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Design and evaluation of cedrela gum based microparticles of theophilline.

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RESUMEN

Objetivo: El objetivo de este estudio fue desarrollar micropartículas de teofilina empleando goma de Cedrela, unas gomas naturales novedosos, como un polímero por pulverización método de secado.

Material y Método: Los parámetros del proceso fueron aerosol de secado diferente temperaturas de 110º, 130º y 150ºC. Las micropartículas fueron evaluadas para características tales como tamaño de partícula, la eficiencia de incorporación, análisis térmico, análisis de rayos X de difracción (XRD) e in vitro de liberación del fármaco.

Resultados: Las micropartículas eran esféricas con morfología de la superficie distorsionada. El tamaño de partícula oscilaron desde 35,6 hasta 58,0 µm dependiendo de la temperatura de secado por pulverización. Calorimetría diferencial de barrido (DSC) estudios revelaron que la teofilina fue dispersado molecularmente a todas las temperaturas de funcionamiento. La liberación del fármaco desde las micropartículas fue inmediata sin tiempo de retraso con liberación completa obtenida a partir de las micropartículas preparadas en la temperatura más alta.

Conclusión: La goma de Cedrela podría servir como un vehículo para la dispersión sólida de fármacos tales como Teofilina por medio de secado por pulverización a una temperatura tan baja como 110ºC. Microesferas obtenidas a esta temperatura eran más pequeños, más de flujo libre y menos susceptible a la aglomeración.

PALABRAS CLAVE: Goma de Cedrela, Liberación de Drogas, Micropartículas, Secado por aspersión, Teofilina.

ABSTRACT

Aim: The purpose of this study was to develop microparticles of theophylline employing Cedrela gum, a novel natural gums, as a polymer by spray drying method.

Materials and Methods: The process parameters were different spray drying temperatures of 110º, 130º and 150ºC. The microparticles were evaluated for characteristics like particle size, incorporation efficiency, thermal analysis, X-ray diffraction (XRD) analysis and in vitro drug release.

Results: The microparticles were spherical with distorted surface morphology. The particle size ranged from 35.6 to 58.0 µm depending on the spray drying temperature. Differential scanning calorimetry (DSC) studies revealed that theophiline was molecularly dispersed at all operating temperatures. The release of drug from the microparticles was immediate with no lag time with complete release obtained from the microparticles prepared at the highest temperature.

Conclusion: Cedrela gum could serve as a carrier for solid dispersion of drugs such as Theophilline by means of spray drying at a temperature as low as 110ºC. Microspheres obtained at this temperature were smaller, more free flowing and less susceptible to agglomeration.

KEY WORDS: Cedrela gum, Drug release, Microparticles, Spray drying, Theophylline.

INTRODUCTION

Microparticles can be designed and produced for the protection of core materials, reduction of gastric irritation, conversion of liquid to pseudo-solid, cell microencapsulation, peptide/protein delivery and for pulsatile drug delivery systems[1]. Previously studied microencapsulating materials due to their biodegradability include poly (D,L-lactide) (PLA) and poly (D,L-lactide-co-glycolide) (PLGA), these have a broad regulatory approval[2]. However their high costs prohibit general use. Other polymers investigated include copolyesters of acrylic and methacrylic acid[3] (Eudragit RS and RL) and cellulose derivatives[4] (ethycellulose, hydroxypropylmethylcellulose (HPMC) and cellulose acetate phthalate. However, some of these anionic polymers tend to react with therapeutic substances like heparin. Further, plasticizers are often needed with ethycellulose to obtain desired film features or drug release profiles[5].

Hence due to the various limitations of different polymers, it is therefore expedient to investigate novel polymeric materials for the encapsulation of therapeutic substances. These investigations usually begin with natural gums due to their ready availability, cost effectiveness, ability to be readily modifiable, potential degradability and generally biocompatible due to their origins[6,7].

