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TECHNICAL DATA SHEET

TDS-LS-17, Edition: Date November 14, 2014

Formulation of multimedia compliant extended release matrix tablets containing Carbopol® polymer

Introduction:

Carbopol polymers are synthetic high molecular weight polymers of acrylic acid cross-linked with either allylsucrose or allylethers of pentaerythritol. The polymers are efficient matrix-forming excipient that offer effective controlled-release properties at significantly low concentrations. Carbopol polymers can be used either alone, as combination of powder and granular grades or in combination with other extended-release excipients for synergistic interactions. Carbopol polymers have been used in several marketed extended release formulations of drugs belonging to all biopharmaceutics classification system (BCS) classes of drugs. Due to the anionic nature of the polymer, drug release from Carbopol polymer matrices may be media reliant. Carbopol polymers have a pKa of 6, so at pH 1.2 they are virtually un-ionized; they will start to ionize at pH 4.5. At lower pH values gel formation occurs even if the polymer is not fully swollen and there are larger regions of microviscosity (lower viscosity). As the pH increases the ionization of the carboxylic acid groups causes maximum swelling resulting in fewer and smaller regions of microviscosity (higher viscosity).

The objective of this study is to understand the multimedia release profiles of extended release matrix tablets containing Carbopol polymers and to develop multimedia compliant formulations of selected model drugs. Two highly soluble, high dose drugs with pH independent solubility have been selected as model drugs for this study. The model drugs are metformin hydrochloride (freely soluble in water; dose 500 mg/tablet) and guaifenesin (soluble in water; dose 600 mg/tablet). 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) are calculated.

Materials:

Metformin hydrochloride USP (Wanbury Ltd, India); Guaifenesin USP (Synthokem Labs Pvt. Ltd. India); Carbomer Homopolymer Type A (**Carbopol**/Carbopol® 971P NF polymer, Lubrizol Corporation, 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); Dibasic calcium phosphate USP (**DCP**, Innophos 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® L100 55**, Evonik Industries, Germany), ammonio methacrylate copolymer, Type B USP NF (**Eudragit® RSPO**, 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).

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Study Design and Evaluation:

Extended release (ER) matrix tablets of metformin hydrochloride (500 mg) and guaifenesin (600 mg) were prepared containing 10% and 20% Carbopol using the aqueous granulation process. The f2 factor for these release profiles were less than 50. The release profile in 0.1N HCl media were higher than in the other two media.

In order to improve the f2 factor, combinations of Carbopol polymers with other co-ingredients were evaluated. The other 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. The following classes of ingredients were selected:

I. **Cellulosic polymers** like hypromellose and carboxymethylcellulose sodium. Several articles have described the use of combinations of Carbopol and cellulosic polymers for ER tablet formulations. [1,2,3]
II. **Non cellulosic polymers** such as Eudragit® L100 55, Eudragit® RSPO and sodium alginate [4,5,6]
III. **Buffers** for modulation of micro-environmental pH like sodium citrate and citric acid [7]
IV. **Diluents** such as maize starch and dicalcium phosphate

The drug release profiles from prepared tablets were tested in three dissolution media (0.1N HCl, pH 4.5 acetate buffer USP and pH 6.8 phosphate buffer USP) and the f2 factors calculated.

The composition of metformin hydrochloride ER matrix tablets with 20% Carbopol is shown in Table 1.

Table 1: Metformin hydrochloride 500 mg ER tablet with 20% Carbopol

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

The composition of guaifenesin ER matrix tablets with 10% and 20% Carbopol is shown in Tables 2 and 3.

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Table 2: Guaifenesin 600 mg ER tablet formulations with 10% Carbopol

Ingredients	Quantity % w/w		
Guaifenesin	84	86.5	79
Carbomer homopolymer Type A USP NF (Carbopol 971P NF polymer)	10	10	10
Coexcipient	5 [a]	2.5 [b]	10 [c]
Colloidal silicon dioxide	0.5	0.5	0.5
Magnesium stearate	0.5	0.5	0.5
Tablet Weight (mg)	**714.29**	**693.64**	**759.49**

Table 3: Guaifenesin 600 mg ER tablet formulations with 20% Carbopol

Ingredients	Quantity % w/w		
Guaifenesin	69	74	59
Carbomer homopolymer Type A USP NF (Carbopol 971P NF polymer)	20	20	20
Coexcipient	10 [a]	5 [b]	20 [c]
Colloidal silicon dioxide	0.5	0.5	0.5
Magnesium stearate	0.5	0.5	0.5
Tablet Weight (mg)	**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

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Results:

Metformin hydrochloride and guaifenesin ER tablets had acceptable physical properties (mechanical strength 20 – 25 kP, friability less than 1%)

Metformin hydrochloride 500 mg ER tablets with 20% Carbopol 971P NF polymer

Metformin hydrochloride release profiles from tablets formulated with Carbopol polymers are shown in Fig. 1-7. Combinations of Carbopol polymers with the following coexcipients resulted in release of metformin with calculated f2 factor above 50

