Individual and Interacting Effects of Formulation Variables on the Tensile Strength and Microbial Survival in Diclofenac Tablets

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A work has been done to study the individual and interacting effects of formulation variables, using a 2³ fractional factorial design. The effects of five variables, namely, relative density of tablets, nature and concentration of binder, compression process, and compression speed on the tensile strength and percent survival of Bacillus subtilis spores in Diclofenac tablet formulations were determined. The effects of these variables were studied both singly and when they interact with each other in two fractional designs (Woolfall, 1964). The first fraction comprised of Nature (N) and Concentration (C) of binder, and Relative density of tablets (D) while in the second fraction, Compression speed (S), Compression process (P) and Relative density of tablets (D) were studied. In the first fraction, concentration of binder had the highest effect on tensile strength with the ranking C > D > N for both DCS (formulation containing Corn starch) and DDCP (formulation containing DCP), and C > N > D for DL (formulation containing Lactose). On the percent survival of Bacillus subtilis, relative density of tablets showed the highest effect with the ranking D > C > N for both DCS and DL, and D > N > C for DDCP. In the second fraction, compression speed generally had a great effect on both tensile strength and percent survival in all the formulations. The results of interactions among the variables showed the highest effect on tensile strength from interaction between concentration of binder and relative density of tablets (C-D) while interaction between compression speed and relative density of tablets (S-D) had the highest effect on percent survival in all the formulations. A fractional factorial design proved suitable in determining the magnitude of both the individual and interacting effects of the variables. The study showed that each of these variables has to be properly considered in producing tablets of satisfactory strength and reduced microbial survival.

Key words: Tablettling, Microbial survival, Tensile strength, Formulations, Factorial experiment

INTRODUCTION

Particles of powders to be used to form compacts should not only be sufficiently compressible, but also need to be strong enough to prevent unwanted breaking during handling, transportation, storage and usage. Bond strength is measurable by the tensile strength (T) of tablets (Itiola and Pilpel, 1986a, 1991). The most common way to determine the crushing strength of a particle is to apply a load diammetrically at room temperature and measure the force needed to cause fracture (Alander et al., 2003).

Microbial contamination of pharmaceutical materials is a problem in tablet production due mainly to heavy microbial burden in raw materials. Contaminating microorganisms are destroyed by different formulation variables, which include compression process, nature and concentration of binder, and method and speed of compression. These variables also affect the mechanical properties of the formed tablets. Mechanical properties of tablets depend to a large extent on plastic deformation and bonding potentials of materials. It is therefore expected that there might be some correlation between the mechanical properties and survival of microorganisms during tablettling.

In the present work, a 2³ fractional factorial design has been used to study the effects of relative density of
Albizia zygia gum is a gummy exudate from the trunk of Albizia zygia tree (family Leguminosae). The gum is normally secreted as a light-yellow liquid. This however hardens on exposure to air, turning to yellowish colour solid and then to dark brown nodules or tears upon ageing. Femi-Oyewo et al. (2004) reported that the mucilage of Albizia zygia gum can be employed as stabilizer and thickener of choice when high viscosity is desired especially in cosmetics, pharmaceuticals and food industries. Also, in the work of Odeku (2005) on assessment of Albizia zygia gum as a binding agent in tablet formulation, it was shown that formulations containing Albizia gum had a faster onset and higher amount of plastic deformation under compression pressure than those containing gelatin. However, work has not been done on the effect of Albizia gum on survival of microbial contaminant in the formed tablets.

Diclofenac was chosen for the study due to its poor compressibility and hence, requires a binder among other excipients to form tablets of satisfactory mechanical strength. Bacillus subtilis, a spore forming bacterium was chosen as the microbial contaminant due to its resistance to destruction by both physical and chemical attacks.

MATERIALS AND METHODS

Materials

The materials used were Diclofenac (Unique Chemicals), Cornstarch, Dicalcium phosphate (DCP) and Lactose (Sam Pharmaceuticals), Gelatin BP (Hopkins and Williams, Chadwell Health), Bacillus subtilis spores (Laboratory stock culture, Department of Veterinary Microbiology and Parasitology, University of Ibadan), Nutrient agar pH 6.0, Nutrient broth pH 6.8, Saboraud dextrose agar pH 5.6, MacConkey broth (Department of Pharmaceutical Microbiology, University of Ibadan.), Albizia gum (from Albizia zygia tree, Botanical gardens, University of Ibadan).

Methods

Collection and purification of Albizia Gum. The trunk of Albizia zygia tree was incised. The exudate was allowed to harden after which it was collected from the tree. The hardened exudate was dried in a hot air oven at 40°C until brittle, and then crushed using a mortar and pestle. The size-reduced particles were further reduced into powder of smaller particles by passing them through an Osterizer blender (Model 857, Willamette Industries). The powdered gum was hydrated in double strength chloroform water for 5 days with intermittent stirring. The resultant mucilage was strained through a clean calico cloth to remove extraneous materials. The gum was then precipitated from solution with 95% v/v ethanol. The precipitated gum was filtered, washed with diethyl-ether and then dried in hot air oven at 40°C (Tyler et al., 1981).

Preparation of powder

The binary mixtures of diclofenac formulations and the excipients were prepared by mixing diclofenac and each of the excipient powders in the ratio of 1:1 (Sujjaareevath et al., 1996). The formulations formed were: diclofenac formulation containing corn starch (DCS), diclofenac formulation containing lactose (DL) and diclofenac formulation containing DCP (DDCP). The formulation percentages are shown in Table I. Each batch was mixed for 5 min in a Kenwood planetary mixer. The powder mixtures were then stored in air tight containers and labelled appropriately.

Preparation of granules

250 g batches each of DCS, DL and DDCP were used. Each formulation batch was dry-mixed for 5 min in a Kenwood planetary mixer and then moistened with either 30 mL of distilled water or appropriate quantities of mucilages and solutions of Albizia zygia gum and gelatin respectively, to give 1% or 4% w/w of the gum and gelatin in the final granule formulation. Massing was continued for 5 min and the wet masses were granulated by passing them manually through a number 12 mesh sieve (1400 µm). The granules produced were dried in a hot air oven for 18 h at 50°C and thereafter re-sieved through a number 16 mesh sieve (100 µm). The granules were stored in air tight containers.

Preparation of inoculum

Overnight culture of 18 h was prepared from Bacillus subtilis spores (Laboratory stock culture obtained from Department of Veterinary Microbiology and Parasitology, University of Ibadan). 1 mL of the overnight culture was placed in 9 mL of sterile distilled water and 2 mL of the culture was placed in sterile glass mortars and allowed to dry at 37°C for 48 h.

Contamination of materials

Quantities (10 g) of the diclofenac formulations were gently mixed in the contaminated glass mortars by the method of increasing quantities (Plumpton et al.,