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Introduction:

The objective of this study was to develop and evaluate how modified release technologies can offer marketing advantages and improve life cycle management of branded compounds. Such technology must offer tangible benefits from both manufacturing and marketing perspectives including overcoming the initial barrier of additional development expenses and the costs associated with market introduction. The branded compounds selected for the study were meant to be representative of the price sensitive commodity markets. This market was chosen due to the need for shortened timelines associated with market introduction and its heightened price sensitivity. Products competing in commodity markets typically have difficulties overcoming price barriers and often have shorter life cycles due to the highly competitive landscape. Although over-the-counter (OTC) and prescription drug markets should have similar results and benefits from a positive outcome, due to the typical timeline associated with market introduction and launch, they were not included in this evaluation.

The modified release formulations used in combination with the branded ingredients were adapted from SCOLR's "self-correcting" hydrophilic polymeric matrix system developed to deliver highly soluble pharmaceuticals. Principles from US Patents 6,090,411 and 6,337,091 were applied in order to develop formulations that had the ability to offer extended release of soluble actives over 12-24 hours in a simple monolithic tablet. These technologies allow for the production of finished tablets and capsules as well as "drum to hopper" preblends that should effectively improve the ability of the branded compound to compete with alternative products in the market. This can be critical to the commodity markets in which manufacturers have access to a variety of sources to choose from. In order for a product design to deal effectively with competition, it must have one of the following characteristics: differentiation; improved performance; and, or, a reduced cost profile. Similar to the OTC and generic drug industries, established brands need to be competitively positioned. Companies competing in this market often allocate significant resources to establish a brand. The arrival of a competitor in the marketplace often induces market erosion and rapid price decline. One strategy in the prescription drug arena is to modify an existing drug by adding value with new intellectual property, and subsequently switching an existing consumer base to a reformulated version of the product in order to maintain some of the original market size ("Evergreening"). For other price sensitive market segments, a similar approach can be used to protect branded and established compounds from market erosion. A few case studies will be covered, including examples for Novasoy soy isoflavone concentrate (Archer Daniels Midland, Decatur, IL), Ester C, calcium ascorbate (Zila/Intercal, Prescott, AZ).

Materials & Methods:

A wide variety of tableting excipients were used in the study formulations. Hydroxypropyl methylcellulose (HPMC) of various grades was purchased from Dow Chemical (Midland, MI). Guar of various grades was purchased from Hercules/Aqualon (Wilmington, DE). Pectin 150 Slow-Set was purchased from Pacific Pectin, Inc. (Oakhurst, CA). NaHCO₃ was purchased from Natrium Products (Cortland, NY). Na₂CO₃ was purchased from Natrium Products (Cortland, NY). Microcrystalline cellulose 102 was purchased from FMC (Philadelphia, PA). Silica Dioxide was purchased from Degussa Ltd. (Macclesfield, Cheshire UK). Stearic Acid was purchased from Ashland Chemical, (Santa Ana, CA). Magnesium Stearate was purchased from Ashland Chemical, (Santa Ana, CA).

Active ingredients were provided by the manufacturer. Novasoy was provided by Archer Daniels Midland (ADM) (Decatur, IL.). Ascorbic acid (Vitamin C) was purchased from BASF/Takeda (Mt. Olive, NJ). Ester C, mineral ascorbate was purchased from Zila/Intercal (Prescott, AZ).

Novel Design of an Oral Monolithic Controlled Release Delivery System for Branded Active Materials.

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Preparation of tablets: (Bench Scale)

All constituents were dry blended on either a low energy tumble blender (Lortone, Seattle, WA) or an 8-quart V-blender (Patterson-Kelley, East Stroudsburg, PA) with a minimum amount of flow agents and directly compressed. Bench scale tablets were compressed using a hydraulic single station pellet press (Carver, Inc. Wabash, IN) at 4 tons.

In vitro dissolution studies:

Dissolution studies were conducted using a USP 26 Type II dissolution apparatus (Erweka DT-70, Erweka Corp. Milford, CT) (Hanson SR8 Plus, Hanson Research Chatsworth, CA) (Vankel 7000, Varian, Inc. Cary, NC) with a paddle speed of 50rpm and bath temperature of 37.0 +/- 1.0 C.

Preparation of tablets (Commercial Scale):

Roughly 100 kg's of blend were loaded into the 10 CF V-blender via a pneumatic loading system. Blending was optimized at 15-20 minutes total blend time. After the initial blending the necessary lubricants and glidants to facilitate tablet manufacture were added and then mixed for 5 minutes to uniformly distribute the lubricant and glidants throughout the blend. The resulting blend was then removed and loaded into the hopper on the rotary tablet press.