- Hypromellose K100 LVCR (Figure 1)
- Hypromellose K4M (Figure 2)
- Sodium CMC medium viscosity (Figure 3)
- Sodium CMC high viscosity (Figure 4)
- Sodium alginate low viscosity (Figure 5)
- Maize starch (Figure 6)
- Sodium citrate (Figure 7)

The faster release in 0.1N HCl for tablets containing Carbopol polymers has been controlled by the synergistic combinations with the above co-ingredients that favor the hydration process. Thus synergistic combination of Carbopol polymer with hydrophilic matrix forming excipients of low and medium viscosity at ratio of 2:1, sodium CMC high viscosity and sodium citrate at ratio of 4:1 and maize starch at ratio of 1:1 resulted in matrix tablets that were able to efficiently control the drug release in the three media. While comparing the dissolution profiles in 0.1N HCl, hypromellose K100 LVCR and sodium CMC high viscosity showed slower release compared to hypromellose K4M, sodium CMC medium viscosity and sodium alginate low viscosity (Figure 8).

Figure 1: Metformin with 20% Carbopol and 10% hypromellose K100 LVCR

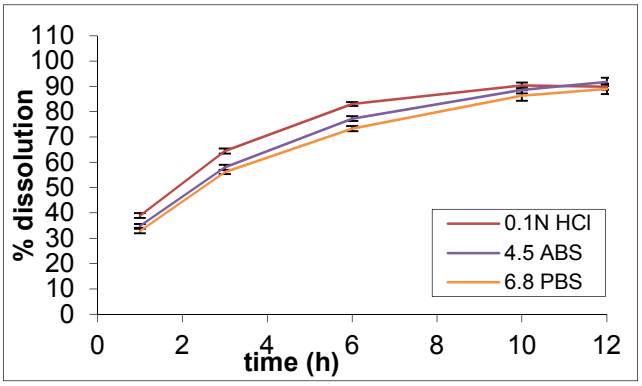

Figure 2: Metformin with 20% Carbopol and 10% hypromellose K4M

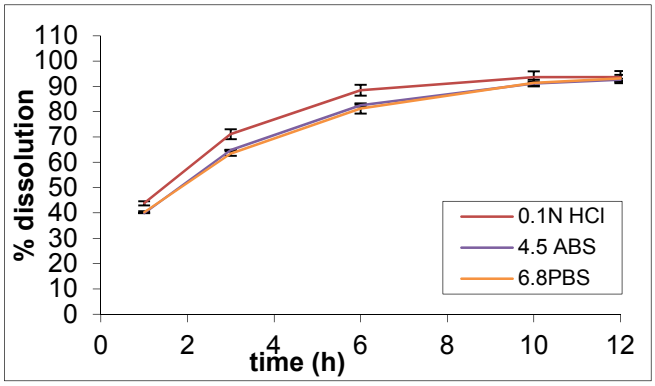

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Figure 3: Metformin with 20% Carbopol and 10% Sodium CMC medium viscosity

