

Scalability Evaluation of Monolithic Controlled Release Gabapentin Formulations for Oral Administration

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Summary

The objective of this work was to develop two 600 mg gabapentin formulations with a 12-hour near linear release profile utilizing patented CDT® technology. The formulas were then evaluated for reproducibility and robustness during scale up operations.

Introduction

Gabapentin is an anticonvulsant prescribed for the control of epileptic seizures; it is also used to relieve the pain of postherpetic neuralgia. Gabapentin is related to the brain chemical gamma aminobutyric acid (GABA) but the exact mechanism of action is unknown.

Gabapentin is 1-(aminomethyl)cyclohexaneacetic acid (C₉H₁₇NO₂) and possesses a molecular weight of 171.24. Gabapentin is a white to off-white crystalline solid with a pKa₁ of 3.7 and a pKa₂ of 10.7. It is freely soluble in both basic and acidic aqueous solutions.

Delivering a high drug load of a highly soluble pharmaceutically active substance in a near linear manner is difficult using traditional sustained release technologies. Two tablet formulations employing novel controlling excipients – electrolytes and amino acids – were developed. The formulations demonstrated the capability to deliver 600 mg of gabapentin in a highly controlled manner over a prolonged period and also demonstrated ruggedness and scalability in manufacture.

Experimental Method

Tablet Manufacture

The self-correcting 600 mg gabapentin tablet formulations were wet-granulated using a V-blender (Patterson-Kelly/Harsco Corporation, East Stroudsburg, PA) with an intensifier bar. The wet granulation was sieved using a size 12 mesh and allowed to tray dry overnight. The granules were then mixed with extra-granular excipients in a V-blender prior to compression. Tablets were manufactured on a Carver single-station press (Carver, Inc. Wabash, IN), a Piccola (Riva) 10-station rotary press (Specialty Measurements Inc. Lebanon, NJ) and a JCMCO model JC-RT-20H rotary press. The Piccola rotary press was outfitted with mechanically-assisted feed frames and was instrumented with main compression, pre-compression, ejection, take-off and turret speed sensors (Specialty Measurements Inc. Lebanon, NJ). Data was captured by accompanying software (The Director®, Specialty Measurements Inc. Lebanon, NJ) for analysis. Similarly shaped (oval) punches and dies (Natoli Engineering. St. Charles, MO) were used during scale-up: the dimensions of the amino acid gabapentin tablets were 0.3120" x 0.7500", and the electrolyte gabapentin tablets were 0.3750" x 7500".

In Vitro Dissolution Testing:

