Lubrizol LifeSciences

Strategies for Multimedia Compliance of Extended Release Tablets with Carbopol® Polymers

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Objective

A key aspect for development of extended release tablets is understanding the drug release under various testing conditions, especially the effect of dissolution medium on the release. The purpose of this study was to evaluate the multimedia release profiles of extended release matrix tablets containing Carbopol polymers and to develop multimedia compliant formulations of selected model drugs.

Methodology

Materials:
Metformin hydrochloride USP (Wanbury Ltd., India), Guaifenesin USP (Synthokem Labs Pvt. Ltd., India), carbomer homopolymer type A (Carbopol® 971P NF polymer, Lubrizol Advanced Material Inc., USA), sodium carboxymethylcellulose USP (Sodium CMC high viscosity, Cekol® 100000 cellulose gum, CP Kelco Inc., USA and sodium CMC medium viscosity, Blanose® 7MF, Ashland Inc., USA), citric acid monohydrate (citric acid) and sodium citrate (Merck Ltd., India), corn starch USP NF (Maize starch extra white, Roquette Inc., USA), methacrylic acid copolymer type C USP NF (Eudragit® L30D and Eudragit® L100 55, Evonik Industries, Germany), colloidal silicon dioxide USP NF (Aerosil® 200 fumed silica, Evonik Industries, Germany), magnesium stearate USP (Ferro Inc., USA), hypromellose type 2208 of low viscosity K100 LVCR (hypromellose K100 LVCR, Benecel® K100 LVCR, Ashland Inc., USA), hypromellose K4M (Metolose® 90SH-4000SR USP, Shin-Etsu Chemical Co. Ltd., Japan), hypromellose E6 (Pharmacoat® 606 USP, Shin-Etsu Chemical Co. Ltd., Japan), sodium alginate low viscosity (Protanal® CR 8133, FMC Biopolymer, USA) and sodium alginate high viscosity (Keltone® HVCR, FMC Biopolymer, USA).

Methods:
Two highly soluble, high dose drugs with pH independent solubility were selected as model drugs for the study: metformin hydrochloride (freely soluble in water; dose 500 mg/tablet) and guaifenesin (soluble in water; dose 600 mg/tablet).

Extended release matrix tablets of metformin hydrochloride and guaifenesin were manufactured containing 10% and 20% Carbopol 971P NF polymer by aqueous granulation process. Additional formulations containing combinations of Carbopol polymers with other co-ingredients were evaluated in order to improve f2 factor. The co-ingredients were selected based on their chemistry, suitability for oral administration (presence in the US FDA Inactive Ingredients Database) and potential to act synergistically with Carbopol polymers – **Table 1**. The following classes of ingredients were selected:

I. Cellulosic polymers like hypromellose and carboxymethylcellulose sodium.
II. Non-cellulosic polymers such as Eudragit® L100 55, Eudragit® RSPO and sodium alginate.
III. Buffers for modulation of micro-environmental pH like sodium citrate and citric acid.
IV. Diluents such as maize starch and dicalcium phosphate

In the case of guaifenesin, a different formulation approach was also tested: coating of the matrix tablets with an enteric film of Eudragit and hypromellose as a pore former. The release profiles were tested in three dissolution media 0.1N hydrochloric acid, pH 4.5 acetate buffer USP and pH 6.8 phosphate buffer USP) and the f2 similarity factors (similarity between dissolution profiles in different media) calculated.

Table 1: Composition of Metformin hydrochloride 500 mg or Guaifenesin 600 mg ER tablets with 20% Carbopol polymer

Ingredient (% w/w)	Metformin Hydrochloride			Guaifenesin		
Metformin hydrochloride	69	74	59	-	-	-
Guaifenesin	-	-	-	69	74	59
Carbomer homopolymer Type A (Carbopol 971P NF polymer)	20	20	20	20	20	20
Coexcipient	10[a]	5[b]	20[c]	10[a]	5[b]	20[c]
Colloidal silicon dioxide	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5
Total	**100.00**	**100.00**	**100.00**	**100.00**	**100.00**	**100.00**
Tablet weight (mg)	*724.64*	*675.68*	*874.46*	*869.57*	*810.81*	*1016.95*

a – Hypromellose K100 LVCR, Hypromellose K4M, sodium CMC low viscosity, sodium CMC medium viscosity, sodium alginate low viscosity, sodium alginate high viscosity, Eudragit L100 55, Eudragit RSPO

b - Citric acid, sodium citrate

c – Maize starch, dicalcium phosphate dihydrate

Results

Metformin hydrochloride and guaifenesin ER tablets had acceptable physical properties (mechanical strength 20 – 25 kP, friability less than 1%) The extended release matrix tablets of metformin hydrochloride and guaifenesin manufactured with 10% and 20% Carbopol 971P NF showed faster release in 0.1N HCl than the other two media.

