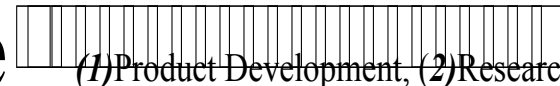


# W4192 Novel Design of a Monolithic Oral Controlled-Release Delivery Formulation for Novasoy® Soy Isoflavone Concentrate

S. J. Turner<sup>1</sup>, C. Federici<sup>2</sup>, M. Hite<sup>2</sup>, R. Fassihi<sup>3</sup>

(1)Product Development, (2)Research & Development, SCOLR, Inc., Redmond, WA 98052, (3)School of Pharmacy, Temple University, Philadelphia, PA.



**Purpose.** To design a novel monolithic, solid oral dosage form capable of displaying improved 12- and 24-hour sustained release *in vitro* dissolution profiles of Novasoy® soy isoflavone concentrate (40%). **Methods.** Three formulations were developed to represent clinically relevant dosage strengths: 50mg of isoflavones released over 12 and 24 hours, and 100mg released over 24 hours. The glycosides and biological components of the Novasoy® raw material are susceptible to acidic conditions; the formulations were designed to withstand surrogate *in vitro* acidic conditions and protect the contents within the tablet core. The formulations were designed to be manufacturable as directly compressible dry blends, avoiding additional costly processing steps. Tablet hardness and friability and blend powder characteristics were examined to ensure ease of large-scale manufacture. Surrogate *in vitro* dissolution tests were developed to more closely approximate the environmental changes the tablet would experience during transit *in vivo*. **Results.** The formulation components and excipients chosen effectively control the rate of hydration at lower pH, maintaining a neutral microenvironment within the tablet core. Upon transition to an alkaline environment the dissolution rate changes, allowing for near complete release (>95%) of the isoflavone payload. The surrogate dissolution profiles show a marked improvement over previous sustained release formulations. **Conclusions.** Results show that readily manufacturable, sustained release formulations of both 125mg and 250mg Novasoy® (50mg and 100mg isoflavones, respectively) are possible over convenient durations of release using this novel monolithic delivery system.

## Introduction

The objective of this project was to provide controlled release formulations of 50mg and 100mg soy isoflavones available as 125mg and 250mg Novasoy® concentrate. Originally formulas exhibiting both 12- and 24-hour release profiles were developed but only the 24-hour formulas were scaled up and completed for manufacture. The Novasoy® raw material consists of soy isoflavones bonded to glucoside carriers which may be cleaved by acid exposure; these controlled release dosage forms protect the majority of the active ingredient from acid cleavage in the stomach by controlled hydration of the tablet core. Controlled release forms of Novasoy® also maximize health benefits of isoflavone supplementation, help to minimize breakthroughs of symptoms such as hot flashes, and improve consumer compliance by reducing the dosing

frequency. These formulations were designed to minimize initial burst release of the active ingredient, to achieve near-complete release, and to ensure manufacturability.

## Materials and Methods

### Materials:

Novasoy® 40% soy isoflavone concentrate was supplied by Archer Daniels Midland Co. (Decatur, IL). Hydroxypropylmethylcellulose (HPMC) was purchased from Dow Chemical (Midland, MI). Pectin was purchased from Pacific Pectin, Inc. (Oakhurst, CA). Anhydrous sodium carbonate was purchased from Spectrum Chemical (New Brunswick, NJ). Dicalcium phosphate was purchased from Astaris LLC (St. Louis, MO).

### Preparation of tablets:

All components were dry-blended with a minimum amount of lubricant and directly compressed using a hydraulic single-station press at the bench scale (Carver, Inc. Wabash, IN) or a 16-station rotary press (Stokes, RD3, DT Industries, Hyannis, MA). Tablets were compressed to no more than four metric tons. For the blending time study, components were blended within a range of 15 to 60 minutes, a small sample taken from the blender, mixed with lubricants, and tableted, while the larger batch continued blending for additional time.

### *In vitro* release study:

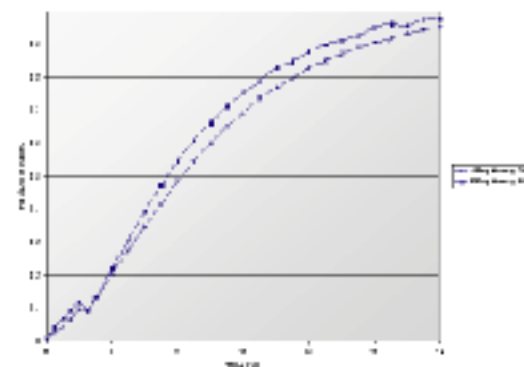
Novasoy® release was determined with six tablets per formulation using a USP 25 Type II dissolution assembly (VanKel VK-7000, Cary, NC; Hansen SR-8 Plus, Chatsworth, CA; and Erweka DT-70, Milford, CT) with a paddle speed of 50±0.1 rpm and bath temperature of 37.0±0.5°C. Dissolution medium was 0.1N HCl, neutralized after 2 hours with 10N NaOH to reflect gastric pH residence time and subsequent passage into a higher pH environment. Samples were detected on-line each hour throughout duration of release using a UV/vis spectrophotometer at 354nm (Varian Cary 50, Cary, NC; and Beckman DU-640, Fullerton, CA); reference standards and maximum absorbance values were used to calculate release.

