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Research Article

DEVELOPMENT AND *IN VITRO* EVALUATION OF MULTIPARTICULATE SYSTEM USING NOVEL COATING MATERIAL FOR CONTROLLED DRUG DELIVERY SYSTEM

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ABSTRACT

The objective of the present study was to develop and evaluate a multiparticulate system intended to utilize natural material for controlled drug delivery system. The system comprising of Cashew Gum coated pellets, designed for controlled drug delivery of Diltiazem hydrochloride. The sugar beads/pellets were loaded with drug (Diltiazem hydrochloride) using microcrystalline cellulose as a spheronizing aid and PVP K30 as a binder. Different coat weights of Cashew Gum 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 core pellets were discrete, spherical or oval with a slightly rough surface whereas the coated pellets were covered with a uniform and continuous Cashew Gum film. Optical microscopic image analysis portrayed that the values of aspect ratio and pellet circularity were close to 1.0 indicating the core pellets were almost spherical in shape. 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, Diltiazem hydrochloride 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: Cashew Gum, Diltiazem Hydrochloride, Multiparticulate System, Fluidised Bed Processor.

INTRODUCTION

Pharmaceutical invention and research 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

Diltiazem hydrochloride was a gift sample from Blue Cross Laboratories Ltd. Nashik, Cashew Gum was collected from Ayurvedic market. Nashik. Microcrystalline cellulose (MCC) and polyvinyl pyrollidine (PVP K30) were kindly donated by Blue Cross Laboratory Ltd., Nashik. The rest of the chemicals of analytical grade, supplied by S. D. Fine Chemicals, Mumbai included potassium dihydrogen phosphate, disodium hydrogen phosphate.

Drug loading of pellets

The dry mass consisting of Diltiazem hydrochloride (20% w/w) and MCC (77% w/w) was dispersed in aqueous solution of PVP K30 (3%w/w) and this dispersion loaded on #12/22 fraction of the pellets into the fluid bed of FBP.

Natural film coating of the drug-loaded pellets

The natural film coating was performed in a FBP. The coating dispersion was prepared by dispersing Cashew Gum in water to obtain homogeneous solution. Purified talc (#100) was dispersed in the fluid bed to avoid sticking of pellets. A #12/22 fraction of the pellets loaded with Diltiazem hydrochloride was charged into the fluid bed of FBP. Four batches of pellets with different coat weights ranging from 3-6% weight gain (w/w) were produced by intermittently applying the natural dispersion on the surface of the drug-loaded pellets. Coating of the coated pellets was stop when theoretical weight gain of 3, 4, 5 and 6% was achieved and pellets were dried in FBP at 100-105^{0}C. The detailed processing conditions for natural film coating are outlined in the Table 1.

Scanning electron microscopy (SEM)

Morphology and surface topography of the core 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 a double-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 core pellets were investigated by optical microscopic image analysis. The image analyzer consisted of an optical microscope (magnification 4×) 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 #12/22 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 #22 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 Carr 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. Carr compressibility index = $100 (\rho_t - \rho_p)/ \rho_t$ and Hausner ratio = ρ_t / ρ_p.

Drug content estimation

The drug content of different batches of the coated pellets was estimated in triplicate. The composition of the core pellet and coating dispersion along with the processing conditions for natural film coating of Diltiazem hydrochloride loaded Pellets allowed to equilibrate in phosphate buffer of pH 6.4 for 24 h. The solution was filtered (0.22 µm, Millipore, India) and assayed spectrophotometrically at 236 nm (Jasco V 530 UV visible spectrophotometer, Japan).

***In vitro* dissolution studies**

Dissolution studies of the coated pellets were performed in triplicate employing USP XIII dissolution rate test apparatus-1 (Electrolab, TDT-06T, India). simulating the GI tract conditions. Weighed quantities of the coated pellets were loaded into the basket of the dissolution apparatus, the pH changes were performed starting with 900 ml of 0.1 N hydrochloric acid for 2 h, mixed phosphate buffer of pH 5.5 for 1 h, phosphate buffer of pH 6.8 for 2 hour followed by mixed phosphate buffer of pH 7.4 till the end of the test. The temperature of the dissolution fluid was maintained at 37±5 ^{0}C with a stirring speed of 100 rpm. The samples withdrawn every hour were filtered (0.22 µm, Millipore) and assayed spectro-photometrically at 236 nm. The raw dissolution data was analyzed to calculate the amount of drug released and percentage cumulative drug released at different time intervals.

