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DIRECT COMPRESSION OF PIRACETAM

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ABSTRACT

It is demonstrated that piracetam undergoes plastic deformation during compression. Incorporation of magnesium stearate dramatically reduces the mechanical strength of the tablets. This effect is much less pronounced when using glyceryl behenate as a lubricating agent.

Silicon dioxide on the contrary increases to a great extent the tensile strength of piracetam tablets. This advantageous impact remains unaffected by addition of magnesium stearate on condition that the drug is mixed with silicon dioxide prior to the addition of the lubricant.

INTRODUCTION

Piracetam (pyrrolidone acetamide) is a psychotropic drug, claimed to be a cerebral stimulant protecting the cortex against hypoxia. It is frequently used in a variety of disorders e.g. alcoholism, vertigo, senile dementia, cerebrovascular accidents and behavioural disorders in children(1). Since a therapeutic dose of 800 mg implicates a rather large tablet volume, there is little room left for additives to improve the compactibility of the drug.

In this paper the compression behaviour of piracetam and the influence of some adjuvants on the mechanical strength of the tablets are studied.

EXPERIMENTAL

Materials : Piracetam was obtained from Pharmachemic (Antwerpen, Belgium). Magnesiumstearate was of Eur. Ph. grade. Colloïdal silicon dioxide (Aerosil 200®) was purchased from Degussa (Frankfurt, G.F.R.) and glyceryl behenate (Compritol 888®) from Gattefossé (Saint-Priest, France).

Methods : Table 1 shows the procentual composition of the formulations evaluated in this study.

Mixing of piracetam with the adjuvants was done in a Turbula mixer (W.A. Bachofen AG, Switserland) at 60 r.p.m. for the time (min) indicated by the number in the formula codename.

TABLE 1

TABLET FORMULATION

FORMULATION CODE NAMES	MATERIALS (Concentrations % w/w)			
	Piracetam	Magnesium-stearate	Glycerol behenate	Silicon dioxide
A	100.0	-	-	-
B1, B15	99.9	0.1	-	-
C1, C15	99.5	0.5	-	-
D5, D15	99.9	-	-	0.1
E15	99.8	-	-	0.2
F15	99.6	-	-	0.4
H15	99.2	-	-	0.8
I15	99.7	0.1	-	0.2
J5, J15	99.5	-	0.5	-
K15	99.3	-	0.5	0.2

The dimensions of the container and the amount of powder in process were kept constant for all formulations.

In formulae I15 and K15 the silicon dioxide and the lubricating agent were incorporated separately hereby doubling the total mixing time to 30 min.

Tablets weighing 500 mg were compressed in an instrumented and computerized eccentric tablet press, equiped with plane-faced punches having a diameter of

11,6 mm(2). Pressure-hardness profiles were obtained by compressing 20 tablets at gradually increasing pressure within 50 to 450 MPa range. After 24 h the crushing strength was determined with a Heberlein hardness tester (Heberlein, Schleuniger, Switserland), equiped with strain gauges to increase the precision of the instrument. Since all tablets showed normal tensile failure, results are expressed as tensile strength ($kg.cm^{-2}$).

Microphotos are taken with a Jeol JXA-50A scanning electron microscope at a magnification of 150 X.

RESULTS AND DISCUSSION

Figure 1 shows the electron scanning microphotos of both the upper and the fracture surface of a tablet made from pure piracetam. The absence of significant fragmentation at the upper surface clearly indicates plastic deformation during compression. In the fractured tablet this conservation of particle integrity is clearly observed. Multiple twin formation within the crystals gives other evidence of plastic behaviour(3).

In figure 2 the effect of mixing time and concentration of magnesium stearate on the tensile strength of piracetam is demonstrated. A distinct reduction in tablet strength can be noticed when the lubricant concentration is increased from 0 % (A) over 0.1 % (B) to 0.5 % (C). As described by Bolhuis et al.(4) this can

