electron Microscopy[4]. (SEM-JEOL, JSM-840A, Japan). The samples were mounted on the SEM sample stab, using adouble-sided sticking tape and coated with gold (200A^0) under reduced pressure (0.001 torr) for 5 min using an Ion sputtering device (JEOL, JFC-1100 E, Japan).

Pellet Shape

The shapes of coated pellets were investigated by optical microscopic image analysis. The image analyzer consisted of an optical microscope (magnification 4X) linked to a computer and a digital camera (Labomed, India). The digitalized images were analyzed by image analyzing software (Digipro version 2, Labomed, India). The maximum (dmax) and minimum (dmin) Feret diameter, circumference and area were recorded for 100 pellets. The two parameters namely the aspect ratio[5] and the pellet circularity[4]were computed using the formulae, Aspect ratio = d_{max}/ d_{min} and Pellet circularity = $4\pi A/P$, where A and P stands for the projected area and the perimeter of the pellet as seen through the microscope.

Particle Size Analysis

The core pellets were subjected to sieve analysis using a set of standard sieves (1700, 1400, 1000, 710, and 600 mm) in a vibratory sieve shaker for a period of 10 min[6]. The weight distribution data were fitted into log-normal distribution and the geometric mean diameter was computed from the log probability plots[7]

Friability

Friability of the core pellets were determined by subjecting 10 g of the core pellets of the 25/30# mesh fraction with 200 glass beads to abrasion in a automated USP friabilator (Electrolab EF-2, India) for 4 min at 25 rotation/min[8]. The abraded samples were sieved using sieve #30 mesh for 2 min. The pellets retained on the sieve were weighed and % friability was calculated from the difference in the weight of pellets before and after friability.

Flow Properties

The Compressibility Index and Hausner ratio of the coated pellets were computed on the basis of tapped bulk density and poured bulk densities. Tapped bulk density (ρ_t) was determined by taking 20 g of the pellets in 50 ml measuring cylinder and tapping it to a constant volume in a bulk density apparatus (Cambell Electronics, India). Poured bulk density (ρ_p) was determined by three- tap method using the same apparatus. Compressibility index = 100 (ρ_t - ρ_p)/ ρ_t and Hausner ratio = ρ_t /ρ_p.

***In vitro* Dissolution Studies**

In-vitro release of Zolpidem tartarte from pellet formulations was investigated by the USP apparatus II (Paddle method). The release medium was 500 mL of 0.1M HCl solution at 37±0.5 °C and the rotating speed of the apparatus was set to 50 rpm for all formulations (pellets). At certain time intervals, 1 ml of sample was withdrawn and immediately same amount of fresh medium (37±0.5 °C) was replaced. For the determination of Zolpidem tartarate amount, the UV absorbances of the samples were measured at 294.5 nm by UV spectrophotometer and total amount of Zolpidem tartarate release was calculated.

Fourier Transform Infrared Spectroscopy

The IR spectrum of the coated pellets was compared with that of Zolpidem Tartarate to confirm the chemical integrity of the drug in the formulations developed[9]. The samples were powdered and intimately mixed with dry powdered potassium bromide. The powdered mixture was taken in a diffuse reflectance sampler and the IR spectra recorded by scanning in the wavelength region of 2.5-25 µm in a FTIR spectrophotometer (Jasco 460 Plus, Japan).

RESULTS AND DISCUSSION

The formulation was designed to study the use of Eudragit NE 40D for successful coating over drug layered pellets. Since pellets prepared without PVP K 30 were found to demonstrate high values of percentage friability (>15%), PVP K30 was used as a binder to impart sufficient mechanical strength to the core pellets. The friability with glass spheres was below 1% (0.71 ± 0.15), indicating that the pellets produced were sufficiently hard to withstand further processing including the Eudragit film coating process in FBP.

It was evident from SEM photomicrographs (fig. 1) that the drug layered pellets were discrete, spherical or oval with a slightly rough surface. Aspect ratio and pellet circularity were two parameters selected for evaluating the pellet shape. The value of aspect ratio for the core pellets (1.11 ± 0.06) was found to be satisfactory and acceptable since the value of aspect ratio approaches 1.00 as the pellets become more spherical. The aspect ratio was found to be less sensitive to detect a significant difference between visually spherical batches of pellets. Pellet circularity was found to be the more sensitive of the two parameters selected. The circularity value of 1.00 corresponds to a perfect sphere. The circularity for the batch of core pellets was found to be 0.98 ± 0.08.

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[10].With the aim to get fine spray droplets the spray nozzle of 1 mm was used at an atomization air pressure of 0.8-0.9 bars. Table 3 shows process parameters during fluidized bed coating of Eudragit NE 30D. The sticking tendency of the pellets was overcome by controlling the spray dispersion application rate. The coating dispersion flow during the coating process was continuous with no spray system blocking and the pellets showed no tendency to aggregate. It was vivid from the photomicrograph (fig. 2) of the coated pellets that the applied film was smooth, continuous and showed good adhesion to the drug layered pellets. Coating loads of more than20% were not employed because lower coat loads have advantages such as lower cost, reduction in processing time, lower weight and smaller size of the dosage form[11-12].

