PHARMACEUTICAL ONLINE

Case Study

How A Placebo Formulation Is Designed For An Oral Solid Dose Product

Source: Metrics Contract Services

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OBJECTIVE

To demonstrate the process by which a placebo formulation was designed for an oral solid dose product that would be dispensed to the patient as a fast-dissolve tablet. The tablet is added to water and the resulting solution is dosed as a antibiotic mouthwash. Placebo matching was required not only for the tablet but also for the solution which the patient took.

BACKGROUND

Clinical studies on solid dose products may require a placebo that is devoid of an active pharmaceutical ingredient. The placebo, in the case of a tablet, should possess the same shape and color compared to the active product. This presents a challenge to the formulator because many active pharmaceutical ingredients (API's) are colored. Active and placebo are often film-coated with a non-functional coating that renders the two tablets virtually indistinguishable to patient and clinician alike.

In this case study, API (X) was an insoluble compound with a yellow-green color and targeted as a fast dissolve tablet for oral solution dosing. Its solubility in solution was aided by a buffer system that adjusted the pH upward, where the API possessed greater solubility. Because the tablet was required to dissolve in [buffered] water in 30 seconds or less, the feasibility of using a film-coat to blind the active from placebo was not considered. The primary approach centered on the use of FD&C lakes to color the tablet (dry) and the use of FD&C dyes to color the resulting solution. The interactive effect of the FD&C dye on the dry tablet as well as the effect of FD&C lakes on the solution were considered.

MATERIALS AND METHODS

Materials

- PROSOLV SMCC® 90 supplied by **JRS Pharma LP**
- D&C Yellow #10 Lake (K7181, 14-18% dye) supplied by **Sensient Technologies Corporation**
- FD&C Yellow #6 Dye (08006) supplied by **Sensient Technologies Corporation**
- FD&C Blue #1 Lake(9903, 38-42% dye) supplied by **Sensient Technologies Corporation**
- FD&C Blue #1 Lake(9901, 11-12% dye) supplied by **Sensient Technologies Corporation**
- Active Tablets, 15 and 30 mg potencies

Manufacturing Equipment

- Glass mortar and pestle
- Single Station press (Globe Pharma MTCM-11)
- Hardness Tester (Key International HT-300)

Analytical Equipment

- Colorimeter (DATACOLOR Spectraflash SF600 Plus)

Formulation Rationale/Experimental

An API (X), with limited aqueous solubility and distinct color, was formulated as a tablet using drug ProSolv SMCC® 90, colloidal silicon dioxide, and magnesium stearate. In addition, to 'standardize' the yellow color difference that the two potencies of active tablet would present to the resulting aqueous solution, 0.1% FD&C yellow #6 dye was added to each formulation. Tablets were compressed using a rotary tablet press.

For purposes of color matching, the placebo formulation omitted the magnesium stearate. Placebo blend was manufactured on a lab scale using trituration process in a mortar, through geometric dilution and incorporation of FD&C dyes and lakes. Tablets were compressed at 0.25 tons using a Carver press.

Both active and placebo tablets had a 260 mg compressed weight.

The first set of experiments (Trials 1 – 3) addressed the requirement that the placebo tablet be the same color as its active comparator. The second set of experiments (Trials 4 – 10) addressed the requirement that the solution resulting from dissolution of the active tablet in 30mL of water match the solution resulting from dissolution of the placebo tablet.

D&C Yellow #10 Lake is a true yellow in the dry state, while FD&C Yellow #6 Dye imparts an orange color to a solution. FD&C Blue #1 Lake is a blue color in the dry state.

All tablet samples were analyzed for their L, a, and b values by colorimetry, to confirm match, placebo to active. The mathematical equation relating overall color difference, DE is related to L, a, and b by the following equation:

$$DE = (DL^2 + Da^2 + Db^2)^{1/2}$$

Each tablet was analyzed using three illuminants: Daylight (D65), Fluorescent (F11), and Incandescent (A) using 10° view angle.