Metformin hydrochloride 500 mg ER tablets with Carbopol 971P NF polymer:
Multimedia dissolution compliance was achieved for Metformin hydrochloride extended release tablets formulated with combinations of:

- Carbopol polymer and Hypromellose K100 LVCR (ratio 2:1) - **Fig. 1**
- Carbopol polymer and Hypromellose K4M (ratio 2:1) - **Fig. 2**
- Carbopol polymer and Sodium CMC high viscosity (ratio 4:1) - **Fig. 3**
- Carbopol polymer and Sodium alginate low viscosity (ratio 2:1) - **Fig. 4**
- Carbopol polymer and Maize starch (ratio 1:1) - **Fig.5**
- Carbopol polymer and Sodium citrate (ratio 4:1) - **Fig. 6**

The faster release in 0.1N HCl from tablets containing Carbopol polymers has been controlled by the synergistic combinations with co-ingredients that favor the hydration process.

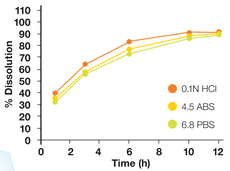

Fig. 1. Metaformin tablets with 20% Carbopol polymer and 10% hypromellose K100 LVCR.

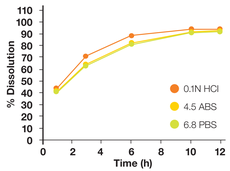

Fig. 2. Metaformin tablets with 20% Carbopol polymer and 10% hypromellose K4M.

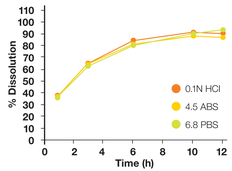

Fig. 3. Metaformin tablets with 20% Carbopol polymer and 5% Sodium CMC high viscosity.

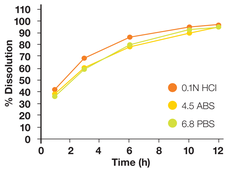

Fig. 4. Metaformin tablets with 20% Carbopol polymer and 10% sodium alginate low viscosity.

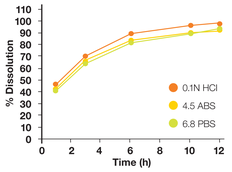

Fig. 5. Metaformin tablets with 20% Carbopol polymer and 20% maize starch.

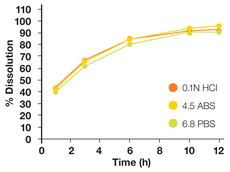

Fig. 6. Metaformin tablets with 20% Carbopol polymer and 5% sodium citrate

Guaifenesin 600 mg ER tablets with Carbopol 971P NF polymer:
Guaifenesin release from tablets formulated with 20% Carbopol and coexcipients is shown in **Fig. 7 – 9.** The following combinations provided multimedia compliant dissolution with calculated f2 factor above 50:

- Carbopol polymer and hypromellose K100 LVCR (ratio 2:1) – **Fig. 7**
- Carbopol polymer and hypromellose K4M (ratio 2:1) – **Fig. 8**
- Carbopol polymer and Sodium alginate low viscosity (ratio 2:1) – **Fig. 9**

Similar to metformin hydrochloride, the synergistic combination of Carbopol polymers with hydrophilic matrix forming excipients (hypromellose K4M, hypromellose K100 LVCR and sodium alginate low viscosity) at ratio 2:1 resulted in matrix tablets efficiently controlling the drug release in the three media.

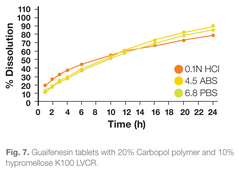

Fig. 7. Guaifenesin tablets with 20% Carbopol polymer and 10% hypromellose K100 LVCR.

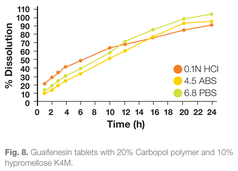

Fig. 8. Guaifenesin tablets with 20% Carbopol polymer and 10% hypromellose K4M.

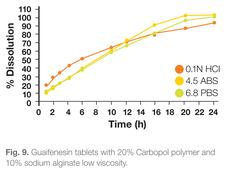

Fig. 9. Guaifenesin tablets with 20% Carbopol polymer and 10% sodium alginate low viscosity.

Guaifenesin release from tablets formulated with 10% Carbopol polymer and 10% hypromellose K4M have shown f2 factor >50 in the three media. An alternative strategy of a porous enteric coating over matrix tablets was also successful in providing multimedia compliant release - **Fig. 10**. The tablet cores containing 10% Carbopol polymer were coated with a porous enteric layer consisting of Eudragit L30D and hypromellose E6 (1:1) at 3% weight gain.

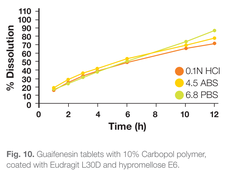

Fig. 10. Guaifenesin tablets with 10% Carbopol polymer, coated with Eudragit L30D and hypromellose E6.

Conclusion

The study demonstrated development of multimedia compliant extended release matrix tablets of metformin HCl or guaifenesin by using synergistic combinations of Carbopol 971P NF polymer and co-ingredients. The findings from this study may be extended to other drugs on a case to case basis.