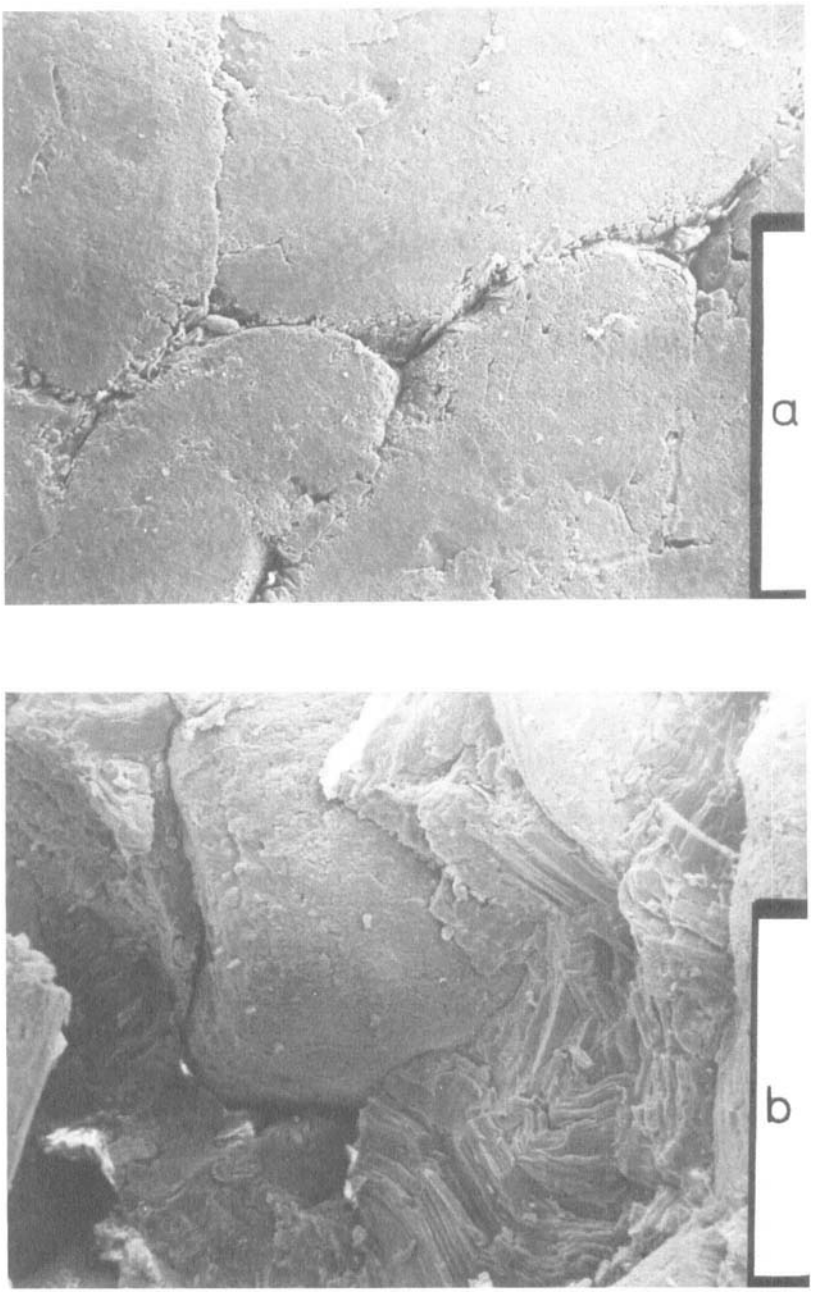

Fig. 1. Electronscanning microphotos of the upper (a) and fracture (b) surface of a piracetam tablet.

