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CARBOPOL® POLYMERS FOR NITROSAMINES (NDMA) COMPLIANT METFORMIN EXTENDED RELEASE TABLETS

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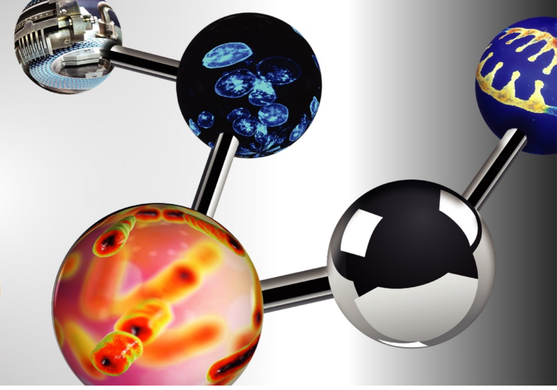


PURPOSE

Development of high dose, small size, stable Metformin HCl ER tablets using Carbopol polymers and their subsequent evaluation for nitrosamines compliance

Small Tablet For High Dose API

OBJECTIVE(S)

- Carbopol polymers are proven to be highly efficient in controlling drug release at low usage level. This increasing manufacturing productivity and improving ease of swallowability and patient compliance.
- Recent guidance documents have been issued by US FDA in relation to unacceptable levels of eight potentially carcinogenic nitrosamine (NDMA) impurities that may be present in drug products. This has resulted in global recalls, Metformin HCl ER tablets being one of the worst affected.

The objectives of the project were:

1. Development of stable, small size, Metformin HCl Extended-Release tablets USP using synergistic combination of Carbopol polymers, buffering agents and other control release polymers
2. Testing of the developed tablet formulations for nitrosamine (NDMA) impurities compliance as per US FDA guidance

METHOD(S)

- Formulations for two strengths, 500 mg and 1000 mg, complying to USP specifications were developed by high shear wet granulation. The list of ingredients used intra-granularly and extra-granularly are depicted in Table 1. The developed formulations were tested for physical parameters, dissolution profile, assay and RS along with nitrosamine impurities for initial and aged samples. Dissolution was carried as per USP Test IV (1000 mL of pH 6.8 phosphate buffer and 100 rpm, paddle).
- Stability studies were conducted as per ICH guidelines at accelerated (40°C/75% RH) and intermediate(30°C /75% RH) conditions for tablets packed in HDPE bottles/ Alu-Alu blister pack.

Table 1: Ingredients used to formulate Metformin HCl ER tablets

Ingredient	Process
Metformin HCl[1]	Intra granular = Use 2% aqueos Carbopol dispersion for granulation
Hypromellose K100M	
Carbopol® 971P NF Polymer	
Magnesium hydroxide[2]	
Magnesium Hydroxide[2]	Extra granular
Hypromellose K100M	
Carbopol® 971P NF polymer	
Carbopol® 71G NF polymer	
Anhydrous colloidal silica	
Magnesium stearate	

[1]Particle size NLT 95% passing through 100# and [2]Within FDA IID limits

RESULT(S)

- Both 500 mg and 1000 mg strength tablets, were successfully formulated at relatively smaller sizes (20-30% smaller than most commercial formulations of respective strengths) - Table 2, Figure 1.
- Reduced tablet weight allows more tablets/batch (~ 20% fewer batches per year), resulting in increased productivity and cost savings for analytical testing, inventory, packaging and storage.

Table 2. Physical properties of Metformin HCl tablets

Physical Properties	500 mg USP	1000 mg USP
Lubrizol Formulations		
Tablet weight (mg) average ±SD	800.4 ± 7.8	1250.2 ± 10.2
Mechanical strength (kP) average ±SD	20.6 ± 0.96	21.6 ± 0.16
Friability @ 100(%)	0.20	0.18
Punch dimensions	17.1 X 8.2 mm, Capsule	20.15 X 9.7 mm, Oval biconvex
Commercial product weight	1030 mg	1450 mg

Fig 1: Metformin HCl 500 mg – size comparison

Lubrizol vs. commercial tablets (both 500 mg dose)

Dissolution Profile: Satisfactory Results Obtained

Multimedia compliance observed for both strengths - Figures 2A and 2B (f2>60)

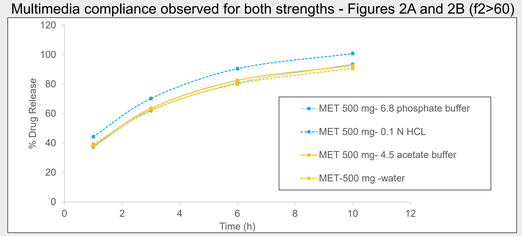


Figure 2A: Multimedia dissolution compliance for 500 mg strength

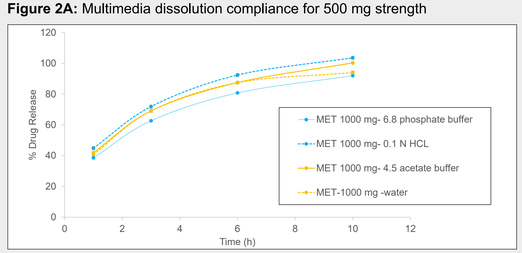


Figure 2B: Multi-media dissolution compliance for 1000 mg strength

Results for 6M ACC studies: Assay, Dissolution, RS and Nitrosamines compliance obtained

The tablets were developed to comply with USP monograph and were stable under accelerated conditions when packed in HDPE bottles – Figure 3, Table 3.

