

# W4194 Novel Design of a Robust and Rugged Oral Monolithic Controlled Release Delivery System for Tramadol Hydrochloride.

C. Federici, S. Turner, M. Hite, SCOLR, Inc. Redmond, WA. 98052, and R. Fassihi, School of Pharmacy, Temple University, Philadelphia, PA 19140

**Purpose.** The purpose of this study was to design robust and rugged monolithic, solid oral dosage forms capable of displaying 12- and 24-hour near zero-order *in vitro* dissolution profiles of tramadol hydrochloride in a novel self-correcting matrix style delivery system. **Methods.** Three formulations were developed to represent clinically relevant dosage strengths: 100mg released over 12 and 24 hours, and 200mg released over 24 hours. The formulations were designed to be manufacturable as directly compressible dry blends and to withstand a variety of *in vitro* testing conditions. Dissolution was performed within a range of media pH from 1.0 to 7.8, in a solution of 0.2% SDS, and with a change of medium from 0.1N HCl buffer to 0.05M potassium phosphate buffer, to ensure the resistance of the system to various conditions through the GI tract. Minor formula variations were also tested to illustrate the robustness of the system. **Results.** Ruggedness of the delivery system was shown by release performance in various media. These formulations showed only slight deviations in release of the API when introduced to changes in pH, ionic strength, surfactant concentration, and slight formula variations. **Conclusions.** Results suggest that readily manufacturable, controlled release formulations of both 100mg and 200mg tramadol hydrochloride are possible over convenient durations of release using this novel monolithic self-correcting delivery system.

## Objectives

The objectives of this project were to create 100mg and 200mg oral dosages of Tramadol Hydrochloride displaying near-linear controlled release with a minimal burst over 12 and 24 hours. These dosage forms should increase drug efficacy and patient compliance by more closely approaching a steady state in the plasma than IR dosage forms, thus reducing pain breakthroughs.

## Materials and Methods

**Materials:** Tramadol hydrochloride was supplied by Zetapharm (New York, NY). Polyethylene oxide (PEO) was purchased from Dow/Union Carbide (Danbury, CT). Pectin was purchased from Pacific Pectin, Inc. (Oakhurst, CA). Anhydrous sodium carbonate was purchased from Spectrum Chemical (New Brunswick, NJ). Microcrystalline cellulose was purchased from Stauber Performance Ingredients, Inc. (Fullerton, CA).

## Preparation of tablets:

All materials were simply dry-blended with a minimum amount of lubricant and directly compressed using a hydraulic single-station press (Carver, Inc. Wabash, IN). Tablets were compressed to four metric tons.

## *In vitro* release study:

Tramadol 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) in deionized water with a paddle speed of 50±0.1 rpm and bath temperature of 37.0±0.5°C. Samples were detected on-line each hour throughout duration of release using a UV/vis spectrophotometer at 270nm (Varian Cary 50, Cary, NC; and Beckman DU-640, Fullerton, CA).

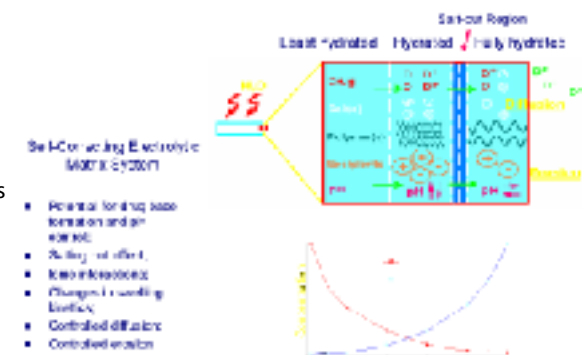
## Results and discussion

### *In vitro* dissolution under standard conditions

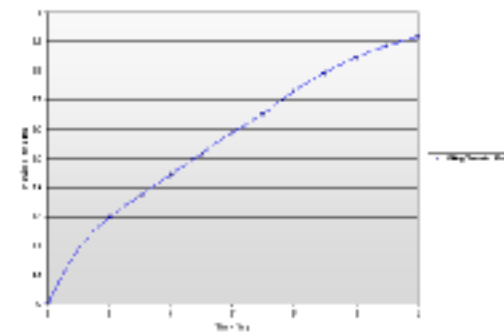
As shown in **Schematic 1**; This diffusion-erosion based matrix system employs an electrolyte in addition to polymer to control API release. The sodium carbonate used in these formulations competes with the polymer for available water molecules, thus retarding the immediate hydration of polymer, while also competing with tramadol for water molecules, controlling immediate release, as is evident in the minimization of a burst effect. As hydration continues, the polymer disentangles, swelling and causing a gel region around the dry core of the tablet. The API molecules will continue to diffuse through this gel layer as water enters, but dissolution is still suppressed by the presence of the electrolyte. Once the electrolyte is solubilized, tramadol can then be released. This addition of electrolyte to the formulation helps minimize the size of the tablet while offering further control beyond a simple active/polymer dry blend.

**Figures 1 and 2** illustrate the release curves of each formulation developed in deionized water at a paddle speed of 50 rpm. In each case there is a slight burst of drug release, followed by a sustained release profile and near complete release. The 100mg 12 and 24 hour formulas both utilize pectin as well as PEO in order to minimize the initial burst effect.

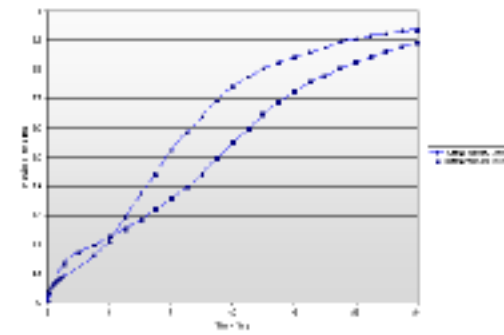
**Schematic 1.** Release Kinetics of formulation.



