Development of Metformin HCl (500mg) Extended Release HPMC-based Matrix Formulation

Application Data

Formulation of Extended Release (ER) Matrices

Metformin hydrochloride (HCl) is an oral anti-hyperglycemic (anti-diabetic) agent that was approved by the FDA in 1994 for treating type 2 diabetes, it has intrinsically poor permeability in the lower portion of the gastrointestinal tract leading to absorption almost exclusively in the upper part of the gastrointestinal tract (absorption window) [1]. Gastrointestinal intolerance is a major concern associated with clinical use of metformin; approximately 10% of adults living with type 2 diabetes are unable to receive metformin treatment because of gastrointestinal intolerance including diarrhea, vomiting, abdominal pain, and constipation.

The primary benefit of an ER formulation of metformin compared to an immediate release (IR) formulation, is to prolong drug absorption in the upper gastrointestinal tract and permit once-daily dosing in patients with type 2 diabetes mellitus, hence, enhancing patient compliance and improving long-term control of diabetes compared with the conventional immediate release formulation of metformin [2].

The objective of this study was to develop a 12-hour ER hydrophilic matrix formulation of Metformin HCl 500mg, employing AnyCoat-C® (HPMC, LOTTE Fine Chemical) with a release profile similar to the marketed brand product Glucophage® XR (reference product).

Materials and Method

The formulation used in this study was generated through Colorcon's HyperStart® C2C formulation service [3], based on scientific principles related to how to formulate hydrophilic matrix tablets for extended release using Hypromellose (HPMC) [4].

HyperStart® C2C is a unique formulation platform for formulators, based on extensive Colorcon experience and formulation database, that empowers them to accelerate their product development process by reducing formulation iterations, saving time and cost, and resulting in speed to market. It was developed using DoE and predictive modelling and provides Colorcon's customers with starting formulations based on product development robustness guidelines, release profile, drug solubility and dose for matrix systems. To request a formulation, visit the Colorcon website: My Colorcon -Tools & Resources [5].

Table 1. Hydrophilic Matrix Formulation Generated by HyperStart® C2C.

	Core Ingredient	Category	MG	%
Intragranular	Metformin HCl	API	500.00	48.54
	Sodium Carboxymethylcellulose*1	Complementary Polymer	50.00	4.85
	AnyCoat-C AN5 (HPMC 2910 5 cP)*2	Polymeric liquid binder	5.50	0.53
Extragranular	AnyCoat-C CN10T Plus *3 (HPMC 2208 100,000 cP)	ER Polymer	365.65	35.50
	MCC PH 102	Diluent	101.97	9.90
	Mg St	Lubricant	7.21	0.70
	TOTAL		1,030.00	100.03

*1 Complementary Hydrophilic Polymer: viscosity 25-50 mPAs of a 2% w/w solution at 25°C.

*2 Polymeric liquid binder sprayed at 5% w/w.

*3 Plus grade: CR grade with tight particle size specification for sustained release hydrophilic matrix tablets applications.

High Shear Wet Granulation and Compression.

Metformin HCl and Sodium CMC (a total of 550 g) were charged into the bowl of a R&D scale high shear (Key International KG5), powders were pre-blended for 5 minutes. This blend was wet-granulated with 104.5 grams of a 5% w/w HPMC solution (AnyCoat-C AN5) that was sprayed employing a Schlick 970/0 S21 spray nozzle at 1 bar. The wet mass was passed through a 12-mesh (1.7 mm) sieve and then dried in a fluid bed (Retsch TG 200) for 12 minutes until a LOD value of 0.73% was achieved. Dried granulation was finally passed through a 16-mesh sieve.

High Shear process parameters employed at the three stages of the wet granulation, along with the drying parameters (dry pre-blend, liquid addition and wet massing stages) are shown in Table 2.

Table 2. High Shear Process Parameters

High Shear Process Parameters		
Impeller speed (all three stages)	RPMs	150
Chopper speed (dry blend)	RPMs	2,000
Chopper speed (liquid addition)	RPMs	1,000
Chopper speed (wet massing)	RPMs	2,000
Wet massing time	Sec	30
Drying time:	min	11
Yield	g	545

AnyCoat-C CN10T Plus and MCC (90 µm) were hand sieved through a 40-mesh screen and mixed with the dried granules for 10 minutes in a twin shell blender. Finally, the magnesium stearate was added, previously screened through a 60-mesh, and blended for an additional 3 minutes.