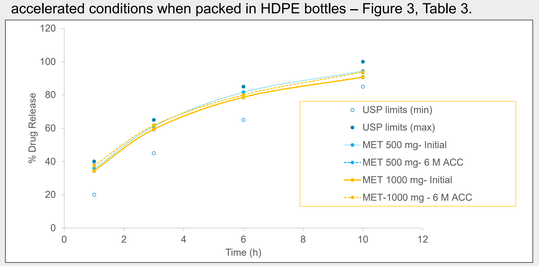


Figure 3: 6 M ACC Results for both, 500 mg and 1000 mg strengths

Table 3. Stability study results for USP compliant Metformin HCl tablets, HDPE Bottle

Tests	USP Specs	Results for 500 mg strength at 6 M ACC	Results for 1000 mg strength at 6 M ACC
Assay (%)	90-100	99.9	97.13
Single max impurity (%)	0.1	0.04	0.06
Total impurity (%)	0.6	0.10	0.16

Selected lots of the tablets were tested at FDA approved testing laboratory as per US FDA guidelines and were found to be compliant for all eight nitrosamine impurities - Table 4.

Table 4: Results of nitrosamine impurity testing for Lubrizol Metformin HCl tablets (500 mg strength)

	Sample Name	Conditions	Results									
			Limits NMT 0.048 ppm		Limit NMT 0.013 ppm						Compliance	
			NDMA	NMBA	NDBA	NDEA	NDIPA	NEIPA	NDPA	NMPA	Scenario 1	Scenario 2
Lubrizol Formulation	F – USP 500 mg	Fresh Lot	ND	ND	ND	ND	ND	ND	ND	ND	Complies	N/A
	F – USP 500 mg	6 Months Ambient	ND	BLOQ (0.006)	ND	ND	ND	ND	ND	ND	Complies	N/A
	F – USP 500 mg	40C/75%RH 6M PVDC	ND	0.010	ND	ND	ND	ND	ND	ND	Complies	N/A
	F – USP 500 mg	40C/75%RH 6M ALU/ALU	ND	BLOQ (0.005)	ND	ND	ND	ND	ND	ND	Complies	N/A
	F- USP 1000 mg	Fresh Lot	ND	ND	ND	ND	ND	ND	ND	ND	Complies	N/A

Total impurities should not be more than 0.013ppm – Scenario 2.

LOQ: for NDMA & NMBA 0.015 ppm; for all other impurities 0.01 ppm.

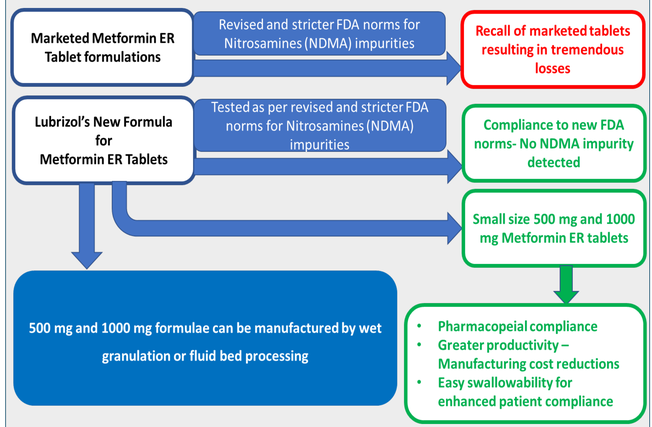
BLOQ: Below limit of quantification.

ND: Not detected according to non validated method. N/A: Not Applicable

NOTE: Studies were performed also on other variants of Metformin HCl ER tablets prepared using Carbopol polymer (IP compliant formulations and 1000 mg USP compliant formulations) and they too have been found to be compliant to Nitrosamines (NDMA) impurities.

CONCLUSION(S)

- Carbopol polymers have been successfully used to formulate high dose, small size and stable Metformin HCl extended-release tablets.
- The tablets complied to Nitrosamines (NDMA) impurities as per US FDA guidance at ambient as well as accelerated stability conditions.
- Additional NDMA testing has been performed on various Carbopol polymer-based Metformin ER tablets for different markets and they have also complied to NDMA impurities.



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