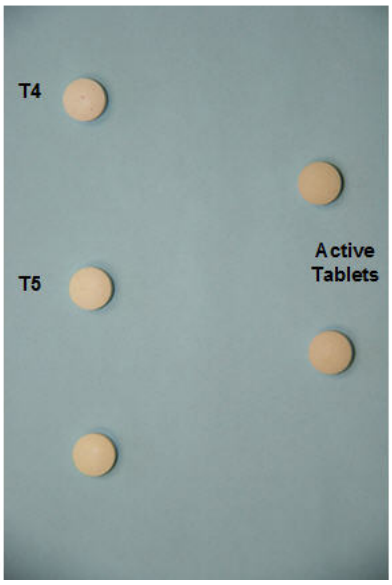
RESULTS

TABLET COLOR MATCHING

Placebo tablets were matched to active tablets by geometric dilution technique and stepwise addition of [F]D&C Lakes (Figure 1). Trial 1 started with 0.015% D&C Yellow #10 Lake and were too light compared to either active tablet. Trial 2 (0.03% D&C Yellow #10) was also too light. Trial #3 (0.06% D&C Yellow #10 Lake) gave a closer match to the active tablets.

FIGURE 1 –Initial 'dry' color matching of placebo and active tablets, Trials 1 –3

FIGURE 2 –Color matching of placebo and active tablets, Trials 4 –6



Colorimetry results of Trials 1 – 3 are shown in Table 1. The active tablets were run as the 'standards'. The DE values, which sum the difference in L, a, and b between active and placebo tablets were 12.86, 12.18, and 9.57, respectively, for Trials 1 – 3. A DE value of 2 to 2.5 is considered nearly indistinguishable to the human eye.

TABLE 1 – Colorimetry Data for Active and Placebo Tablets, Trials 1 – 10

Sample	L Value	A Value	B Value	DE (A illuminant)
Active Tablet	88.31	-3.49	21.03	
Trial 1	96.46	-1.26	9.49	12.86
Trial 2	96.71	-2.01	10.80	12.18
Trial 3	96.53	-3.17	14.96	9.57
Trial 4	94.74	-1.50	12.56	9.51
Trial 5	95.08	-2.47	16.14	7.65

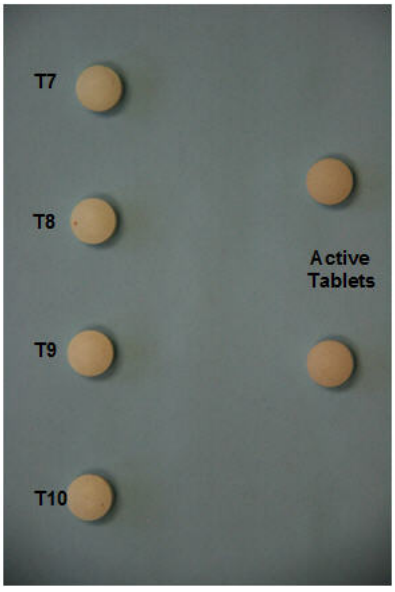
Trial 6	95.23	-3.44	19.30	6.92
Trial 7	94.02	-5.25	16.79	7.25
Trial 8	94.58	-3.37	17.53	6.72
Trial 9	92.96	-3.19	16.70	7.09
Trial 10	94.29	-3.92	18.14	6.35

Because the active tablets, both 15 and 30 mg potencies, had a 'standardized' amount of FD&C Yellow #6 Dye (0.1%) to standardize the solution color that the dissolved tablets would impart, the placebo required similar consideration. To account for the three tablets already made (trials 1-3, each 260 mg), 19.22 mg FD&C Yellow #6 Dye was added to the remaining 19.22 grams of blend. Trial 4 was too red/orange after addition of the Yellow #6 Dye (Figure 2). An additional 12.0 mg D&C Yellow #10 Lake was added to the blend stepwise in 6.0 mg increments (Trials 5 and 6, respectively) but both gave tablets that were too red/orange compared to active (Table 1). To bring the red/orange color out of the placebo, FD&C Blue #1 Lake (high dye content), 0.5 mg, was added to the blend (Trial 7). The resulting tablet was too blue/green (Figure 3 and Table 1). Diluting out the effect of the Blue #1 Lake with additional Prosolv (18.18 grams), D&C Yellow #10 Lake (24.0 mg) and FD&C Yellow #6 Dye (18.3 mg) was not effective (Trial 8, Figure 3, Table 1).