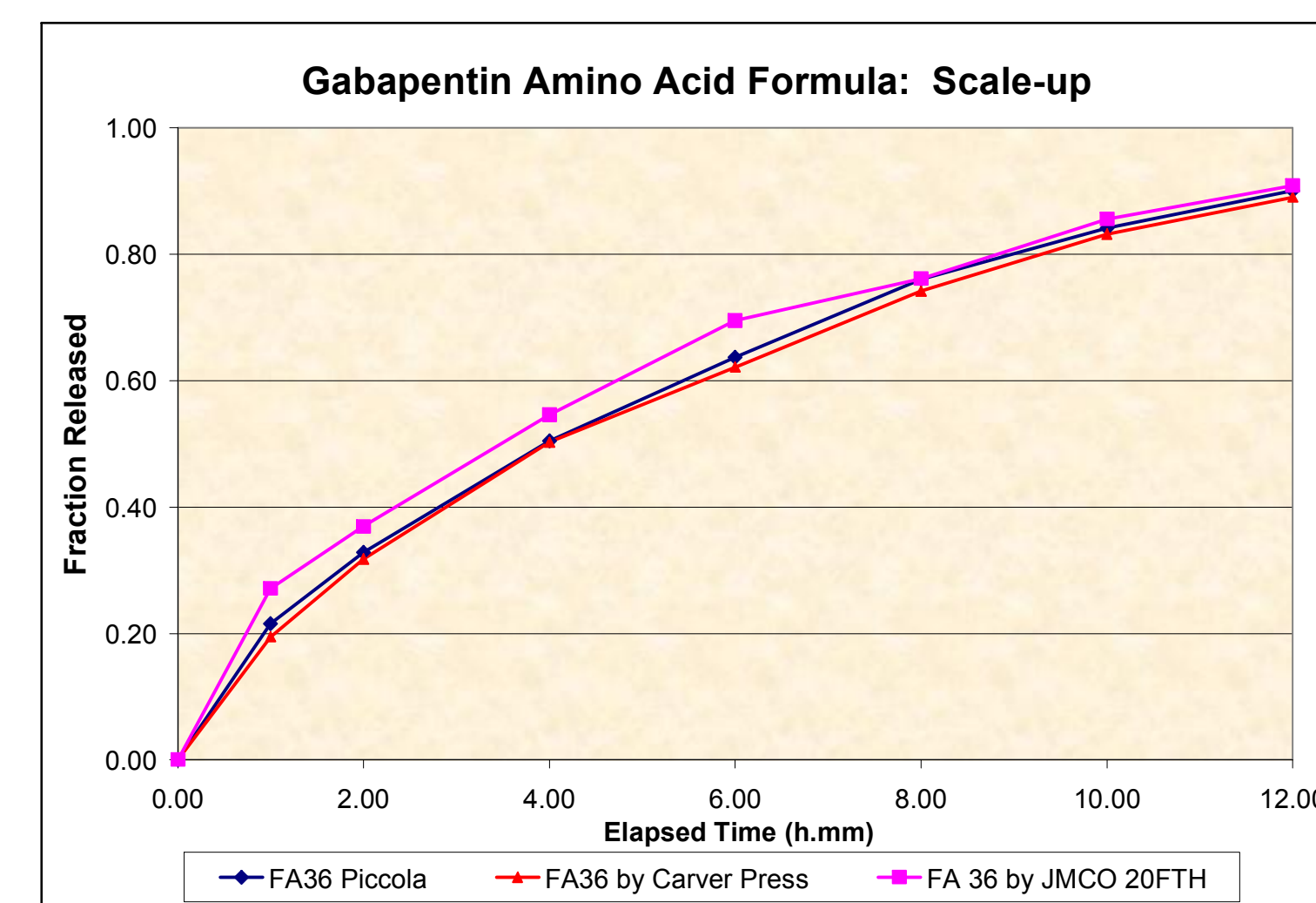
In vitro dissolution studies were conducted using a USP Type II apparatus with 900mL dH₂O at 37°C and 50rpm paddle speed. Samples were removed every 60 min over 12-18 hr via peristaltic pump. Samples were either analyzed directly for gabapentin via UV-Vis spectroscopy @ 215nm, or complexed with ninhydrin and detected @ 402nm.