Tablet Manufacture

1,030mg tablets were compressed using a 10-station rotary tablet press (Piccola B tooling, Riva, Argentina, instrumented by SMI, US), fitted with 19.8mm capsule shape, TSM B type, normal concave tooling. A tabletability study was carried out in a range of 10 to 50 KN of compression force, at a constant turret speed of 40rpm (Dwell time ≈ 38msec), NO pre-compression force was applied. Hardness was measured with a hardness tester (Schleuniger, Germany).

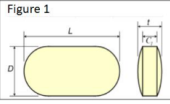
Tensile strength of the Metformin ER matrices was calculated with the Pitt Newton Stanley Equation (Equation 1) [6].

$$\sigma = \frac{2}{3} \cdot \frac{10 \cdot F_c}{\pi \cdot D^2} \cdot \left(\frac{2.84 \cdot t}{D} - \frac{0.126 \cdot t}{C_l} + \frac{3.15 \cdot C_l}{D} + 0.001 \right)^{-1}$$

Equation 1.

σ = Tensile Strength
Fc = Breaking Force also known as P = fracture load
D = Width
t = Tablet thickness
CL = Tablet belly band thickness

Figure 1



Dissolution Testing

Drug release was measured according to the USP Monographs (2024): "Metformin Hydrochloride Extended-Release Tablets", USP Test 1 [7]. Testing was carried out in a USP compliant dissolution bath (DISTEK) using Apparatus II (paddle with sinkers) at 100rpm. The dissolution medium was 1,000mL phosphate buffer pH 6.8 at 37.0+0.5ºC. An Agilent 8453 UV-visible spectrophotometer, fitted with a 1cm cell was used for the detection of Metformin HCl at 232nm. Testing was performed over a 12-hour time.

The release exponent n from the Equation 2 [8] was used to determine the mechanism of drug release. This equation was only applied to the first 60% of the dissolution curve. Values between 0.5 and 1.0 for n indicate anomalous (non-Fickian) transport of drug release suggesting that diffusion and swelling/erosion mechanisms are contributing to release of the drug, whereas values of 0.5 indicates a pure (Fickian) diffusion mechanism.

Equation 2:

$$Q = kt^n$$

Equation 2.

Q = fraction of drug released in relation to time t
k is a constant (characteristics of polymer system and the drug).

n = release exponent

- 0.5 = Fickian diffusion
- 0.5 < *n* < 1.0 Anomalous (non-Fickian) transport
- 1.0 = Case II transport
- *n* > 1.0 Super-Case II transport

Results and Discussion

Physical Characterization

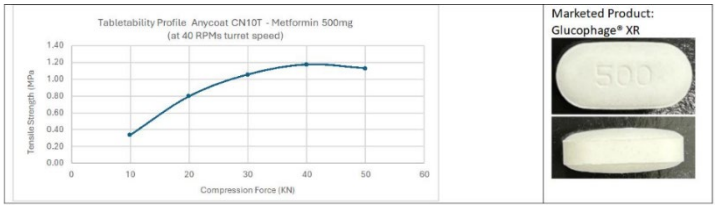
The values for the bulk and tap densities were 0.530 g/mL and 0.625 g/ml, respectively. Carr's compressibility index of the formulation was 14.89% indicating that the granules had good flow properties. Particle size was 416 µm, which is appropriate for the intended tablet size. Flow Index (FloDex) was 5, indicating a very low internal friction coefficient and suggesting excellent flow and a low coefficient of variation of average weight [9]; flow rate was 51 g/min.

Table 3. Granulation Properties

Granulation Properties		
LOD before (dry powders):	%	0.56
LOD: (damp mass):	%	13.54
LOD: (after drying):	%	0.73
Bulk density	g/mL	0.530
Tapped Density	g/mL	0.625
Compressibility	%	14.89
Flodex: flow index (orifice)	mm	5
Flodex: flow rate	g/min	51
Particle Size - geometric mean diameter:	µm	416
Particle Size Distribution d (15-85%)	µm	241-718

Tablet weight variation was found to be less than 1%, which is also an indication of good flow of material during compression. The matrices exhibited friability values below 0.1% at all compression forces (10-50 KN). Tabletability profile is shown in Figure 2, a tensile strength above 1 MPa was achieved at a compression force of 30 KN, indicating acceptable mechanical properties as suggested by the Manufacturing Classification System [10].

Figure 2. Tabletability profile of HyperStart® C2C formulation of Metformin HCl ER matrices based on AnyCoat-C CN10T Plus (HPMC 100,000cP).



