Study of High Dose Vitamin C (1000 mg) ER Hydrophilic Matrix Tablet using METHOCEL™ as the Rate Controlling Polymer

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Introduction

The purpose of this work was to develop and study a high dose vitamin C (1000 mg) extended release (ER) tablet formulation using a hydrophilic matrix system coated with a moisture barrier film coating system, with an 8-hour release profile.

ER formulations are widely used to reduce dosing frequency and maintain a desired therapeutic effect over a longer duration. Many nutraceutical products are formulated as immediate release dosage forms and maximum absorption of the active ingredients is achieved by ingestion of several spaced doses throughout the day. However, to improve consumer compliance and better dosing effect, it is beneficial to develop ER formulations for nutraceutical formulations.

Vitamin C is a highly crystalline and water-soluble ingredient that is well recognized for the vital role it plays in supporting immunity and is available in various dosage forms. The ER formulations of vitamin C are mainly used to treat scurvy or prevent deficiency.[1] The required daily dose of vitamin C ER tablet formulations varies from 500 mg to 1.5 g.[2,3] From a formulation perspective, vitamin C presents tableting challenges due to its poor flow, low compressibility, and high dose for ER matrices.

Methods

Vitamin C (1000 mg) ER tablets were prepared using high shear granulation with Starch 1500®, partially pregelatinized starch as a binder. METHOCEL™ K100LV Premium Cellulose Ethers was used as the extended-release excipient. The formulation composition is outlined in (Table 1).

Table 1: Composition of Vitamin C ER 1000 mg Tablets

Ingredients		% w/w	mg/tablet
Intragranular	Vitamin C (Ascorbic acid) (Shandong Luwei Pharma)	66.667	1000.05
	METHOCEL K100LV (IFF)	10.000	150.00
	Starch 1500 (Colorcon)	3.660	54.90
Extra Granular	METHOCEL K100LV (IFF)	10.000	150.00
	MCC PH 102 (Avicel)	8.923	133.85
	Aerosil (Degussa)	0.250	3.75
	Magnesium Stearate (Ackros)	0.500	7.50
Total		100.000	1500.00

Manufacturing of Tablets Using High Shear Granulation Method:

Vitamin C and METHOCEL™ K100LV were passed through ASTM #40 mesh screen. The granulation binder of Starch 1500 was prepared in water (room temperature) at 20% w/w solids. Dry mixing of the intragranular blend was performed in a rapid mixer granulator (Bowman and Archer, 2L, India) at low impeller speed followed by wet massing using the Starch 1500 dispersion. Wet granules were dried in an

oven at 30-35°C to achieve a loss on drying (LOD) of not more than 2.0%. The dried granules were passed through a multi-mill fitted with a 1.5 mm screen. The extra granular ingredients (METHOCEL™ K100LV, MCC, and colloidal silicon dioxide) were weighed and passed through ASTM #40 mesh screen. Both intra and extra granular ingredients were blended (Rimek Kalweka, India) for 10mins at 20rpm followed by lubrication with magnesium stearate, previously passed through ASTM # 60 mesh screen, for 2 mins. The powder blend was tested for flow properties and tablets were compressed (Karnavati, Rimek Minipress SF II, India) using 21.5 x10.8mm, standard concave tooling.

Matrix tablets were coated in a perforated coating pan (O'Hara Labcoat LCM) with Nutrafinish® Moisture Protection Coating to 3.0 % weight gain (WG) using 20% w/w solids in water.

Tablet Testing:
Tablet physical properties were tested for weight, hardness, thickness, friability after 100 rotations in a U
SP friabilator, % assay and dissolution profile using 900.0mL phosphate buffer, pH 3.0, paddle method using a sinker, at 50 rpm for 12 hours.

Stability Testing:
Coated tablets were packaged in 100 cc HDPE bottles, stored at 30°C/65% RH and 40°C/75% RH for 3 months, and evaluated for assay and dissolution profile.

Results

The powder blend showed satisfactory properties for rotary compression in comparison with the API (Table 2).

Table 2. Physical Properties of Powder Blend

Parameters	Vitamin C Blend	Vitamin C
Bulk density, g/ml	0.625	0.806
Tapped density, g/ml	0.862	1.19
Compressibility index, %	27.5	32.258
Hausner ratio	1.38	1.476
LOD, %	2.76	0.25

a) *Tablet Physical Properties:*
Vitamin C ER Tablets showed good hardness ~16 kP and low friability of ~0.33% at 100 rotations. Coated tablets were smooth and elegant in appearance (Figure 1).