The aim of the study was to determine the suitability of the gum extract of *Cedrela odorata* as a carrier in drug delivery systems. The gum is a polysaccharide exudate from the plant *Cedrela odorata* (Fam: Meliaceae). Cedrela gum (CG) is hydrophilic with a pH of 5.2 of 1.0%w/v solution and of medium viscosity. Theophylline was used as the model drug.

MATERIALS AND METHODS

Materials

The materials used were Theophilline (Sigma Chemicals, St. Louis, MO), Cedrela gum was extracted from the incised trunk of *Cedrela odorata* from the Botanical Garden, University of Nigeria (Ibadan, Nigeria) and purified using the established methods [8] thus CG was hydrated in 0.5: 95.5 (v/v) $CHCl_3$/water mixture for 5 days with intermittent stirring; extraneous materials were removed by straining through a muslin cloth. The gum was precipitated from solution using absolute ethanol. The precipitated gum was filtered, washed with diethyl ether, and then dried in hot air oven at 40 °C for 18 h. The gum was pulverized using a laboratory blender and the size fraction < 170 µm was used.

Methods

Characterization of Cedrela gum:

The pH of 1% w/v CG was determined using a pH meter (Horiba pH Meter F-21 Horiba Co. Ltd., Kyoto, Japan). The swelling index of the polymer was determined by the *European Pharmacopoeia* method[9]. Particle densities were determined using the helium pycnometer (Ultrapycnometer 1000, Quantochrome, USA).

Preparation of Theophylline microparticles

Different ratios of the drug:gum were dissolved in water and dispersion was effected by means of a spray drier and the effect of different spray conditions were also evaluated. X-ray diffraction showed that the drug was completely amorphous in the gum at a drug to gum ratio of 1:5. Dispersions of drug and gum at this ratio where then spray dried at temperatures of 110, 130 and 150°C. The particle size and size distribution were then determined and drug release studies were also carried out (Table 1).

Angle of repose

Microspheres were passed through a funnel and the height (h) and radius (r) of the base of the cone formed were determined. The angle of repose was estimated from[10]:

$$\text{Tan } \theta = h/r$$

Percentage production yield and incorporation efficiency

The percentage production yield was calculated as the weight of final product obtained at the end of the spray drying process with respect to the starting weight of the dry materials. Theophiline in microparticles of each formulation was extracted in phosphate buffer (pH 6.6) and the drug concentration determined using a UV spectrophotometer (Pharmaspec UV-1700, Shimazu Co.) at a wavelength of 272nm. The percent incorporation efficiency was calculated from actual drug content in weighed quantity (10mg) of microparticles (Ma) and theoretical amount of drug in microparticles calculated from quantity added in the manufacturing process (Mt) from the following equation[11,12] :

$$\%\text{incorporation efficiency} = Ma/Mt \times 100$$

Table 1. Spray conditions for the Cedrela gum-based theophiline microparticles

Inlet temperature	110 oC	130oC	150oC
Outlet temperature	32 – 40	34 – 43	36 – 47
Air flow rate (L/h)	500	500	500
Orifice pressure	65	65	65
Spray pressure	0.13MPa	0.135MPa	0.135MPa
Feed rate (ml/min)	10	10	10

Table 2. Characteristics of prepared Theophiline loaded microparticles

Inlet temperature (°C)	Yield (%)	Drug Content (%)	Angle of repose (θ)	Zeta potential (mV)	Mean particle size (µm ± S.D)[a]
110	26.5	76.2 ± 1.3	18	-35.2 ± 0.7	5.6 ± 2.31
130	22.7	73.4 ± 0.2	42	-33.8 ± 1.1	22.7 ± 4.22
150	15.8	78.1 ± 0.1	51	-34.1 ± 0.9	58.0 ± 6.52

a. n=3

Scanning Electron Microscopy

Scanning electron microscopy was used to study the morphology of the surface of the particles. The samples were mounted onto the stages and were coated with gold-palladium under vacuum condition using ion sputter (JFC-1100e, JOEL Ltd., Japan). Observation was done using a scanning electron microscope (JSM-T330A, JOEL Ltd., Japan).