The drug content (%w/w) of different batches of coated pellets were found to be 95.62±0.39, 96.76±0.24, 98.92±0.54 and 98.59±0.15 for pellets T1, T2, T3 and T4 respectively. The drug content was found to decrease with increase in the coat weights applied. The values of the Hausner ratio for T1, T2, T3 and T4 pellets were found to range from 1.08±0.258, 1.07±0.367, 1.01±0.158 and 1.03±0.248 respectively which confirmed the free flowing nature of the coated pellets.

In vitro dissolution studies of zolpidem tartarate from different pellets were performed in 0.1 M HCl using USP Type II dissolution test apparatus. *In vitro* release experiments were evaluated in order to investigate the release of drug from the drug coated. Table 2 shows the cumulative % drug release of Eudragit NE 40D coated pellets.

The release pattern of the drug loaded pellets is shown in Figure 3. The release behavior of batches T1-T4 changes due to variation in the concentration of Eudragit NE 40D, As increase

the concentration of Eudragit NE 40D the drug release was decreased.

The FTIR spectra of the drug and the physical mixture with the different excipients confirmed the absence of the interaction between the drug and the excipients. The drug Zolpidem tartrate showed OH stretching (bonded) at 3541.63 cm^{-1}, CH aliphatic stretching at 2911.99 cm^{-1} and C=O stretching at 1634.38 cm^{-1}.The hydroxypropyl methylcellulose (HPMC) showed OH stretching (bonded) at 3457.74 cm^{-1} and CH aliphatic stretching at 2832.92 cm^{-1}.

Eudragit NE40D showed C-H stretching of aromatic ring at 3070.12 cm^{-1} and C=O stretching at 1644.98 cm-1. Sodium lauryl sulphate showed OH stretching (bonded) at 3545.49cm^{-1} , CH aliphatic stretching at 2915.84 cm^{-1} and C=O stretching at 1634.38 cm^{-1}

The results collectively establish the industrial feasibility of the FBP to develop controlled release multi-particulate systems. The coated multi-particulates produced by precisely monitoring the coat weights applied can be used to control the drug release.

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Table 1: Composition of Controlled release formulation

Sr. No.	Ingredients (gms)	T1	T2	T3	T4
Drug layer					
1	Sugar pellets (25/30#)	50	50	50	50
2	Zolpidem Tartarate(API) USP	1.25	1.25	1.25	1.25
3	HPMC E5LV U.S.P.	4	4	4	4
5	PVP30K LR	2	2	2	2
6	SodiumLauryl Sulphate AR	0.2	0.2	0.2	0.2
7	Isopropyl alcoholAR	20	20	20	20
8	Talc LR	1.75	1.75	1.75	1.75
9	0.1N HCL	60	60	60	60
Controlled Release Layer					
1	Eudragit NE 40D	10	16.5	33.3	50
2	Talc LR	4	4	4	4
3	Puriied Water	30	30	30	30

Table 2 : Dissolution study Eudragit NE 40D coated pellet

Time (minutes)	Cumulative drug released* (%)			
	T1	T2	T3	T4
30	24.15±0.25	13.13±0.36	6.93±0.14	2.69±0.37
60	32.93±0.36	28.60±0.15	10.19±0.25	5.13±0.54
90	37.18±0.14	34.21±0.14	14.16±0.19	7.59±0.31
120	50.13±0.25	50.24±0.25	17.59±0.15	9.06±0.40
180	56.93±0.19	55.43±0.15	26.07±0.36	14.82±0.38
240	61.08±0.16	60.45±0.35	34.17±0.24	18.09±0.53
300	68.78±0.21	69.12±0.14	41.24±0.21	25.38±0.64
360	75.10±0.32	74.62±0.26	49.22±0.31	31.52±0.52
420	78.13±0.14	77.89±0.32	60.37±0.45	36.29±0.18
480	84.35±0.25	81.85±0.14	68.04±0.50	41.26±0.36
540	88.53±0.39	85.43±0.15	76.85±0.39	44.90±0.14
600	93.58±0.17	88.81±0.35	83.88±0.60	53.57±0.35

*Mean±S.D. (n=3)

Table 3: Process parameters during fluidised bed coating

Sr.no.	Process parameters	Conditions
1	Non – pareils (sugar pellets)	50 gms
2	Spray rate	1.10-1.50 rpm
3	Atomizing air pressure	0.8-0.9 bar
4	Product temperature	33-35^{0}C
5	Inlet temperature	60-70 ^{0}C
6	Fluidizing pressure	0.5-0.6 bar