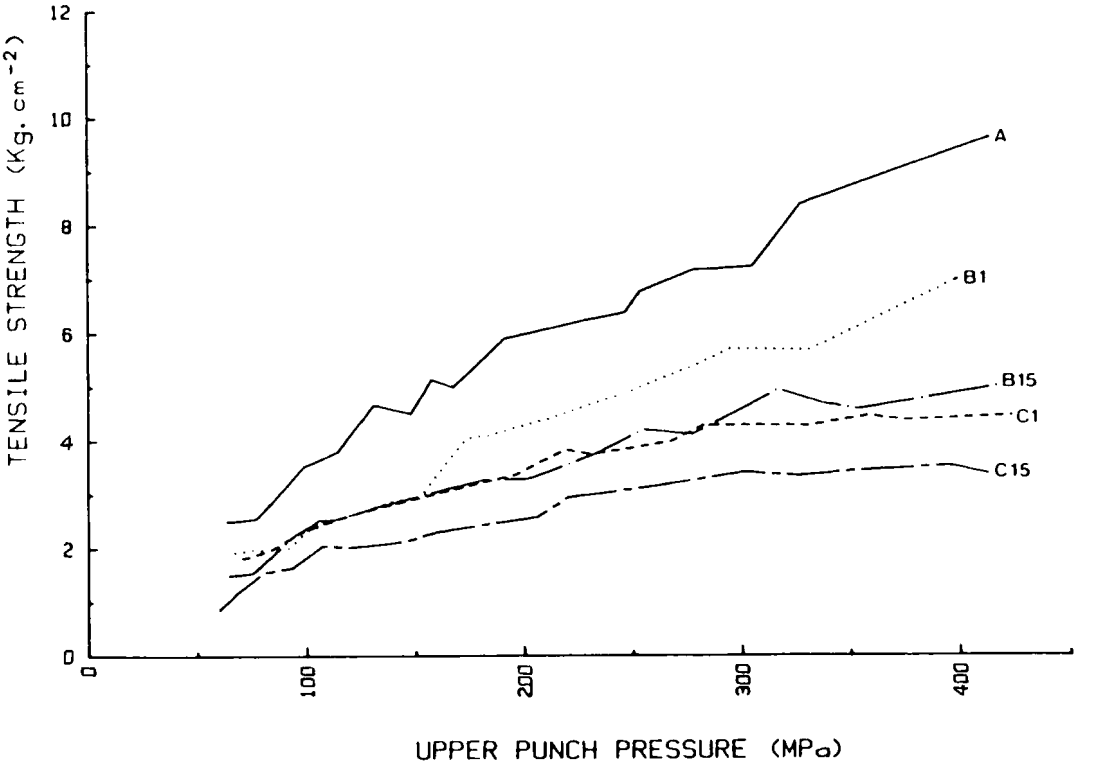

Fig.2. The effect of mixing time and concentration of magnesium stearate on the tensile strength of piracetam tablets, (Key : table 1).

be attributed to the formation of a magnesium stearate film around the drug crystals preventing effective bonding of the plastically deforming particles during compression. As mixing time increases from 1 min (B1, C1) to 15 min (B15, C15), the effect becomes more pronounced, indicating the completion and subsequent thickening of the lubricant layer on the substrate surface as mixing proceeds.

As shown in figure 3 the incorporation of increasing concentrations silicon dioxide has an opposite