The tablet press utilized was a standard 16 station IPT "B" tooled rotary tablet press (Stokes BB-2, DT Industries Hyannis, MA) with power control to facilitate a maximum turret speed around 25 revolutions per minute (RPM). The power control was set at 18 RPM for consistency in order to evaluate any difference in each sample run. A target tablet hardness of 18 to 22 kp. The fill weight for the tablets was set such that the low range was 101% of the total formulation weight, with a target at 104% and an upper limit set at 108%. This allowed for 100% label claim tablets and a +/-4% weight variation.

Dissolution setup and procedure for isoflavone tablets: Tablet dissolution was performed in a USP Type II apparatus at 50 rpm and 37°C. Dissolution medium was 900mL of 0.1N HCl (pH=1.2); 8.8mL of NaOH was added after two hours to represent transition in-situ from stomach to intestine. Data points were collected every hour for 24 hours. After completion of the exam, a maximum dissolution determination was performed by increasing paddle speed to 250 rpm for 1 hour and collecting a final data point. UV detection was performed at 354 nm; maximum absorbance values of tablets and reference standards were used to calculate fractional release of the active ingredient.

Dissolution setup and procedure for Vitamin C tablets: Tablet dissolution was performed in a USP Type II apparatus at 50 rpm and 37°C. Dissolution medium was 900mL of deionized water (pH=7.0). Data points were collected every 2 hours for 12 hours. After completion of the exam, a maximum dissolution determination was performed by increasing paddle speed to 250 rpm for 1 hour and collecting a final data point. UV detection was performed at 265 nm; maximum absorbance values of tablets and reference standards were used to calculate fractional release of the active ingredient.

Dissolution setup and procedure for Ester C tablets: Tablet dissolution was performed in a USP Type II apparatus at 50 rpm and 37°C. Dissolution medium was 900mL of deionized water (pH=7.0). Data points were collected every 2 hours for 12 hours. After completion of the exam, a maximum dissolution determination was performed by increasing paddle speed to 250 rpm for 1 hour and collecting a final data point. UV detection was performed at 265 nm; maximum absorbance values of tablets and reference standards were used to calculate fractional release of the active ingredient.

Results and discussion:

Branded compounds can experience significant market erosion due to direct and indirect competition from other non-branded equivalents. After initial launch and establishment of the brand, this increased competition directly results in loss of margin and reduced returns. By incorporating value adding strategies utilized in the pharmaceutical industry to protect and prevent margin loss, a branded ingredient provider can reduce the risk of market erosion and enhance product lifecycle. This has particular relevance for branded products due to the investment of significant resources in establishing a brand and market pressures to ensure a good return on these investments. One logical value adding strategy is the incorporation of intellectual property that prolongs the potential lifecycle of a given product or compound. The use of a controlled delivery vehicle to enhance the ingredients performance and offer differentiation from competitors is one such type of intellectual property. The increased cost of developing a new drug or new brand are driving companies to find ways to extend the duration of sales and preserve their existing product franchises. As depicted in **figure 1**, the average cost of development today is approximately 800 million dollars¹. When this size expenditure is compared to the speed and relatively modest costs of reformulating an existing product, this alternative merits serious consideration. It is also estimated that up to 70% of New Chemical Entities (NCEs) do not generate enough revenue during their average lifecycle to recoup the initial expenses during research and development (**fig.1**)¹. When utilized properly, a branded ingredient provider can protect margins by offering these novel products that may not be available by any other means.

Figure 1. Average cost of developing a new drug since 1976, as compared to cost of developing new value added formulation¹.

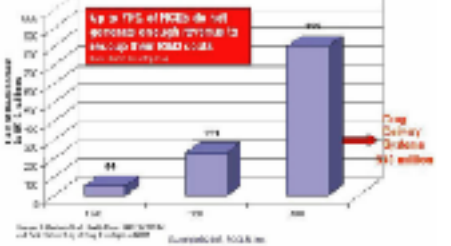
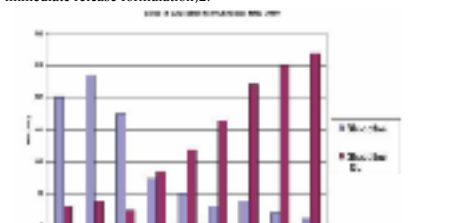


Figure 2. Effect of introducing value added formulation to prolong branded product lifecycle. (As compared to the sales (US \$) of original immediate release formulation)².