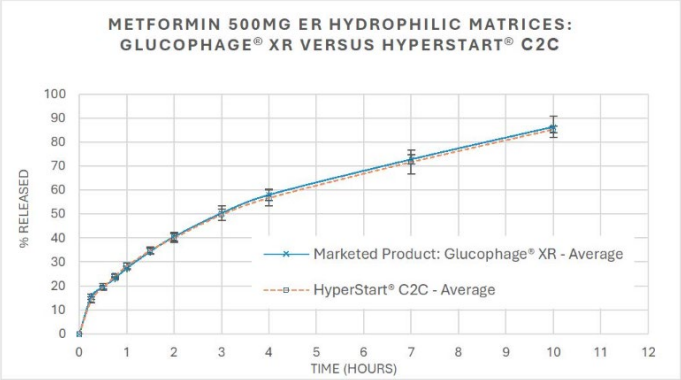
Formulating ER matrices of Metformin HCl presents formulation challenges due to its high dose (marketed dose strengths from 500 to 1,000mg), poor inherent compressibility, and high-water solubility (>300mg/ml at 25°C). The tensile strength of the marketed product was measured and corresponds to 0.84 MPa, with the following physical characteristics: hardness of 21.95 Kps, thickness of 6.9 mm, length of 19.2 mm, width of 9.4 mm, and cup depth of 1.4 mm. Although this tensile strength value appears to be relatively low, it is crucial to consider the manufacturing conditions.

The marketed product is produced on a large scale with significantly shorter dwell times during the compression process. Consequently, it is highly likely that when the formulation presented in this study undergoes scale-up, its tensile strength will decrease to values similar to those observed in the marketed product. This anticipated reduction in tensile strength can be attributed to the shorter dwell times typically associated with large-scale manufacturing processes.

Drug Release

The drug release profile of the marketed product (Glucophage® XR) and the formulation generated through the HyperStart C2C service were compared and are showed in Figure 3.

Figure 3. Drug release profiles of Glucophage® XR versus HyperStart® C2C formulation based on AnyCoat-C CN10T Plus. (n=6)



The release exponents and the constants for both formulations are presented in Table 4.

Table 4. Release Mechanisms (Equation 2) from Dissolution Data.

Drug Release Kinetics Analysis		
	Marketed Product Glucophage® XR	**HyperStart® C2C**
Release exponent (n):	0.47	0.49
Kinetic constant (k)	28.3	27.9
Coefficient of determination (R^2)	0.9961	0.9996

Release exponents of both products were close to 0.5, indicating a predominantly diffusion-based drug release mechanism [8]. This release mechanism was expected as a combination of influencing factors on drug release [4] such as (i) the presence of a high molecular weight HPMC (100,000 cP) at a 35.5% concentration in the formulation, (ii) the implementation of a polymer blend strategy (inclusion of Sodium CMC) increasing gel strength [11,12] and resulting in a decreased rate of drug diffusion and suppression of gel erosion during the dissolution test period, and finally (iii) the selection of an insoluble diluent (MCC).

As of the kinetic constant (k), very high k values were observed from both products (28.3 and 27.9) which are typical from high dose + highly soluble APIs, observed as marked burst effect release from the matrix.

The comparison of both, release exponent and kinetic constant permit to conclude that there is no difference in the in-vitro drug release rate and extend from both Glucophage® XR and the formulation generated through the HyperStart C2C service.

Drug release profile from the HyperStart C2C formulation was also compared to Glucophage® XR product using f2, a similarity factor [13]. Value of f2 between 50 and 100 ensures equivalence of the two dissolution profiles. The calculated value of f2 was 94 indicating similarity.

Conclusion

A consistent and robust extended-release hydrophilic matrix tablet utilizing AnyCoat-C CN10T Plus (HPMC 2208, 100,000 cP) was developed using Colorcon HyperStart® C2C formulation service.

The formulation manufactured with AnyCoat-C CN10T Plus produced tablets with consistent weight uniformity, low tablet friability and a tabletability profile that indicates that the compression process is scalable to large scale of manufacture with tensile strength values (> 1MPa) similar to those found on the marketed product (≈ 0.84 MPa).

HyperStart® C2C formulation, based on AnyCoat-C CN10T Plus, matched the drug release kinetics (similar release exponent and kinetic constant) of Glucophage XR 500mg product, confirming that AnyCoat-C CN10T Plus offers a robust performance that is comparable to the hydrophilic polymer used on the marketed product.

This study demonstrated that the HyperStart® C2C service platform, along with the global infrastructure of Colorcon´s laboratories provide an unmatched customer service model.

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