Fourier transform infrared spectroscopy

The IR spectrum of the coated pellets was compared with that of Diltiazem hydrochloride 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 Cashew Gum for successful coating of 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 natural film coating process in FBP.

It was evident from SEM photomicrographs (fig. 1) that the core 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. Talc being an important component of the coating dispersion is known to reduce the porosity of the natural 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[10]. With the aim to get fine spray droplets the spray nozzle of 1 mm was used at an atomization air pressure of 1.0-1.8 bars. 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 photomicrographs (fig. 2) of the coated pellets that the applied film was smooth, continuous and showed good adhesion to the cores. Coating loads of more than 20% 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].

The drug content (%w/w) of different batches of coated pellets were found to be 17.34 ± 0.46, 17.00 ± 0.49, 16.69 ± 0.37 and 16.25 ± 0.49 for pellets DH_1, DH_2, DH_3 and DH_4 respectively. The drug content was found to slightly decrease with increase in the coat weights applied. The values of the Hausner ratio and Carr Compressibility Index for DH_1, DH_2, DH_3 and DH_4 pellets were found to range from 1.02 ± 0.01 to 1.06 ± 0.02 and 2.45 ± 1.09 to 6.36 ± 2.30, respectively which confirmed the free flowing nature of the coated pellets. The dissolution profiles of the coated pellets with different weight gains are shown in fig. 3. The studies portrayed that the drug release from coated pellets depended on coat weights applied.

The pellets DH_1 released all their contents within 5 h. of dissolution as they failed to have any control over the drug release. This can be attributed to the low coat weights applied (3% w.g).

The pellets DH_2 released 35.08 ± 2.01% of the drug during the first 5 hours these pellets released 64.92% of the drug by the end of 10 h of dissolution. An amount of 23.65 ± 1.15% was found to be released at the end of 5 hours of dissolution and released the entire drug by 12 h. The pellets DH_4 exhibited a limited drug release (14.92 ± 0.72%) at the end of the first five hours of dissolution and released the entire drug by 12 h. The limited drug release during the first five hours can be attributed to the controlled release property of the natural film at the increased coat loads. The release rates were slower at higher coat weights, which could be due to increased diffusional path length and tortuosity at higher coating loads [12]. The pellets DH_4 was found to be the best formulation as minimum drug was released within 5h. The IR spectrum of Diltiazem hydrochloride exhibited the characteristic absorption peaks at 3055.66cm^{-1}

(aromatic C-H stretching), 3034.44cm^{-1} (aromatic C-H stretching), 2965.98cm^{-1} (aliphatic C-H stretching), 2837.74cm^{-1} (O-CH_3 C-H stretching), 2389.37cm^{-1} (amine HCl N-H stretching), 1743.33 cm^{-1} (acetate C=O stretching), 1679.69 cm^{-1} (lactum C=O stretching), 839.85cm^{-1} (o-substituted aromatic C-H out-of-plane deformation) and 781.03cm^{-1} (p-substituted aromatic C-H out-of-plane deformation). The IR spectrum Diltiazem hydrochloride at 2837.74cm^{-1} (O-CH C-H stretching), 1743.33cm^{-1} (acetate C=O stretching), 1678.73cm^{-1} (lactum C=O stretching) and 839.85cm^{-1} (o-substituted aromatic C-H out of plane deformation). These IR spectral observations confirmed the lack of chemical interaction between the drug and other excipients used. 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.

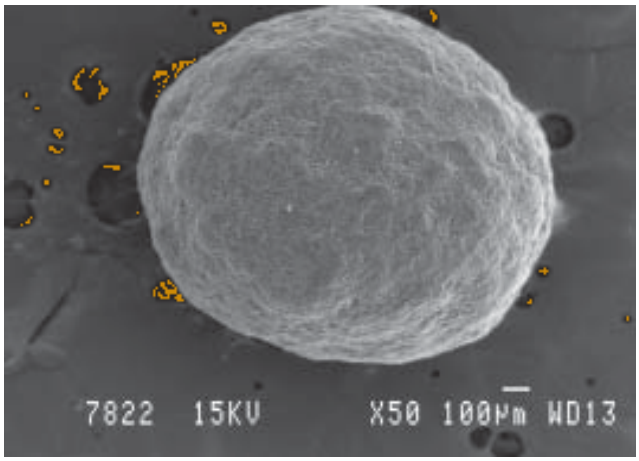

Fig. 1: SEM Photomicrograph of cashew gum coated pellets of Diltiazem hydrochloride