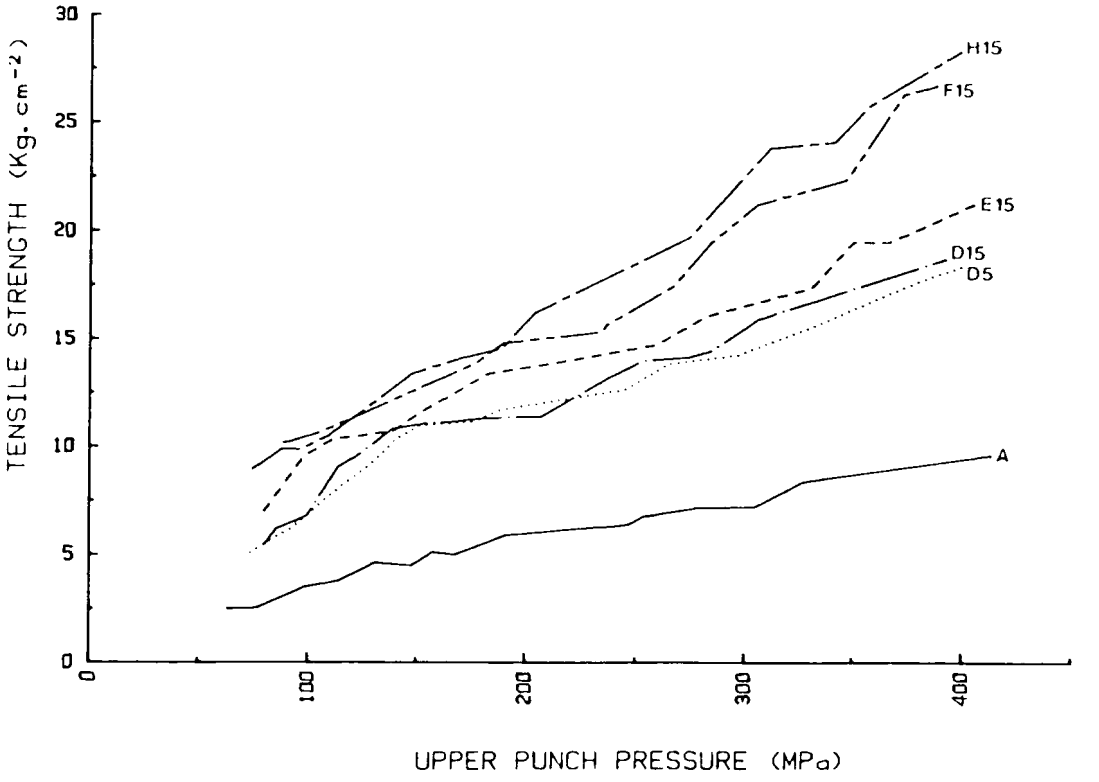

Fig.3. The effect of silicon dioxide concentration on the tensile strength of piracetam tablets, (Key : table 1).

effect on the mechanical strength of the piracetam tablet. The tensile strength is doubled at the 0.1 % (D5, D15) and even tripled at the 0.4 % level (F15). It may be assumed that the hydroxyl groups of the silicon dioxide molecules, adhering to the piracetam crystals, enhance particle bonding strength by the formation of hydrogen bounds. In contrast to the shear dependent delamination of magnesium stearate, the colloidal silicon dioxide is more directly available to the substrate, which explains the fact that differing

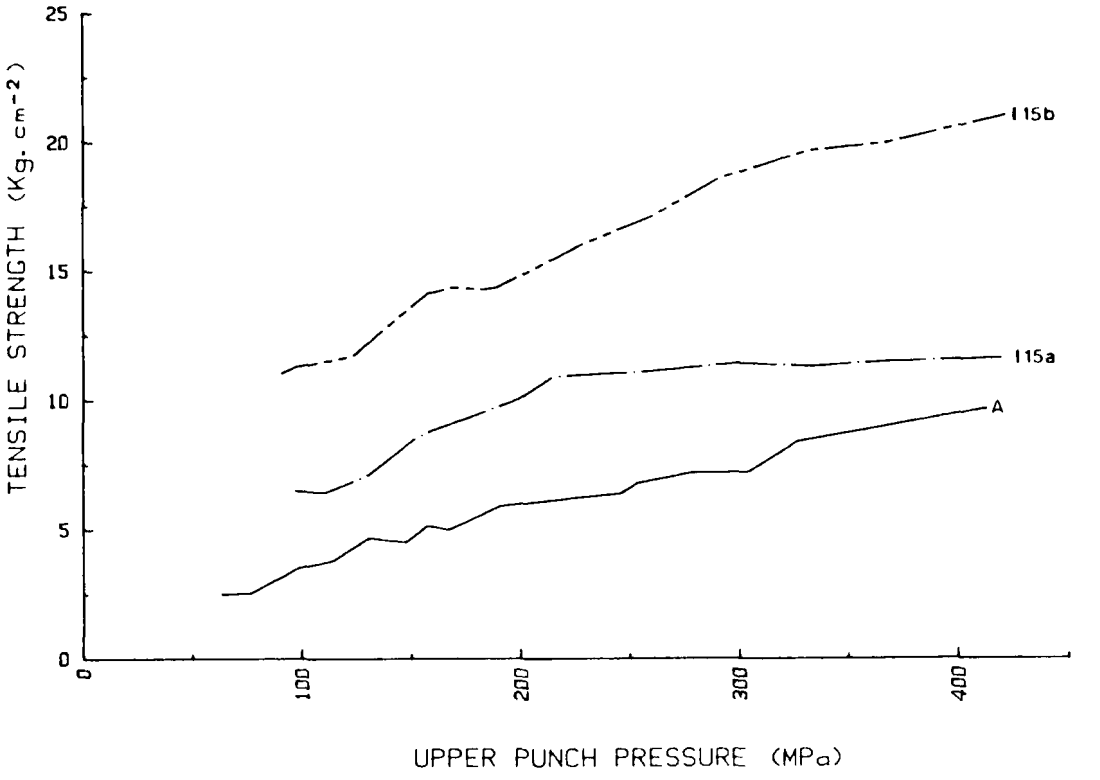

Fig.4. The effect of mixing sequence on the tensile strength of piracetam tablets when magnesium stearate is incorporated before (I15a) or after (I15b) the addition of silicon dioxide, (Key : table 1).

the mixing time from 5 min (D5) to 15 min (D15) has no significant impact on the results.

