Lubrizol LifeSciences

Development of Small Size, Compendial and Multimedia Compliant Metformin HCl Extended Release Tablets Using Carbopol® Polymers

Vikrant Chadawar[1], Kedar Chikhalikar[1], Komal Talwadekar[1], Meenakshi Prasad[1], Sandip Chavan[1], Murty Vyakarnam[2], Elena Draganoiu[2]

[1]Lubrizol Advanced Materials India Pvt. Ltd., Mumbai, India, [2]Lubrizol Advanced Materials, Inc., Cleveland OH, USA

Objective

Carbopol® polymers are efficient gel matrix formers and allow, when used alone or in synergistic combinations with other hydrophilic polymers, to achieve a desired target release profile at high drug loading and small tablet size.

Metformin HCl is a high solubility, high dose drug. Due to its shorter half-life, frequent administration of immediate release formulations is required to achieve the desired therapeutic effect. Several extended release (ER) dosage forms of metformin HCl have been developed to reduce the frequency of administration.

The objective of this study was to develop metformin HCl 1000 mg USP extended release tablets with high drug loading (80%) using Carbopol polymers.

Methodology

Metformin HCl (Wanbury Ltd., India), Carbopol 971P NF and 71G NF polymers (Lubrizol Advanced Materials Inc., USA), hypromellose Metolose® 90SH 100000 SR (Shin-Etsu Chemical Co. Ltd, Japan), colloidal anhydrous silica (Aerosil® 200 fumed silica, Evonik Industries, Germany), magnesium stearate (Ferro Inc., USA).

Method:
Metformin HCl 1000 mg extended release tablets were formulated at high drug loading (80%) using a synergistic combination of Carbopol polymers and hypromellose as matrix forming agents – **Table 1**. Due to poor compressibility of metformin and the high dose, a high shear aqueous granulation was necessary.

Table 1: Composition (w/w) of Metformin HCl 1000 mg ER tablets

Ingredient (%)	% w/w
Intra-granular	
Metformin hydrochloride	80.00
Carbopol 971P NF polymer	8.80
Hypromellose K100M (Metolose 90SH 100000 SR)	5.20
Water	*q.s.*
Extra-granular	
Carbopol 71G NF polymer	5.20
Colloidal anhydrous silica	0.32
Magnesium stearate	0.48
Total	**100.00**
Tablet weight (mg)	*1250*

Metformin HCl, Carbopol 971P NF polymer and hypromellose K100M were granulated with 6.5% water, according to the parameters – **Table 2**. The granules were blended with Carbopol 71G NF polymer, glidant and lubricant.

Table 2: Processing conditions for granulation

Process	Time (min)	Impeller (RPM)	Chopper (RPM)
Dry mixing	10	150	-
Water addition	2	250	1500
Wet massing	1	250	2880

The lubricated blend was compressed into tablets using 20.15 x 9.7 mm oval shaped punches, to target tablet weight 1250 mg and hardness (25-30 kP).

Metformin HCl 500 mg extended release tablets were formulated at same drug loading (80%) to achieve significant reduction in tablet size and compressed using 14.00 x 9.00 mm oval punches to target weight 625 mg and hardness 25-30 kP.

Metformin HCl 1000 mg extended release tablets were evaluated for physical parameters and dissolution as per USP 38-NF 33 test 4 monograph (type 2 apparatus, 100 rpm, 1000 ml pH 6.8 phosphate buffer). In addition, to assess the robustness of the formulation, release studies were conducted for multiple agitation rates (75, 100 and 150 rpm in pH 6.8 phosphate buffer) and multimedia dissolution (in 0.1N hydrochloric acid, pH 4.5 acetate buffer USP and pH 6.8 phosphate buffer USP).

Long term (30°C/65% RH) and accelerated (40°C/75 % RH) stability studies were conducted for tablets packed in PVC/PVDC blister and HDPE container, as per ICH guidelines.

Results

Tablet properties:
The physical properties of the tablets were satisfactory - **Table 3**.

Table 3: Tablet properties

Weight (mg)	1255.7 ± 0.87
Thickness (mm)	7.45 ± 1.12
Hardness (kP)	27.9 ± 0.98
Friability (%) @ 100 revolutions	0.14
Friability (%) @ 300 revolutions	0.23

Drug release:
The drug release met USP specifications and showed low intra-batch variability. The agitation rate did not have an impact on the dissolution, similar release profiles being obtained at 75 – 150 rpm - **Fig. 1**.

Similar drug release was achieved in all tested dissolution media – **Fig. 2**, with similarity factor (f2) values > 50 - **Table 4**.

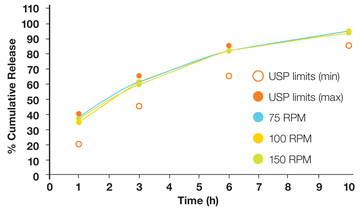

Fig. 1. Effect of agitation rate on drug release from Metformin HCl ER tablets 1000 mg (n=6 ± SD)

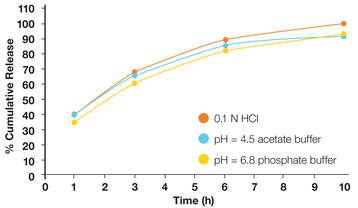

Fig. 2. Effect of dissolution medium on drug release from Metformin HCl ER tablets 1000 mg (n=6 ± SD)

Accelerated and long term stability – 6 months – data for metformin HCl extended release tablets packed in PVC/PVDC blister or HDPE container indicated that the physical properties and drug release were consistent, within the defined limits - **Fig. 3**.

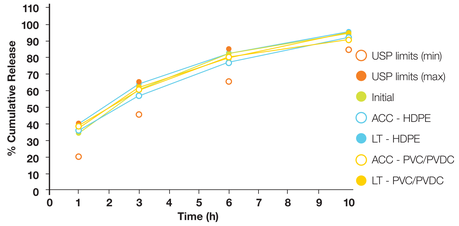

Fig. 3. Accelerated (ACC) and long term (LT) stability studies – 6 months – of Metformin HCl ER tablets 1000 mg packed in PVC/PVDC blister or HDPE container (n=6 ± SD)

Table 4: Similarity factor (f2) values in different dissolution media.

F2 value between 0.1 N HCl and 6.8 phosphate buffer	60.7
F2 value between pH 4.5 and 6.8 phosphate buffer	76.6
F2 value between 0.1 N HCl and pH 4.5 acetate buffer	65.9

Conclusion

- Metformin HCl 1000mg USP extended release tablets with high drug loading (80%) were successfully developed using synergistic combination of Carbopol polymers and hypromellose as matrix forming agent.
- The formulation was suitable for extended release tablets with multimedia and multiagitation compliant release profile.
- This was demonstrated to be a viable formulation to manufacture small size metformin HCl extended release mono- or bi-layer tablets.