One successful example of the application of controlled release reformulation can be seen in the market conversion of Glucotrol to Glucotrol XL. As seen in **figure 2**, Pfizer introduced an extended release reformulation as sales declined for the original branded immediate release (IR) formulation². The result was very successful in

that not only was Pfizer able to convert the original consumer population, but the newer value added formulation offered improved performance and resulted in increased sales over the original formulation. One potential application of this strategy can be seen in the recently developed Novasoy Daily™ line of products offered by ADM.

ADM has spent significant resources establishing the Novasoy brand of soy isoflavone concentrates. International and domestic competition forces the price of these soy commodities down over time and reduces margins making it increasingly more difficult for companies to ensure growth and profits of the brand. By developing an extended release soy isoflavone (AAPSPharmSci Vol. 4, No. 4, Abstract W4192 (2002))³ SCOLR was able to provide ADM with a product line that potentially protects the sales of the branded ingredient (**figure 3a & 3b**). Several formulations were developed to provide ADM with the ability to meet their current customer's needs. Several pure isoflavone tablet and capsule formulations were developed as directly compressible pre-blends that offered manufacturers the ability to produce controlled delivery formulations without covering the costs of development (**fig. 3a**). Additional formulations were developed to meet specific customer's needs. **Figure 3b** highlights one particular example, where a manufacturer can purchase a pre-blend that can be mixed with up to 300mg of additional vitamin premix then filled in to a conventional two piece hard shell capsule. ADM now has the ability to offer extended release pre-blends for tableting and encapsulation in addition to the regular isoflavone concentrates to existing and new manufacturing customers. Companies previously excluded from custom formulation development programs now have the ability to purchase a drum-to-hopper preblend that offers significant and novel advantages over conventional immediate release and competitive sustained release (SR) isoflavone formulations (**figure 4**). For the oral supplement markets, these formulations offer ADM the ability to sum the costs of excipients and active ingredients and thus sell the preblend for a premium. The preblends have been well received due to the nature of increased productivity and lower costs associated with multiple incoming QC steps normally associated with producing tablets or capsules. A manufacturer can purchase the preblend, tumble with a conventional lubricant or glidant as needed for processing and produce a unique tablet or capsules that offers improved products performance, increased consumer compliance and product differentiation among other benefits.

Figure 3a. In Vitro release profile of pure isoflavone concentrate tablet formulation for ADM. Developed as "drum to hopper" directly compressible pre-blends.

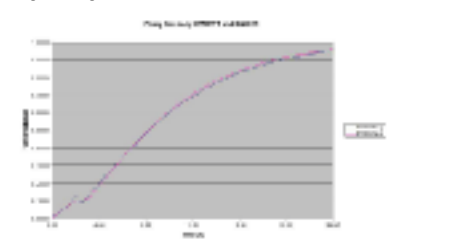


Figure 3b. In Vitro release profile of two piece hard shell capsule formulation for ADM. Developed as customized matrix pre-blend that works with manufacturer adding up to 300mg of additional vitamin premix.

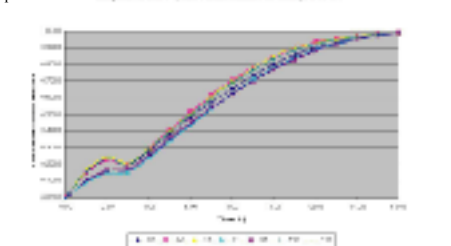
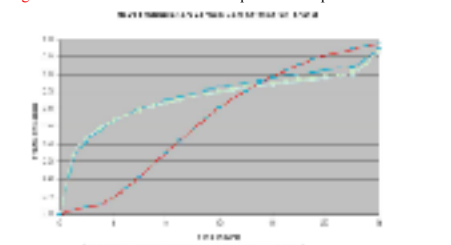


Figure 4. Novel formulations as compared to competitive formulation.



Another example can be seen with controlled release Vitamin C tablets and capsules. Finished controlled release tablets and capsules have held a stable position in the supplement industry and have been proven to be a solid strategy for manufacturers of these finished goods. Vitamin C is a highly price sensitive and volatile commodity. Market fluctuations due to supply issues and fierce competition force manufacturers to sell bulk tablets to the industry at a loss or with extremely low margins. The ability of a manufacturer to sustain loss leader sales and maintain profitability is mainly due to "bundling" strategies driven by package sales of higher margin novel products. Chewable and extended release Vitamin C tablets sell at significantly higher margins that their immediate release counterparts. This is mainly due to product differentiation and improved consumer demand. A manufacturer can "bundle" the sales of novel formulations along with the conventional immediate release counterparts. This strategy allows the manufacturer of these bulk tablets to secure accounts while maintaining margins. These CR and chewable tablets have been instrumental in the manufacturer to get or maintain sales of the entire product line. The improved margins captured by these novel formulations offset any potential losses or low margins typically seen in the IR sales.