Results and Discussion

Amino Acid Formula

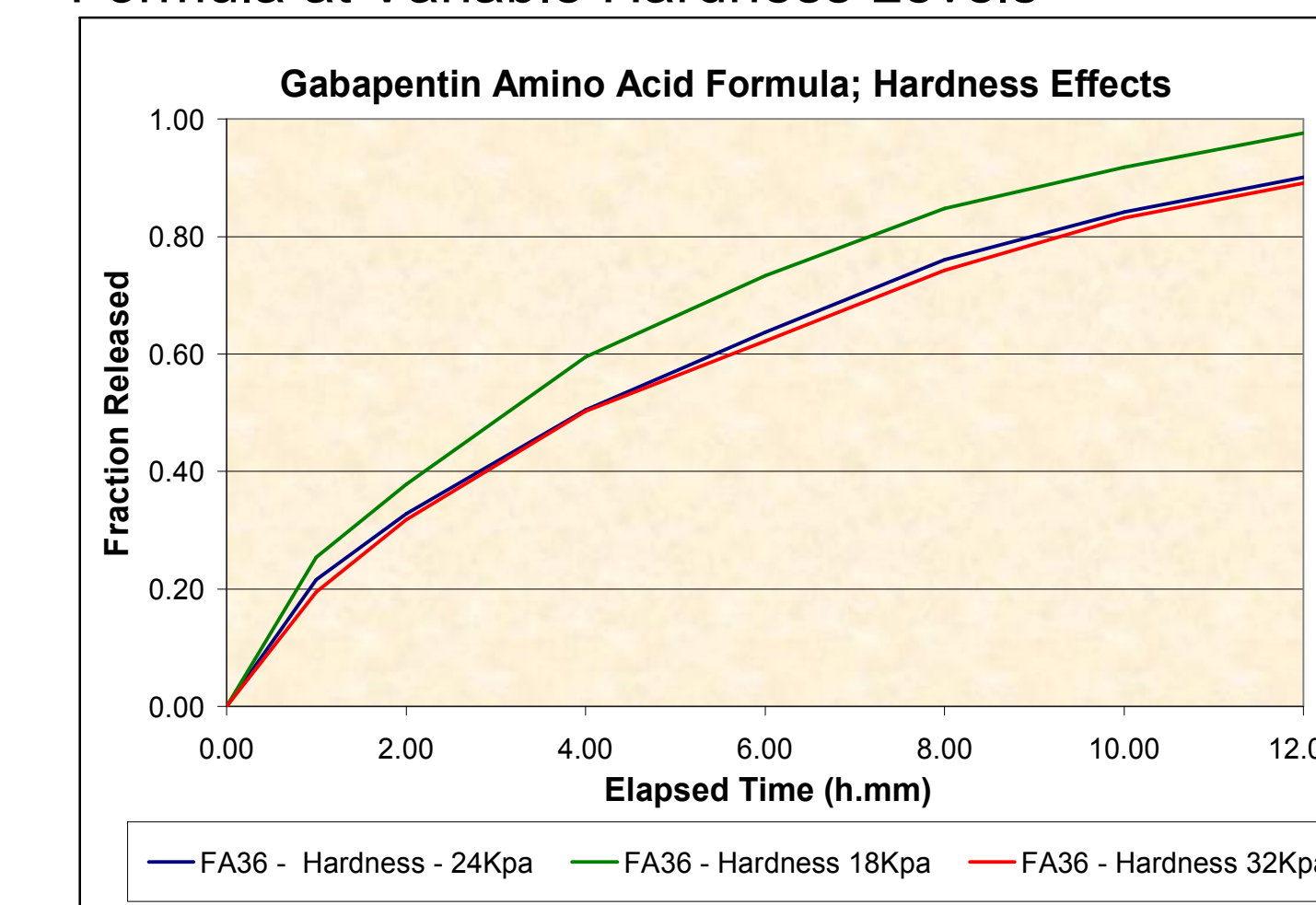
The gabapentin formulation utilizing amino acids to control the release of gabapentin was shown to be very rugged, and highly reproducible at various production scales and on various equipment. Tablets were compressed on a Carver press and manufactured at a 15 g scale, a Piccola press manufactured at a 1 kg scale and a JCMCO press at a 2 kg scale. The amino acid gabapentin formula performed similarly in dissolution regardless of type of press used and scale of batch. (Figure 1.)

Figure 1. – Dissolution of Amino Acid Gabapentin Formula; Variable Presses and Scale.



In addition, the amino acid gabapentin formula tablets compressed to three different ranges of hardness had very similar dissolution rates indicating a robust formula.