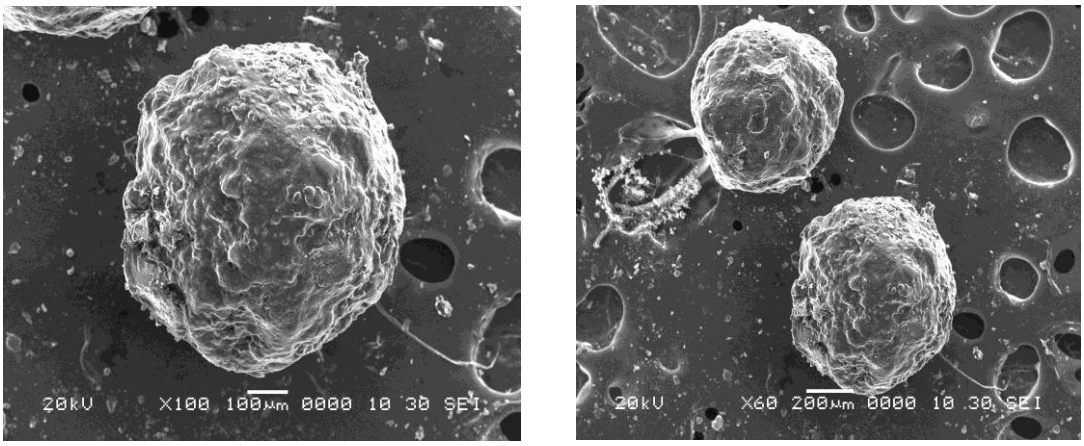

Fig. 1: SEM Photograph of Drug loaded pellets

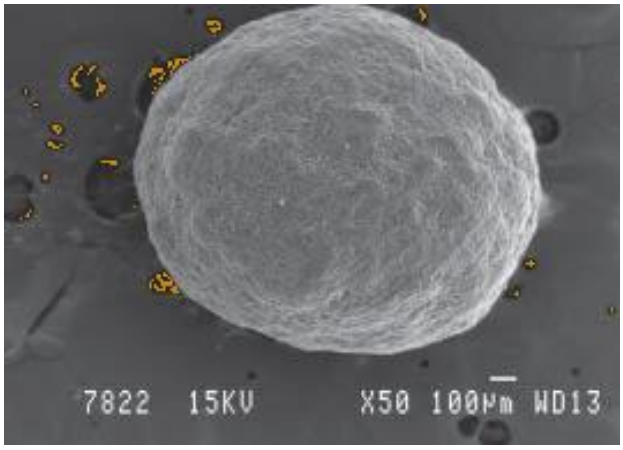

Fig. 2: SEM Photograph of Eudragit NE 40D coated pellet

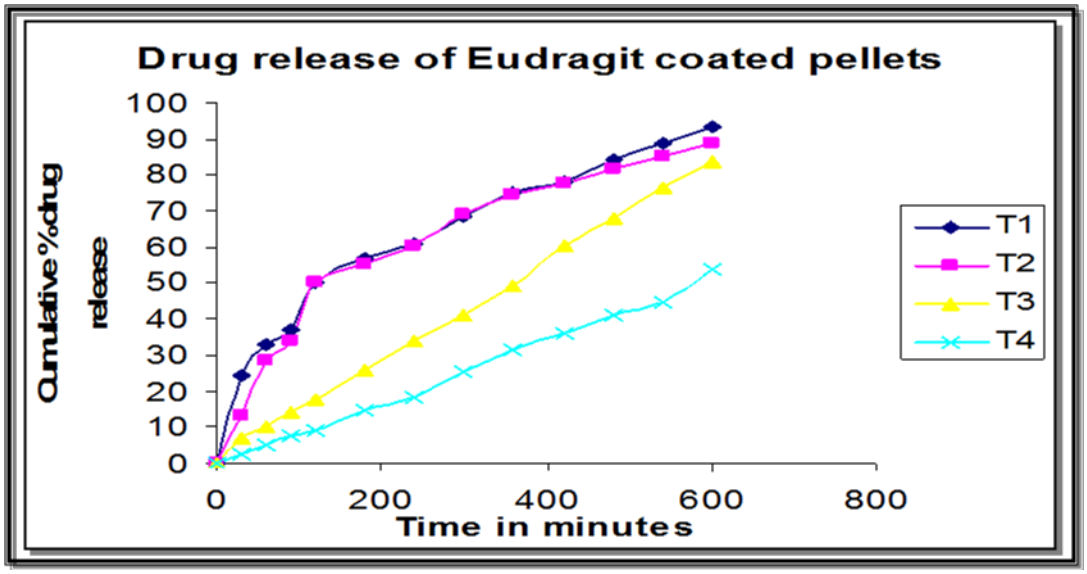

Fig. 3: Drug release from Eudragit NE 40D coated pellets

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