**Figure 1.** Release profile of developed 100mg Tramadol 12hr formulation.



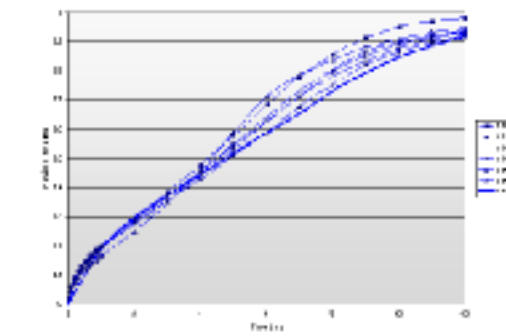
**Figure 2.** Release profiles of 100mg and 200mg Tramadol 24hr formulations.



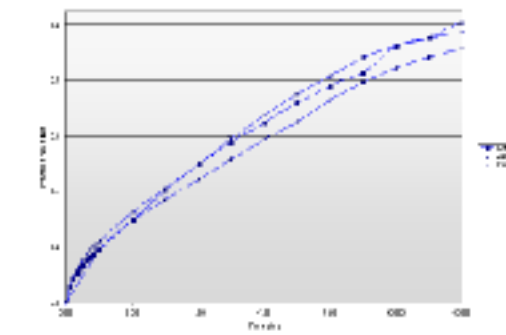
### *In vitro* dissolution with physiologically relevant media

Each formulation was tested within a pH range of 1.0 to 7.8, approximating levels found through the GI tract. These formulations performed well, with minimal variation in release profile under different conditions. **Figure 3** shows the variation of the 100mg 12 hour formulation. Drug release is fairly similar through 4 hours, after which point the deviation is slightly higher, with release in neutral dH2O being slightly slower and less complete than at other pH levels. Performance of the other two formulations is similar with the exception of dissolution in 0.1N HCl, which yielded faster release toward the latter end of the curve. These formulations were also tested in a combination of HCl/KCl and KH2PO4 buffers to approximate gastric residence time and a subsequent transition into a higher pH environment, and in 0.2% SDS medium to determine the effect of surfactant concentration on release. **Figure 4** illustrates the robust performance of the 100mg 12 hour dosage form in these media compared with that in dH2O.

**Figure 3.** Dissolution of 100mg Tramadol 12hr formulation over a range of physiological pH.



**Figure 4.** Dissolution of 100mg Tramadol 12hr formulation in various media.



### *In vitro* dissolution under varying hydrodynamic conditions

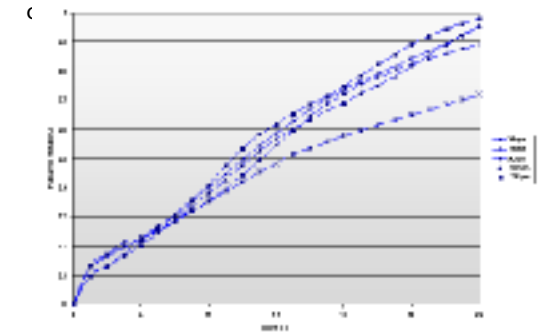
These formulations were tested under a range of 25-125 paddle rpm in deionized water to determine their susceptibility to dose-dumping when exposed to elevated erosional forces. **Figure 5** is an example of the ruggedness of the system, illustrating low variability in release rate under conditions of 50 rpm and higher; release is slower at lesser rpm due either to lesser erosional action or the lack of non-saturated medium contacting the tablet surface for dissolution at this speed.

### *In vitro* dissolution of slight formula variations

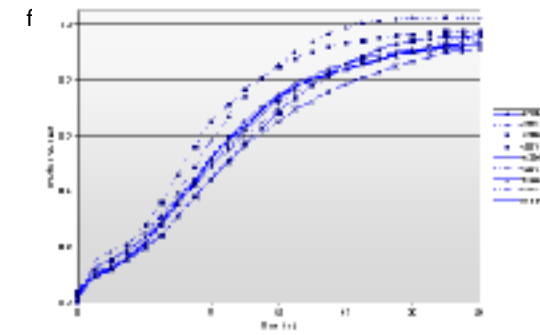
In order to assess the effect of manufacturing variability on drug release from these formulations, slight changes in the level of each component of the formula were tested under standard conditions *in vitro*. Results, as shown in **Figure 6**, generally exhibited small deviation from the release of the

control formula, except in the case of decreased polymer or decreased API, which exhibited faster release after approximately 4 hours.

**Figure 5.** Dissolution of 200mg Tramadol 24 hour in a range



**Figure 6.** Dissolution of 100mg Tramadol 24 hour with slight



## Conclusions

These three formulations have proven to be robust and rugged to the extent that API release is only marginally affected under *in vitro* conditions of a range of pH values, surfactants, accelerated hydrodynamics, and slight component variations. We anticipate ease of manufacture with minimal impact on release characteristics and good *in vivo* results with respect to dose-dumping and pH variation effect

## References:

- \* Dayer P, Collart L, Desmeules J. The pharmacology of tramadol. *Drugs*. 1994;47(Suppl 1):3-7.
- \* Kim H, Fassihi R. A new ternary polymeric matrix system for controlled drug delivery of diltiazem hydrochloride. *Pharm Res* 1997; 14(10): 1415-21
- \* Lee CR, McTavish D, Sorkin EM. Tramadol: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in acute and chronic pain states. *Drugs*. 1993; 46:313-40.