FINAL COLOR MATCHING

From Trials 7 and 8, it was necessary to source a lower dye concentration of FD&C Blue #1 Lake. Therefore, a low dye content lake (11-13% dye loading) was used for further trials. Trial 9 started with 0.10% FD&C Yellow #6 Dye, 0.125% D&C Yellow #10 Lake, and 6.25 ppm FD&C Blue #1 Lake (11-13% dye loading) in Prosolv SMCC® 90. This gave a close match. Increasing the concentration of Blue #1 Lake to 12.5 ppm provided the best visual match (Trial 10, Figure 3, Table 1)

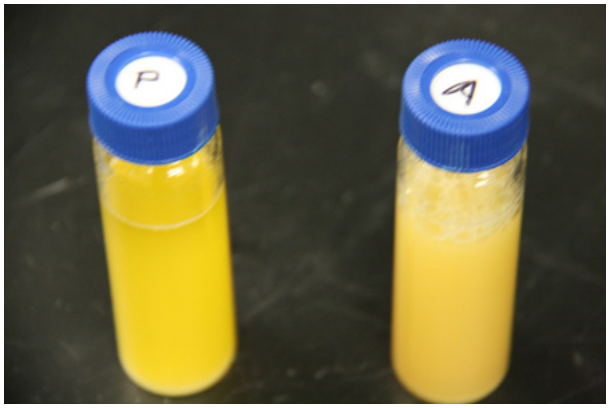
FIGURE 3 —Dry Color-Matching of Placebo Tablets, Trials 7 —10



SOLUTION COLOR MATCHING

A placebo tablet compressed from Trial 10 was compared with an active tablet with respect to color of solution after placing tablet in a dosing vial with 30mL of water. The solutions both displayed a yellow-orange color after 15 seconds of shaking (Figure 4). The presence of drug in the active solution caused some initial foaming and imparted a slight cloudiness to the solution. Also, the active bottle had some drug suspended, as the API possessed limited solubility in water. Inclusion of a buffer (high pH, results not shown) tablet that would accompany both active and placebo tablets rendered complete solubilization of active and presented a better match, active to placebo.

FIGURE 4 – Solution Color-Match of a Placebo (Trial 10) and Active Tablets in 30mL Water and After 15 seconds of Shaking



DISSCUSSION AND CONCLUSIONS

Visually, Trial 10 provided the best match of placebo tablet to active tablet. Although a DE value of 2 – 2.5 is generally considered indistinguishable to the human eye, the placebo to active match in this study was considered acceptable, with a final DE of 6.35 in Trial 10. Also, the clinical study utilized two different strengths of active (15 and 30 mg), and a placebo match to both tablets simultaneously would have been impossible. The **A** illuminant (incandescent tungsten filament light) was considered most representative of what a patient might visualize upon taking a dosing kit home with either active or placebo tablet. However, patients were not given both active and placebo tablets simultaneously in the clinical design.

The different method by which placebo tablets and active tablets were manufactured contributed some variability in the color matching capability. Incorporation of the Yellow #6 dye in a uniform manner proved difficult on a small scale. The placebo tablets were observed to have some small (intense) red specks that were less conspicuous in the active tablets. Although the placebo tablets were compressed on a single station press at a hardness that attempted to match the sheen of the active tablets compressed on a 16-station rotary press, the reflectance of light was influenced by the difference of sheen.

ACKNOWLEGEMENTS

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