X-ray Diffraction

The X-ray diffraction (XRD) patterns of loaded and unloaded gum samples were recorded on an x-ray diffractometer PXRD analysis was performed with a Rigaku Geigerflex powder X-ray diffractometer (Rigaku Denki, Japan). The scanning rate was 4°/min over a 2-theta range of 5 ~ 40°.

Differential Scanning Calorimetry

Differential Scanning Calorimetry (DSC) (DSC-6200, Seiko Instruments Inc., Japan) equipped with a liquid nitrogen cooling system was used to measure the thermal behaviour of the powders. In the analysis, 3-5mg of sample powder was placed in an aluminium pan and examined at a scanning rate of 10°C/min from 20 to 200°C.

Particle size analysis

Particle size and particle size distribution was measured using a laser diffraction particle size analyzer (LDSA-2400, Tonichi Computer Applications, Japan) equipped with dry feeder.

Zeta potential determination

The microparticles were dispersed in distilled water and the zeta potential determined using a Zetasizer 3000HS (Malvern Instruments, United Kingdom).

In vitro drug release study

Dissolution studies were performed according to JP XIV (paddle method) using dissolution test apparatus (NTR-VS6P, Toyam Sangyo C., Ltd.) equipped with auto sampler (PAS-615, Toyama Sangyo Co., Ltd.) and UV spectrophotometer (Pharmaspec UV-1700, Shimazu Co.). Weighed quantities of the microspheres were placed in the medium (900 mL distilled water) set at 37°C temperature and 50 rpm paddle rotation speed. The amount of Theophiline released was determined spectrophotometrically at 272 nm. All measurements were performed in triplicate and the mean value and standard deviation determined.

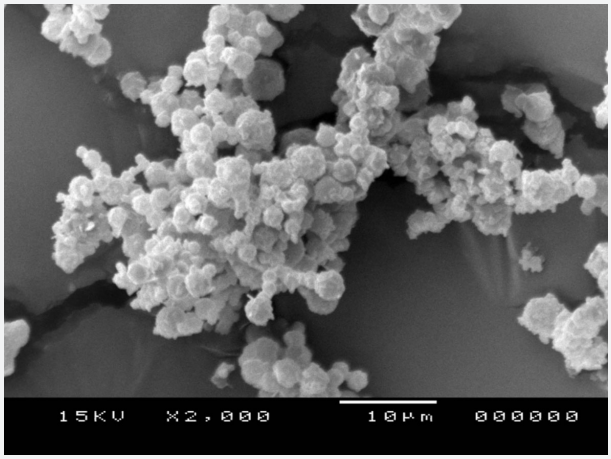
Data analysis

The experiments were conducted in triplicate and data were analyzed by One-way ANOVA using GraphPad Prism version 5.00 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com at 0.05 level of significance.

RESULTS AND DISCUSSION

Spray drying has been found to be a good technique for the preparation of microparticles as it is a one-step process which is easy and rapid and also combined drying of the feed and embedding of the drug into a one step operation[13]. All CG microparticles were spherical with smooth surfaces with no hole or rupture on the surface, except for the unloaded gum (Figure 1). The mean particle sizes varied with inlet temperature of the spray drying process with sizes ranging from 5.6 to 58.0 µm for the 110°C and 150°C respectively (Table 2). The study shows that particle size and shape can be influenced and controlled during processing through the choice of a suitable particle preparation method and variation in the processing conditions, in this case the processing temperature. It was clear that the diameter was highly dependent on the inlet temperature, as the temperature increased the diameter

Figure 1. SEM of microparticles at 130 °C



increased significantly ($p < 0.05$). The particle size is an important property of microspheres as it can influence the biopharmaceutical properties of the particle preparations[14].

