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The effect of gamma radiation on the tableting properties of some pharmaceutical excipients

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Abstract

Gamma radiation should provide an acceptable method for the sterilization of tableting excipients provided there are no deleterious effects on tableting properties. Three direct compression excipients and maize starch were exposed to gamma radiation at doses of 0, 5, 10 and 25 kGy. Tablets were compressed on an instrumented rotary press. No measurable differences were found between the tableting properties of the irradiated and non-irradiated materials. The effectiveness of maize starch as a disintegrant was not affected by radiation.

Key words: Radiation; Tableting excipient; Tableting parameters

1. Introduction

Tableting excipients such as celluloses, starches and sugars are suitable substrates for microbial growth and, depending on the source of supply, may have a high bioburden. Such solids cannot be sterilized by the traditional methods of moist heat, dry heat and filtration. Gaseous sterilants such as ethylene oxide can be used but problems may arise due to incomplete penetration into all regions of the powder and difficulties in removing traces of the gas and its byproducts. Gamma radiation offers an alternative sterilization method and readily penetrates powdered solids leaving no residues. However, it is first necessary to demonstrate that high-energy radiation has no deleterious effects on the tableting properties of the materials.

A number of parameters have been proposed as measures of the ability of powders and granules to form coherent tablets following compaction. During the initial stages of compaction, the powder particles rearrange and undergo some recoverable elastic deformation. Above a certain stress (the yield stress), the particles undergo permanent deformation. Bonding occurs between the new 'clean' surfaces created during permanent deformation but a coherent tablet requires that the strength of these bonds is sufficient to withstand the strains created by elastic recovery during decompression and ejection from the die.

To investigate whether or not gamma radiation has any effect on the compression characteristics

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of three directly compressible excipients, tableting parameters were determined, for both irradiated and non-irradiated samples, that relate to particle deformation (yield stress, P_y, and peak offset time, t_{off}), interparticulate bonding (force of failure, F_f) and elastic recovery (Young's modulus, E).

The effect of gamma radiation on the properties of maize starch as a tablet disintegrant was also investigated.

2. Experimental

Microcrystalline cellulose (Avicel PH102, FMC, Philadelphia, PA), pregelatinized starch (Sta-Rx-1500, Colorcon, West Point, PA), and spray processed lactose (Foremost, Baraboo, WI) were lubricated before radiation by mixing with 0.5% w/w magnesium stearate (Mallinckrodt, St. Louis, MO), in closed jars on a Fisher Kendall mixer for 5 min. Approx. 30 g lots of each sample were filled into plastic zipper storage bags and exposed to gamma radiation from a ^{60}Co source in a Gammacell 220. The dose rate was 2.5 kGy/h. The exposure time was varied so that the radiation dose delivered was 0, 5, 10 and 25 kGy. The zero dose provided a control on temperature/storage/transportation effects on the materials. Samples of maize starch (Best Foods, Vancouver, BC) were exposed to the same radiation doses. 5% w/w was mixed with a direct compression acetaminophen (Rhodapap, Rhone Poulenc Santé, Shelton, CT) for 10 min and then lubricated as above.

20 tablets were prepared using an instrumented Manesty Betapress over a range of peak pressures, P_{max}, using 0.5 inch flat-faced IPT tooling at a turret revolution time of 1 s. Details of the instrumentation and interfacing with an IBM compatible computer for data acquisition and analysis have been described previously (Oates and Mitchell 1989, 1990).

The strength of the tablets when subjected to diametral compression, was measured using a CT-40 tablet strength tester (Systems Engineering, Nottingham, U.K.) after storage times of 24 h and 3 months.

The disintegration times of the acetaminophen tablets were determined using the disintegration test of the USP XXII (without the disk) after storage for 24 h and 3 months.

All materials were stored, tableted and tested in a tableting room under conditions of controlled temperature and humidity (approx. 20°C and RH 30%).

3. Results and discussion

The decrease in porosity, p, of the powder bed, with the applied stress, P, is given by:.

$$\ln(1/p) = KP + C \text{ (Heckel, 1961)} \quad (1)$$

where K and C are material-dependent constants. K was determined from the slope of a plot of $\ln(1/p)$ vs P_{max}, where each value of $\ln(1/p)$ was determined at P_{max} on the corresponding pressure-time compression profile (Dwivedi, 1992). The reciprocal of K was taken to be numerically equal to the mean yield stress, P_y (Hersey and Rees, 1970; Roberts and Rowe, 1987). As shown in Table 1 the values of P_y were unaffected by gamma radiation over the dose range studied.

For many materials during the compression phase of the compression cycle, it has been shown

Table 1
Yield stress and Young's modulus of non-irradiated and irradiated excipients

Material	Radiation dose (kGy)	Yield stress (MPa)	Young's modulus (GPa)
Avicel PH102	0	73.4 (3.4) [a]	4.6 (0.7) [a]
	5	76.1 (4.5)	4.8 (0.7)
	10	75.2 (4.4)	4.5 (0.8)
	25	74.4 (4.1)	4.8 (0.8)
Spray processed lactose	0	170 (8.7)	5.1 (1.2)
	5	170 (11)	5.3 (1.0)
	10	170 (12)	5.3 (1.6)
	25	169 (11)	4.9 (1.2)
Sta-Rx-1500	0	38.2 (8.8)	4.0 (1.0)
	5	46.7 (3.6)	3.8 (0.6)
	10	43.1 (5.1)	3.8 (0.8)
	25	39.3 (6.7)	3.7 (0.8)

[a] Value (95% confidence interval).