There are relatively few suppliers of extended release and chewable formulations currently offering bulk tablets, because relatively few delivery technologies can support the delivery of Vitamin C due to both price barriers and the difficulty to effectively formulate a functional product due to the materials properties. Vitamin C's high solubility and high degree of oxidation and breakdown make it difficult to formulate a functional product. Conventional first generation systems like wax or hydrophilic matrices along with simple film or functional coatings make up the vast majority of products on the market. As seen in **figure 5**, the extended release formulation offers tangible benefits over the IR

formulation. Released in a prolonged fashion, the performance of the finished tablet should be superior to the IR version in that absorption is closer to the rate at which ascorbic acid is absorbed and metabolized⁴⁻⁷. These improvements should offer more efficient utilization of ascorbic acid and provide prolonged plasma ascorbate levels⁴⁻⁷. (**Figure 6**) The low cost of production and intellectual property protection offered by novel SCOLR formulations add significant value above and beyond that available to first generation CR systems.

Figure 5. In Vitro dissolution profiles of Vitamin C (ascorbic acid) tablets⁴.

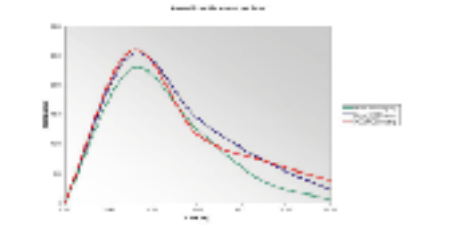
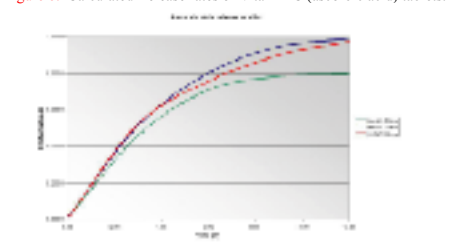


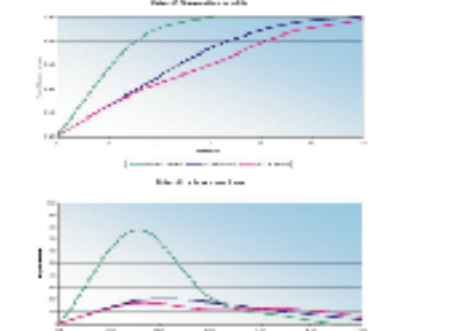
Figure 6. Calculated Release rates of Vitamin C (ascorbic acid) tablets.



Another example can be seen with Zila Nutraceuticals Ester C mineral ascorbate. Mineral ascorbates have been shown to provide higher plasma ascorbate levels when compared to conventional ascorbic acid preparations⁸⁻¹³. The two patents that support the branded raw material were filed in 1987 and 1990 and will expire in 2007 and 2010 respectively. Prior to the end of the patent protection, Zila could use the same strategy that Pfizer used for Glucotrol. When formulated as a controlled release preparation, Ester C should benefit similarly to ascorbic acid. By prolonging the release and availability of Ester C, higher and prolonged levels of plasma ascorbate should be possible. This allows Zila to directly compete with the specialized SR Vitamin C markets. If successful, Zila could support the resulting product with additional human data and convert the existing consumer population over to the new improved novel formulations. As seen in **figure 7**, SR formulations offer tangible benefits over the conventional IR versions. The release rate of the sustained formulations offer improved steady state levels. These should result in improvements over more rapidly, less controlled formulations on the market.

SCOLR, Inc.

Figure 7. In Vitro dissolution profiles and calculated release rates for novel Ester C formulations.



Conclusions: Modified release formulations can help branded ingredients and products maintain competitive advantage in a commodity price-driven market. The same strategies used in the branded drug industry apply to other markets, including the price sensitive natural products industry. By incorporating technologies which allow for premium pricing through product differentiation companies no longer have to fall prey to reduced margins and market erosion often driven by competition among other sources and suppliers. Even when little to no control exists over the price of active ingredients, manufacturers or producers of branded products can utilize proven strategies from the branded drug industry to add value to their product and prolong the potential lifecycle. The examples of Novasoy®, Vitamin C and Ester C® have shown that delivery technologies, such as the formulations presented, offer a high degree of product differentiation when compared to conventional IR products and may improve potential product performance and/or efficacy. The model of utilizing delivery systems to offer added value to the consumer helps increase brand awareness and ensure consumer loyalty, which in turn will help companies prolong the life cycle of their branded ingredients & products.

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