## Results and discussion

### *In vitro* dissolution results:

The two final formulas developed exhibit shallow first-order release curves over 24 hours, with nearly 100% of the active ingredient released at the end of the time period, as

illustrated in **Figure 1**. Approximately 10% of the total is released in the first two hours, representing release in acidic gastric conditions. The small dip in the release curve is a result of using two different reference sources to calculate the extent of release in different media. The rate of release is controlled in this matrix system by a diffusional-erosional mechanism of polymer disentanglement upon hydration, and a salting-out of the electrolyte in preference to the active ingredient. Pectin was used in addition to HPMC in these formulations to help control hydration under acidic gastric conditions, and the sodium carbonate utilized may aid in creating a higher pH microenvironment surrounding the dry core of the tablet as it hydrates.



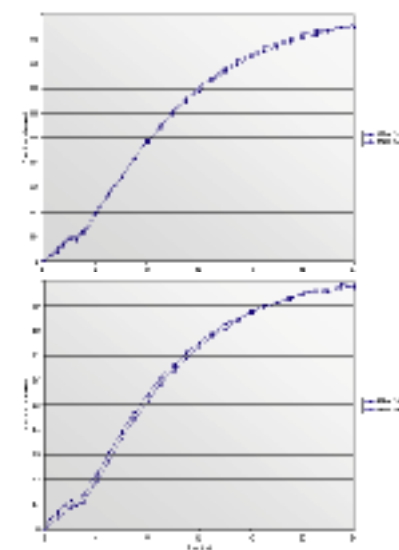
**Figure 1.** *In vitro* dissolution profiles of 125mg and 250mg Novasoy® 24-hour formulations.

### Scale-up optimization:

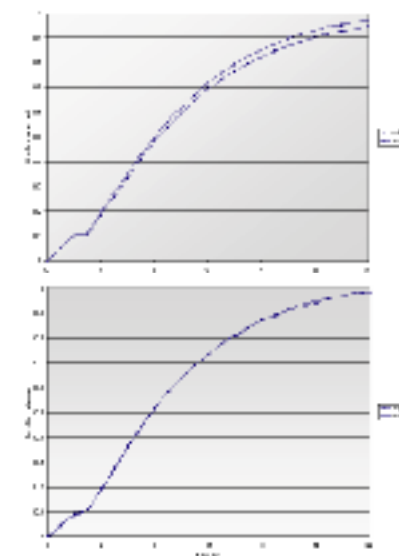
Both of the final 125mg and 250mg 24-hour formulations exhibited scale-up reproducibility and robustness in manufacturing conditions. These products are to be sold as pre-blend material which will be shipped to and tableted at customers' facilities, so manufacturing flexibility and reproducibility is critical. **Figure 2** shows the minimal variation between two pilot batches of both the 125mg and 250mg formulas. These formulations were tested to ensure valuable throughput on a high-speed tableting press. Dissolution results from batches run at different target hardness levels show little variability, yielding a wider range of acceptable tablet characteristics and offering flexibility to the manufacturing facility, and predicting reduced variability between different manufacturing sites and equipment.

**Figure 3** illustrates the similarity between production batches tableted at different final hardness ranges. Impact of

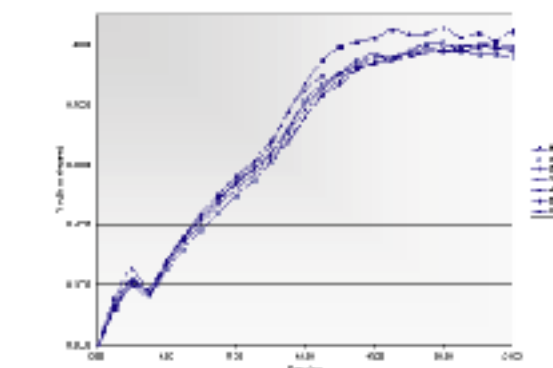
blend time on dissolution performance was also studied: blend time between 15 and 60 minutes before addition of lubricants did not significantly affect release rate, although after 40 minutes the blend showed signs of cohesion and poorer flow characteristics. Release profiles of the 250mg 24-hour formula are shown in **Figure 4**.



**Figure 2.** Reproducibility of scale-up batches for 125mg and 250mg 24-hr formulas.



**Figure 3.** *In vitro* release profile of 125mg and 250mg Novasoy 24-hr formulation manufactured at different tablet hardness ranges (14-18 and 18-22 kP).



**Figure 4.** Release profile of 250mg 24-hr formula with a range of blend times.

## Conclusion

We were able to produce 125mg and 250mg Novasoy® 24-hour release dosage forms. These tablets exhibited the desired release profile with the characteristics of near-complete release and minimal initial burst effect. These dosage forms can be simply manufactured by dry blend and direct compression, and will be available as a drum-to-hopper pre-blend with only the addition of minimal lubricant necessary. Blending time and tableting press conditions affect the finished tablet and isoflavone release \*only slightly, predicting good reproducibility between different manufacturers.

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## References

- \* Isoflavones increase bone density and bone mineral content in the spine. American Journal of Clinical Nutrition 68 (6S) 1375S-1397S (1998)
- \* Potter SM, Baum JA, and Teng H, et al., Soy protein and isoflavones: their effects on blood lipids and bone density in post-menopausal women, Nutrition 68(6 Suppl): 1375S-1379S.
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**Special Thanks to Archer Daniels Midland (ADM) for supplying Novasoy® Soy Isoflavone Concentrate.**