Production yield was observed to be low (Table 2) which has been found to be characteristic for this method[13,15]. This could be attributed to powder adhering to the cyclone walls[16] or particularly for this work, due to the small quantity of materials processed in each batch. The microparticles had good incorporation efficiency between 75% and 78%. The microparticles were also negatively charged indicating the molecular dispersion of theophilline in the negatively charged gum. This indicates good prospects for the bioadhesive potentials of the CG based microparticles as polyanionic polymers have been reported to be more effective bioadhesives than polycationic or non-ionic polymers[16,17]. Particles obtained at the lowest temperature had the best flow properties as shown by the angle of repose. This could be due to less tendency to agglomerate with more agglomeration observed with increase in operating temperature.

Figure 2. X-ray diffraction patterns of Theophylline:Cedrela (1:5) gum solid dispersions at different spray-drying temperatures

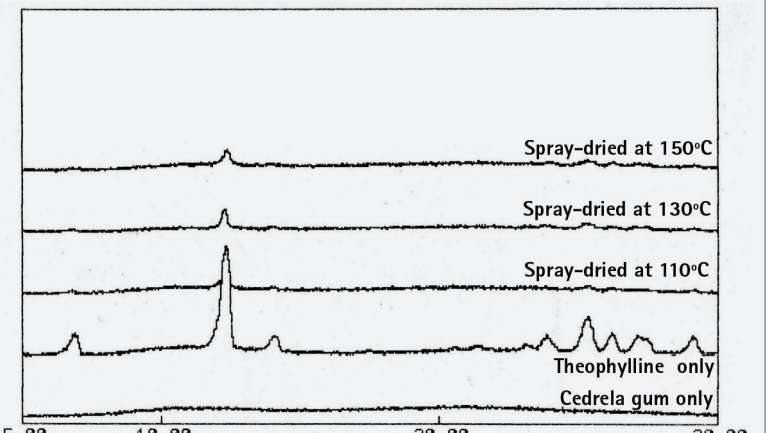


Figure 2 shows the X-ray diffraction patterns of various samples, including the solid dispersions and pure materials of both gum and drug. These studies are valuable in the investigation of the crystallinity of drugs in polymeric microparticles. Theophiline showed many sharp peaks due to its crystalline structure. However, the diffraction pattern of CG did not show any peak which is indicative of its amorphous structure. Theophilline showed characteristic intense peaks between 2θ of 5 and 30. However, no intense peaks were observed for the gum and drug-loaded microparticles at the same range, indicating amorphous nature of drug after entrapment into the cedrela gum microparticles by spray drying. Further, the peaks of the crystalline drug were gradually decreasing with increasing temperature of operation.

The DSC thermograms of the spray-dried microparticles (Figure 3) showed the disappearance of the theophylline endotherm indicating the transformation from the crystalline to the partially amorphous state. The amorphous state of drug leads to a high-energy state which results in enhanced solubility. This confirms the readings obtained from the X-ray diffraction patterns.

The drug release profiles of the microparticles prepared at the different temperatures are given in Figure 4. Drug release was rapid with no lag time observed. Total drug release was obtained from microparticles sprayed at 150°C. This could be due to reduced viscosity and consequent thinner films of gum coating the drug at higher temperature of processing.

Cedrela gum could serve as a carrier for solid dispersion of drugs such as Theophilline by means of spray drying at a temperature as low as 110°C. Microspheres obtained at this temperature were smaller, more free flowing and less susceptible to agglomeration.

Cedrela gum is a biocompatible polymer which with drug delivery potentials. The method of microencapsulation by spray drying was simple, reproducible and easy to scale up and not dependent on the solubility of the drug and polymer. However further studies are required to establish the bioadhesive properties of the gum and any correlation between gum concentration and drug release.

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Figure 3. DSC thermogram of spray-dried theophylline:cedrela gum microparticles at different drug:gum ratios.