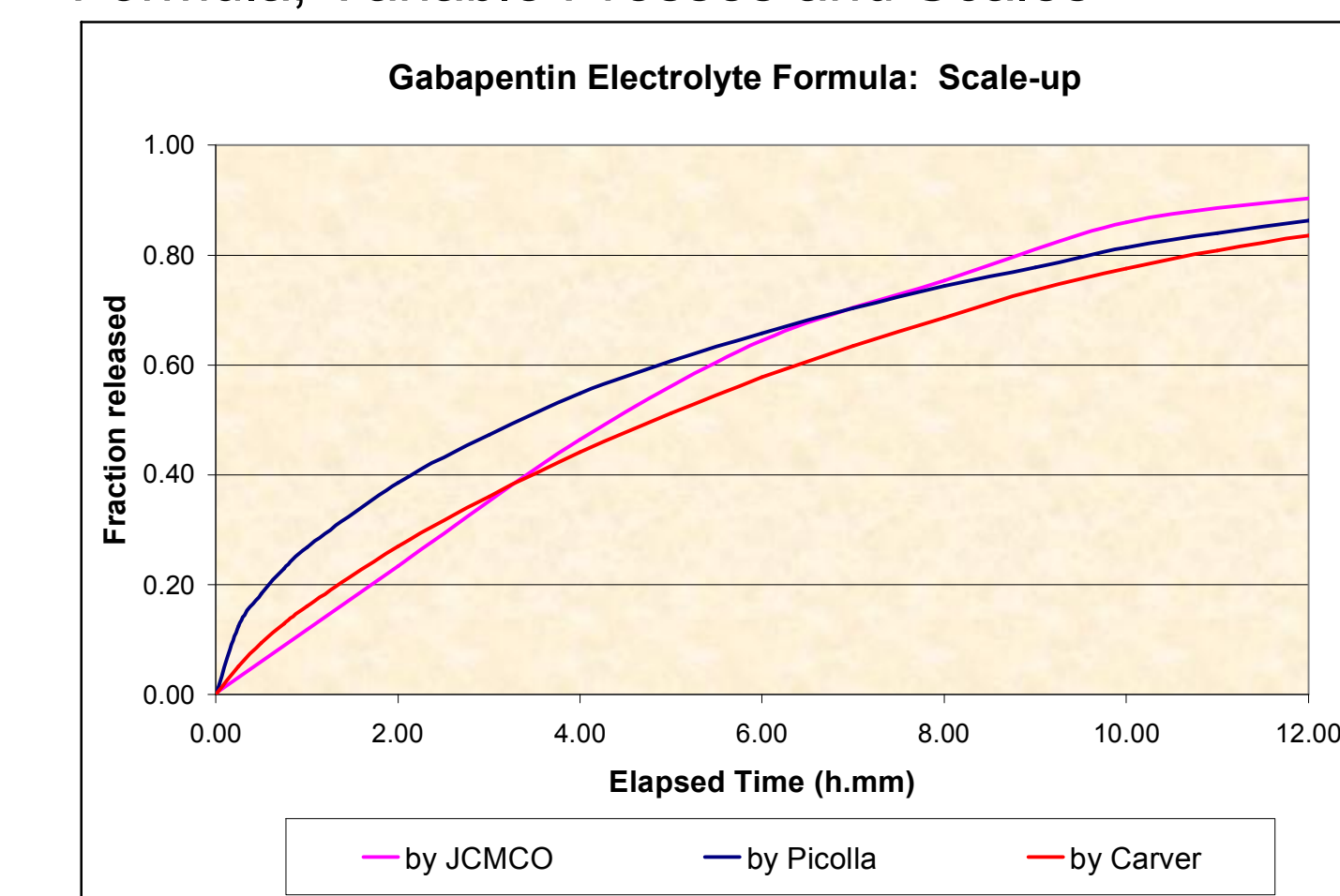
Figure 2. - Dissolution Rate of Amino Acid Formula at Variable Hardness Levels