The combination of both adjuvants (I15) still gives higher tensile strength values although the mixing sequence is here a predominant factor. This competitive action between both adjuvants for coating the surface of a crystalline material was reported earlier by several investigators(5-7). As illustrated in figure 4, mixing the silicon dioxide before adding the magnesium stearate

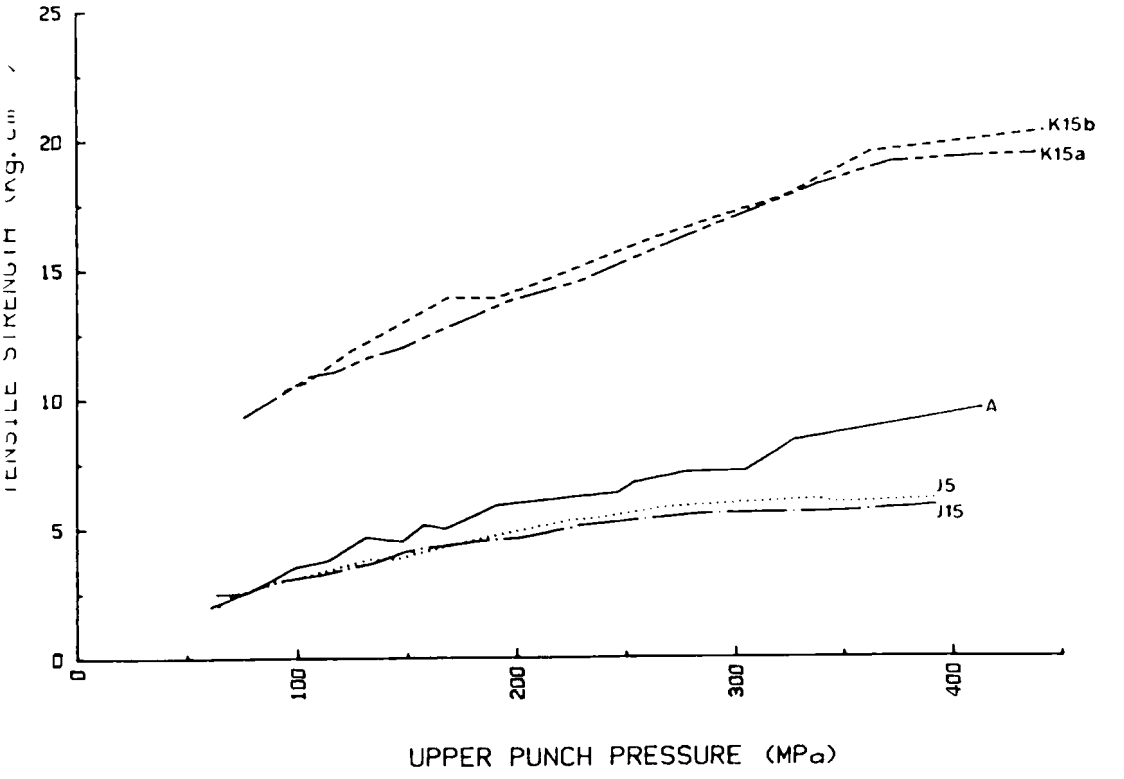

Fig.5. The effect on the tensile strength of piracetam tablets of the mixing time of glyceryl behenate (J5, J15) and the addition of the silicon dioxide before (K15b) or after (K15a) the incorporation of the lubricant, (Key : table 1).

(I15b), hardly alters the advantageous effect of the first. However when lubricant is incorporated prior to the silicon dioxide (I15a) the increase in tablet strength is clearly reduced.

Figure 5 presents the pressure-tensile strength profiles of formulations J and K, both containing glyceryl behenate as lubricating agent. Although good lubrication is obtained, the deterioreous impact on tablet strength is limited compared with the effect caused by

magnesium stearate. Additionaly the results are not significantly affected by mixing time (J5 and J15) nor by the mixing sequence when silicon dioxide is added (K15a, K15b), suggesting a different action mechanism of this lubricant.

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