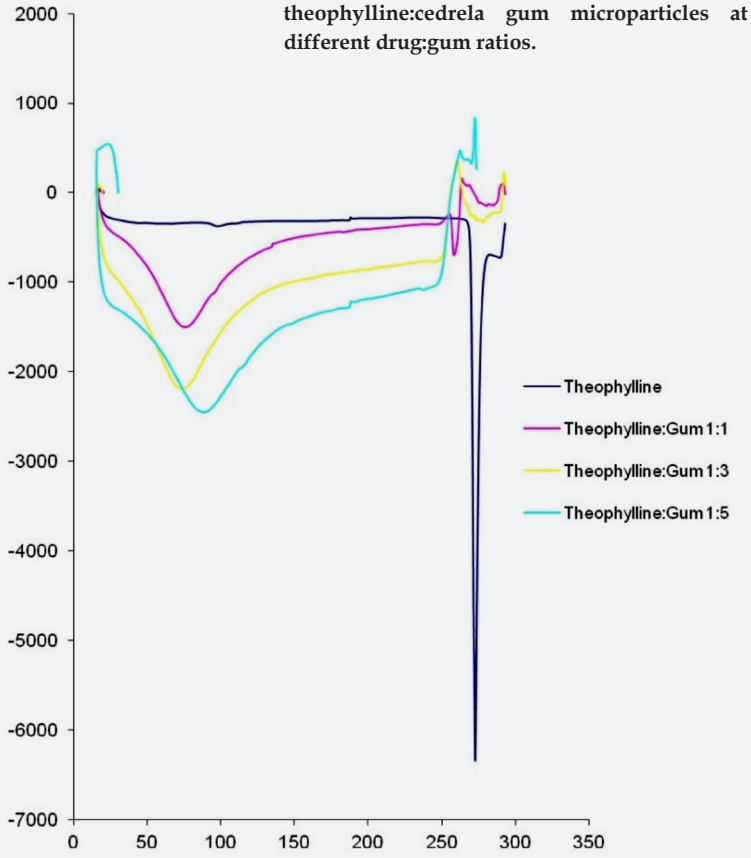
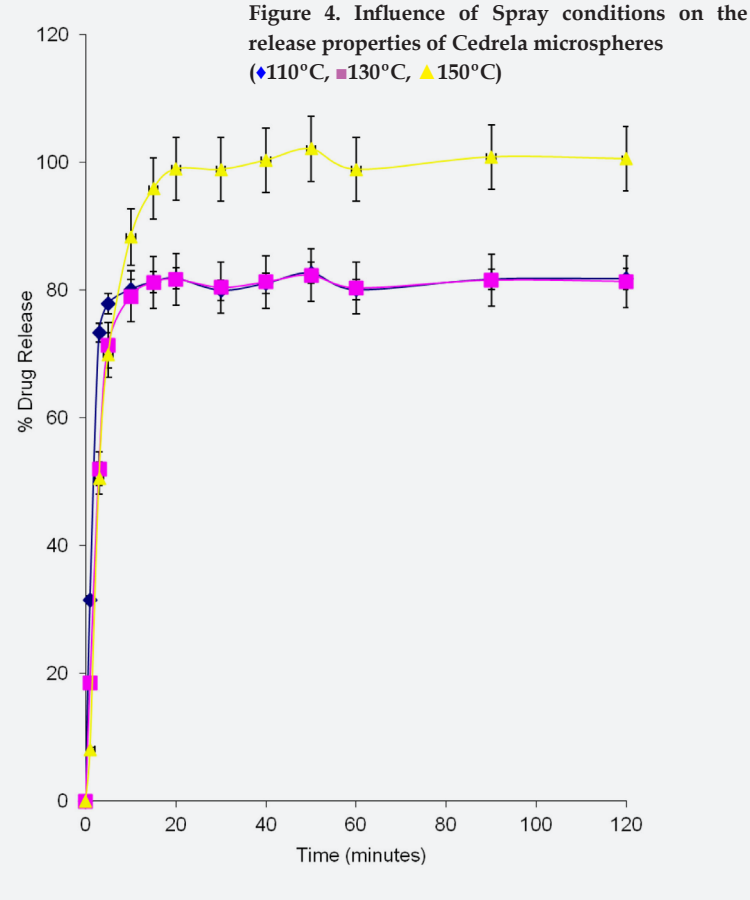


Figure 4. Influence of Spray conditions on the release properties of Cedrela microspheres (♦110°C, ■130°C, ▲150°C)



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