Figure 1. Comparison of Vitamin C ER Uncoated and Coated Tablets

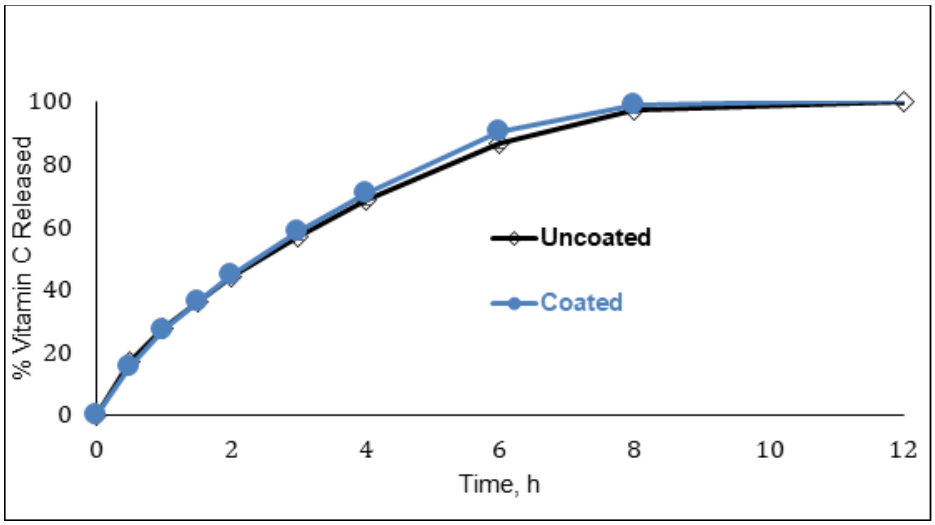
b) *Drug Assay and Dissolution Profile:*
A drug assay of 98-100% was achieved for uncoated and coated tablets. Matrix tablets showed consistent 8-hour drug release profile with f_2 values >75 (Figure 2).

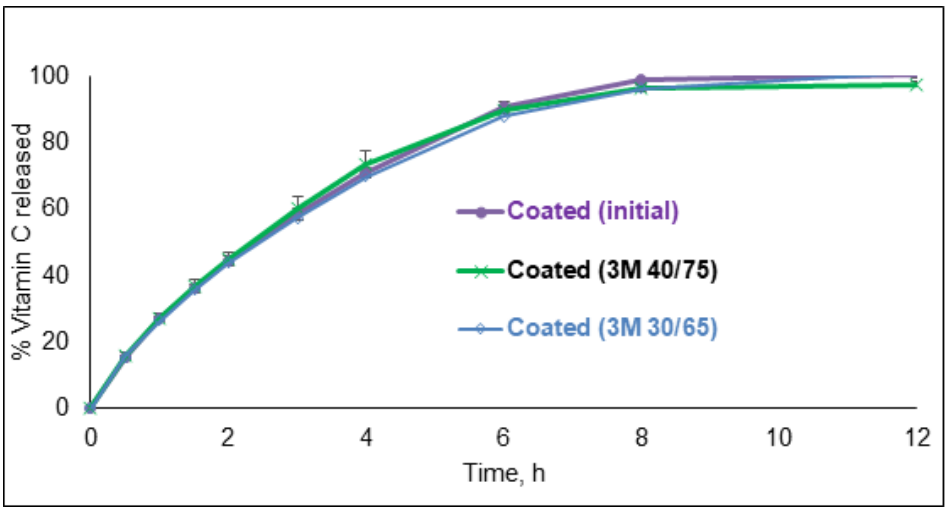
c) *Stability Testing:*
The physical appearance of tablets coated with the Nutrafinish moisture barrier coating showed no signs of discoloration following the 3-month 40ºC/75% RH stability study, whereas uncoated tablets showed slight discoloration. At the end of 3rd month stability, the assay result was found to be more than 95% in the coated tablets (Table 3) and there was no significant difference in the drug release profile observed with f2 values of more than 75 (Figure 3).

Table 3. Stability Data of Drug Assay

Initial	3M at 40°C/75% RH	3M at 30°C/65% RH
98%	96%	97%

Figure 2. Drug Release from Uncoated vs. Coated 1000mg Vitamin C ER Tablets





Conclusions

METHOCEL™ K100LV was successfully used as a hydrophilic matrix polymer along with Starch 1500 as a binder to design a high dose (1000 mg) vitamin C ER formulation.

Nutrafinish moisture barrier coating was successfully used for coating the vitamin C ER formulation which remained stable over the stability period of 3 months.

References

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