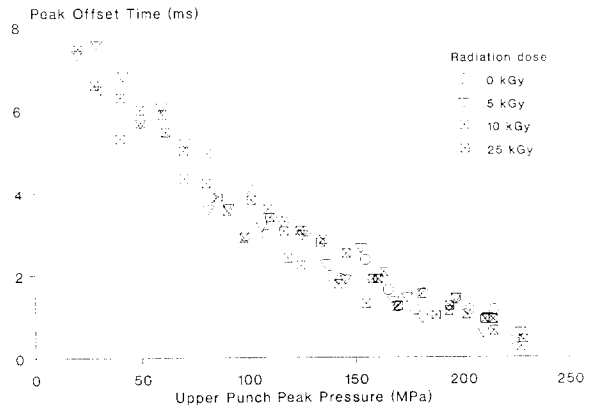

Fig. 1. Peak offset time with upper punch peak pressure for both gamma irradiated and non-irradiated Avicel PH102.

that P_{max} is reached before the position on the press where the upper and lower punches are vertically aligned with the centers of the compression roll support pins (Oates and Mitchell, 1989; Dwivedi et al., 1991). The difference between the time taken to reach P_{max} and the time to reach the dead center position is referred to as t_{off}. Since the distance between the upper and lower punch faces is approximately constant during t_{off}, the decrease in stress during t_{off} occurs under conditions of approximately constant strain (Dwivedi et al., 1991). Thus, t_{off} is indicative of stress relaxation at constant strain.

Fig. 1 shows the decrease in t_{off} with increases in P_{max} for Avicel PH102 after exposure to various doses of gamma radiation. Since all the values can be superimposed on a single curve, it is apparent that t_{off} was not affected by radiation. Similar plots were obtained for Sta-Rx-1500 and spray processed lactose.

In general, an increase in compression force leads to an increase in the number of interparticulate bonds and hence an increase in tablet strength. Fig. 2 shows the increase in F_f with P_{max} for spray processed lactose tablets. Avicel PH102 forms much stronger tablets, and Sta-Rx-1500 leads to much weaker tablets than spray processed lactose, however, both materials show a similar increase in F_f with P_{max}. More importantly from the viewpoint of this work, the results for all three direct compression excipients show that radiation prior to tableting had no effect on tablet strength after storage for either 24 h or 3 months.

Young's modulus of elasticity is a measure of the stiffness of materials and is directly related to the intermolecular energy of the crystal. Any changes in material properties due to gamma radiation may be reflected in the value of E. Dwivedi et al. (1992) have shown that E can be estimated from the axial expansion of a tablet in the die during the decompression phase of the compression cycle. The values obtained for about 25 pharmaceutical solids were in reasonable agreement with those determined by conventional methods. The results in Table 1 clearly show that radiation had no effect on the E values for Avicel PH102, spray processed lactose or Sta-Rx-1500.

The acetaminophen tablets containing maize starch as a disintegrant all disintegrated within 1 min both when tested 24 h after tableting and again after storage for 3 months. The results in Table 2 show that the properties of maize starch as a disintegrant were unaffected by gamma radiation over the dose range studied.

The USP XXII states that "although 2.5 Mrad (25 kGy) of absorbed radiation was historically selected, it is desirable and acceptable in some cases to employ lower doses..." According to Jacobs (1985), where there is a low level of con-

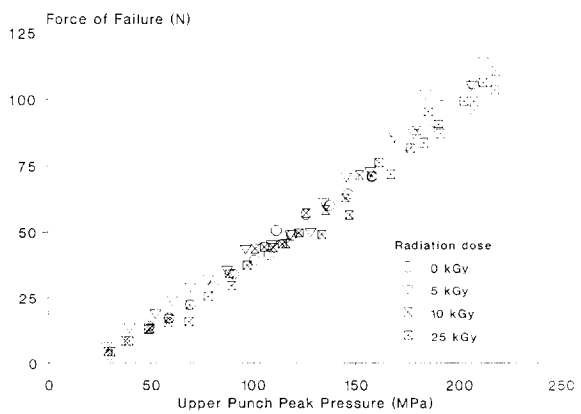

Fig. 2. Force of failure with upper punch peak pressure for both gamma irradiated and non-irradiated spray processed lactose tablets after storage for 24 h.

Table 2
Effect of radiation of maize starch on disintegration time of acetaminophen [a] tablets

Tablet storage time	Radiation dose (kGy)	Disintegration time (s)
24 h	0	54 (4.2) [b]
	5	48 (2.1)
	10	58 (8.8)
	25	54 (9.7)
3 months	0	56 (12)
	5	56 (5.1)
	10	47 (3.0)
	25	58 (7.4)

[a] Rhodapap DC-P3.
[b] Mean (standard deviation) of six tablets; USP disintegration test (without disk).

tamination, doses in the order of 5–10 kGy are acceptable. It is apparent from the results in this study that doses up to 25 kGy do not affect the measured tableting properties of Avicel PH102, spray processed lactose, or Sta-Rx-1500, or the disintegrant action of maize starch.

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