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Improved extended release highly loaded drug compositions using Carbopol® polymers in combination with suitable microenvironmental pH modulators

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BACKGROUND

Metformin HCl remains the first-line treatment for management of type 2 diabetes with doses of 500 – 1000 mg per tablet. Considering the increased frequency of dysphagia in diabetes, it is necessary for patient compliance to formulate stable compositions with higher drug loading and reduced tablet size.

Carbopol® polymers are crosslinked polymers of acrylic acid (pKa = 6 ± 0.5). They are highly efficient matrix former excipients at low inclusion levels allowing for high drug loading in controlled release tablets.

PURPOSE

The purpose of the study was to evaluate Carbopol® polymers, in combination with microenvironmental pH modulators (buffering agents), to achieve improved stability and high drug loading in Metformin HCl extended release tablets.

METHODS

Extended release Metformin HCl tablets were prepared by high shear aqueous granulation using Carbopol® polymers in combination with other controlled release agents (hypromellose or sodium-CMC). Microenvironmental pH modulators (magnesium carbonate, magnesium oxide, magnesium hydroxide, sodium bicarbonate, sodium acetate, sodium hydrogen phosphate, trisodium phosphate, calcium carbonate, and potassium carbonate) were included to improve stability at high drug loading (62 – 80%).

The tablets were evaluated for chemical stability by HPLC after exposure to forced degradation conditions (80 °C and 75 % RH for 5 days).

Based on the outcome of the forced degradation, formulations of Metformin HCl 500 mg extended release tablets were further developed to meet USP dissolution requirements and tested for stability under ICH accelerated conditions (40±2 °C/75±5%RH). The composition of the optimized formula is shown in Table 1.

Table 1. *Metformin HCl tablet composition*

Ingredient (%w/w)	
Intra-granular	
Metformin hydrochloride	62.50
Hypromellose K100M CR	21.70
Carbopol® 971P NF polymer	2.00
Magnesium hydroxide	5.80
Extra-granular	
Carbopol® 971P NF polymer	3.00
Carbopol® 71G NF polymer	3.00
Talc	1.00
Magnesium stearate	1.00
Total	*100*
Tablet weight	*800 mg*

RESULTS

The formulations containing combinations of Carbopol® polymers and magnesium-based buffering agents (magnesium hydroxide and magnesium oxide) showed improved stability at high drug loading when tested under forced degradation conditions - Table 2.

Batch #	Buffer type	Metformin HCl (%w/w)	Carbopol® polymers (%w/w)	Buffer (%w/w)	Formulation pH	Impurity (%w/w)	Physically stable
1	Magnesium carbonate	80.0	9.12	4.8	5.6	0.5	No
2	Magnesium hydroxide	69.4	8.94	6.9	5.6	0.1	Yes
3	Magnesium hydroxide	77.4	8.79	5.0	6.5	0.2	Yes
4	Magnesium oxide	80.0	9.12	4.8	6.4	0.1	Yes
5	Magnesium oxide	77.4	8.79	5.0	8.6	0.3	Yes
6	Sodium bicarbonate	83.3	2.67	6.1	5.0	0.2	No
7	Sodium bicarbonate	80.0	6.55	2.4	6.0	0.4	No
8	Sodium bicarbonate	80.0	9.12	4.8	5.6	0.7	No
9	Calcium carbonate	80.0	9.12	4.8	5.4	0.8	No
10	Potassium bicarbonate	80.0	9.12	4.8	5.4	0.8	No
11	Sodium hydrogen phosphate	80.8	9.12	4.0	6.0	0.9	Yes
12	Sodium acetate	77.4	8.79	4.1	4.7	0.97	Yes
13	Trisodium phosphate	77.4	8.79	4.0	5.6	0.99	Yes

Table 2. *Forced degradation results for Metformin HCl formulations containing Carbopol® polymers and pH modulators (buffering agents)*

Among the buffering agents studied, magnesium hydroxide and magnesium oxide led to the lowest impurity levels and physically stable formulations. Inclusion of bicarbonates or carbonates was not recommended due to carbon dioxide generated during stability testing.

Metformin HCl 500 mg extended release tablets were developed based on the forced degradation results, using Carbopol® polymers and magnesium hydroxide as a buffering agent (Table 1). A 15% reduction in tablet size in comparison with commercial benchmark was achieved (Figure 1). The tablets met the USP Test 4 dissolution requirements and were stable for 6 months under ICH accelerated stability conditions (Figure 2, Table 3).

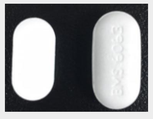

Fig. 1. *Size of Metformin 500 mg tablets (Carbopol polymer based formulation vs. commercial reference)*

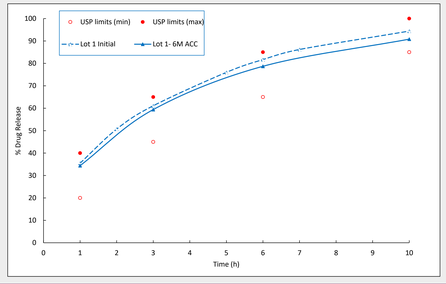

Fig. 2. Dissolution *(USP Test 4) of Metformin HCl 500 mg extended release tablets (Lot 1) - initial and after 6 months accelerated stability*

Property	USP specs	Results (6-month accelerated stability) ACC
Assay (%)	90-110	99.91
Single max impurity (%)	0.1	0.02
Total impurity (%)	0.6	0.02

Table 3. *Properties of Metformin HCl 500 mg extended release tablets (Lot 1) after 6 months accelerated stability*

CONCLUSIONS

Combinations of Carbopol® polymers and magnesium containing microenvironmental pH modulators (magnesium hydroxide and magnesium oxide) provided improved stability and high drug loading in Metformin HCl tablets. Metformin HCl 500 mg extended release tablets were successfully formulated to meet USP dissolution requirements and achieve stability under ICH accelerated conditions. An international patent application PCT/US2018/030380 has been published that discloses this work and the technology.

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