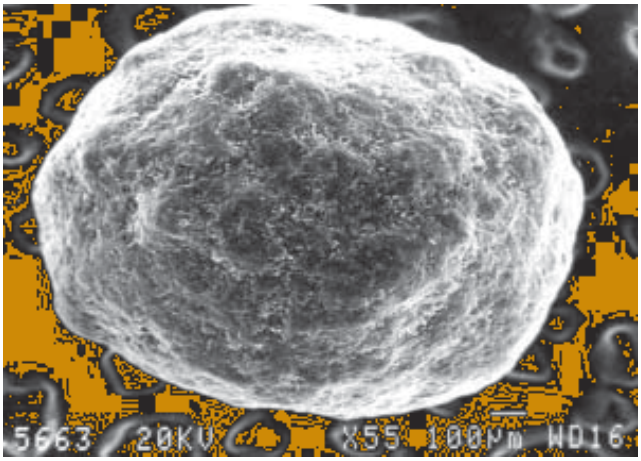

Fig. 2: SEM Photomicrograph of drug- loaded core pellets

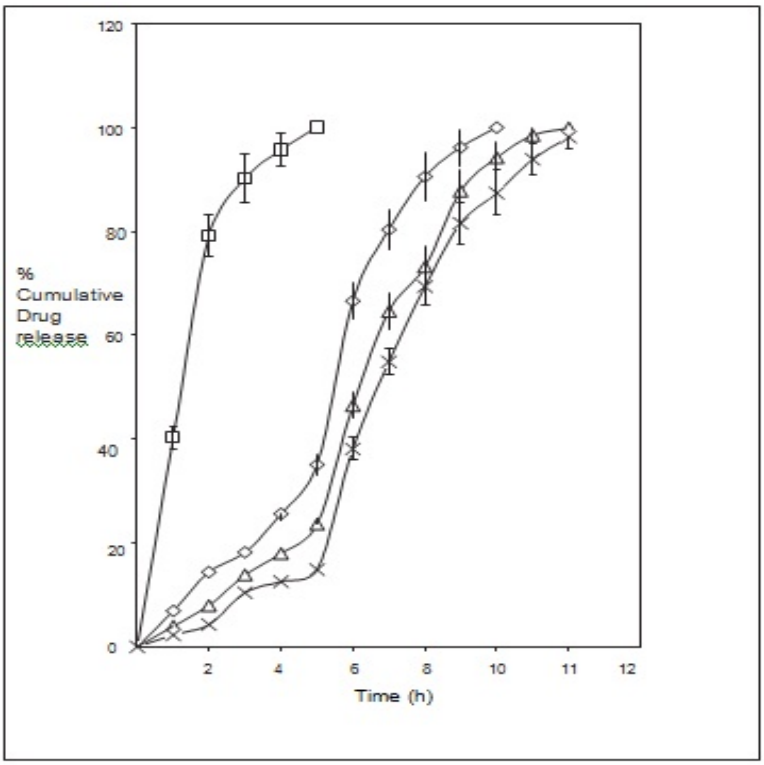

Fig. 3: Release profile of diltiazem hydrochloride from Cashew Gum coated pellets

Release profiles of Diltiazem hydrochloride from Cashew Gum - coated pellets, DH_1 (×), DH_2 (Δ), DH_3 (◊) and DH^4 (□). Each point represents mean of three determinations.

Table 1: Core pellet and coating dispersion composition along with the processing conditions for natural film coating

Core pellet composition (%w/w)		Coating dispersion composition (%w/w)		Processing condition	
Diltiazem HCL	20	Cashew Gum	3.0-6.0	Spray rate	0.6-2.5rpm
MCC	77	Purified Water	q.s.	Air flow	0.8-1.5 bars
PVP K30	03			Atomizing air pres.	1.0-1.8 bars
				Inlet air temp.(set)	30-38^{0}C
				Product temp.	25-30^{0}C

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