Electrolyte Formula

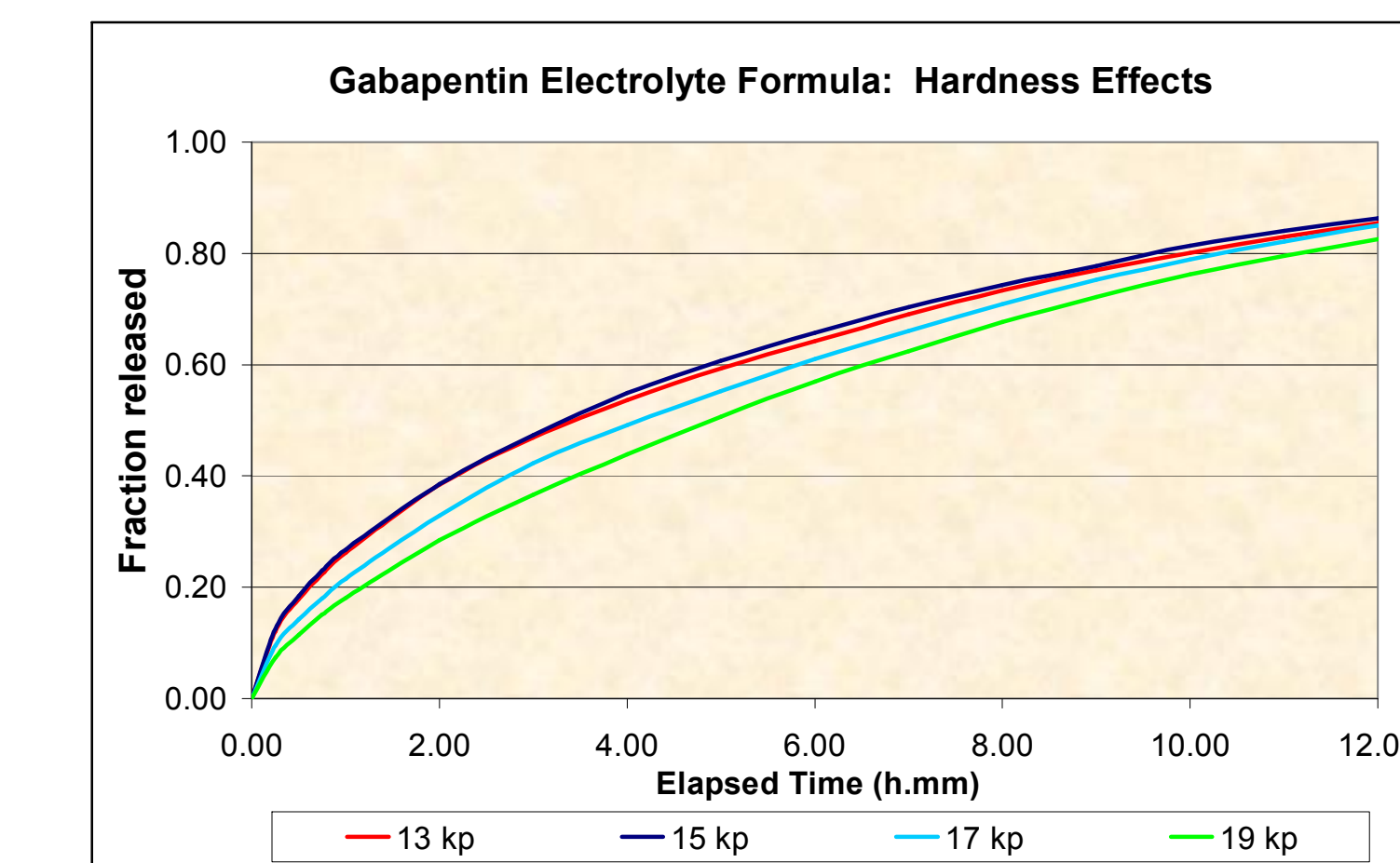
In the case of the electrolyte gabapentin formulation, excellent reproducibility, as shown by dissolution, was also demonstrated between tablets manufactured on the Carver, Piccola and JCMCO tablet presses. (Figure 3.)

Figure 3. – Dissolution of Electrolyte Gabapentin Formula; Variable Presses and Scales



As shown by Figure 4 below, the electrolyte gabapentin formulation also shows robustness in dissolution when compressed to variable hardness.

Figure 4. - Dissolution rate of electrolyte formula at variable hardness levels



Conclusion

Two near linear 12 hour gabapentin formulas utilizing alternative forms of SCOLR Pharma's patented controlled-release technology were developed. These formulas were proven to be both robust and reproducible during scale-up operations.

References

U.S. Patent 6337094 (Kim, et al, 2002). *Matrix for Controlled Delivery of Highly Soluble Pharmaceutical Agents*

U.S. Patent 6090411 (Pillay, et al, 2001). *Monolithic tablet for controlled drug release.*