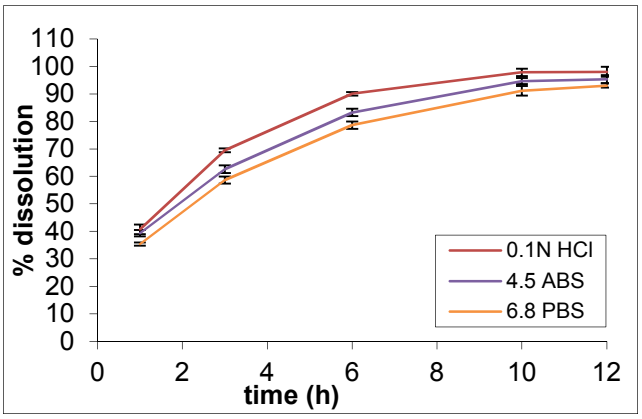

Figure 4: Metformin with 20% Carbopol and 5% Sodium CMC low viscosity

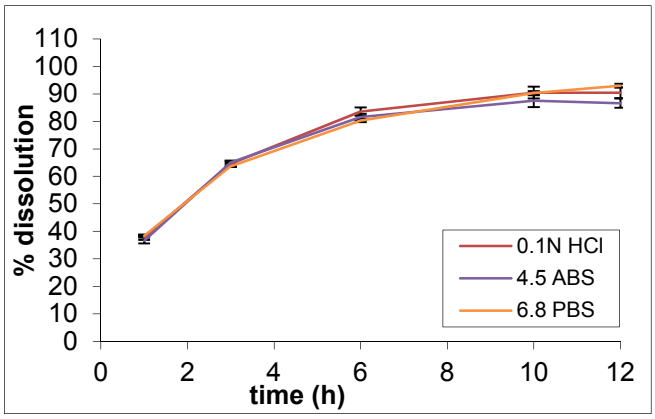

Figure 5: Metformin with 20% Carbopol and 10% sodium alginate low viscosity

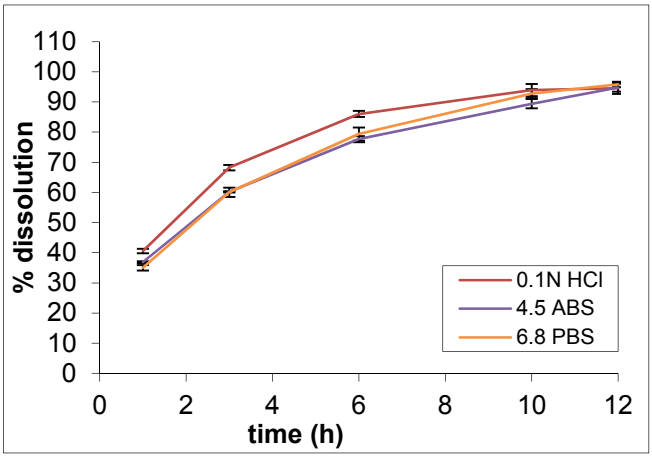

Figure 6: Metformin with 20% Carbopol and 20% maize starch

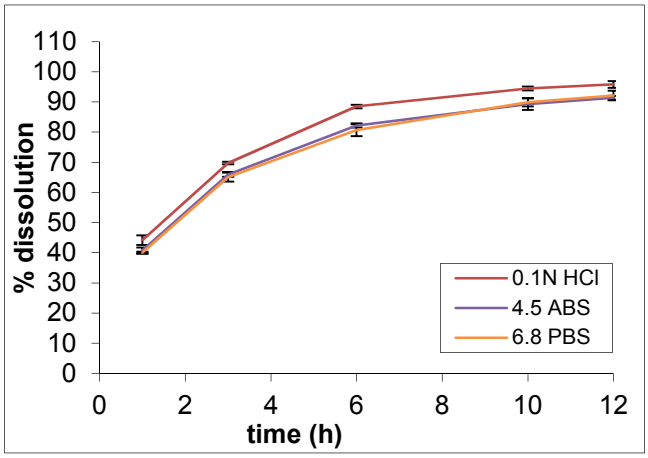

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Figure 7: Metformin with 20% Carbopol and 5% sodium citrate

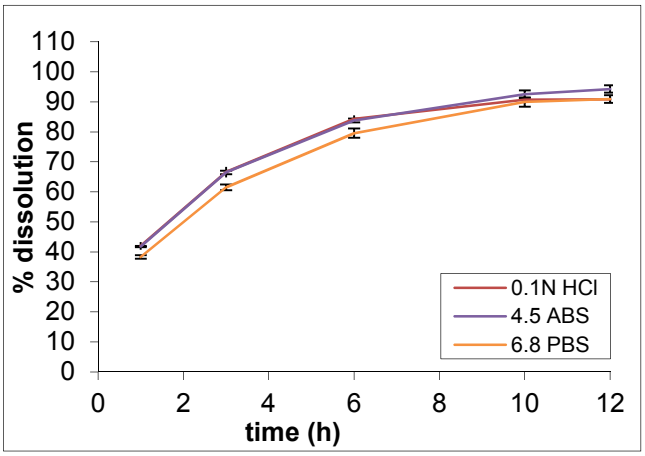
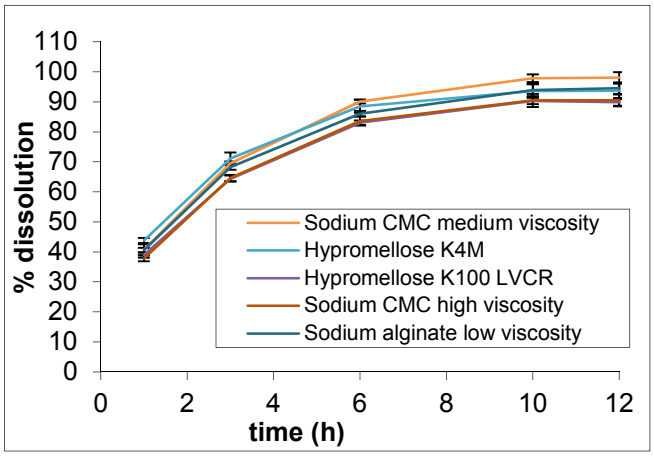


Figure 8: Comparative release of metformin HCl with 20% Carbopol and other polymeric excipients in 0.1N HCl



Guaifenesin 600 mg ER tablets with 10% Carbopol 971P NF polymer

Guaifenesin release from tablets formulated with 10% Carbopol polymer and coexcipients is shown in Fig. 9-10. Guaifenesin release from tablets formulated with 10% Carbopol and 10% Metolose 90SH 4000SR have shown f2 factor >50.

Another approach by formulating porous enteric coated matrix tablets was also successful in providing multimedia compliant release. The tablet cores containing 10% Carbopol were coated with porous enteric layer consisting of Eudragit L30D and hypromellose (1:1) weight gain 3%.

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Figure 9: Guaifenesin with 10% Carbopol and 10% hypromellose K4M

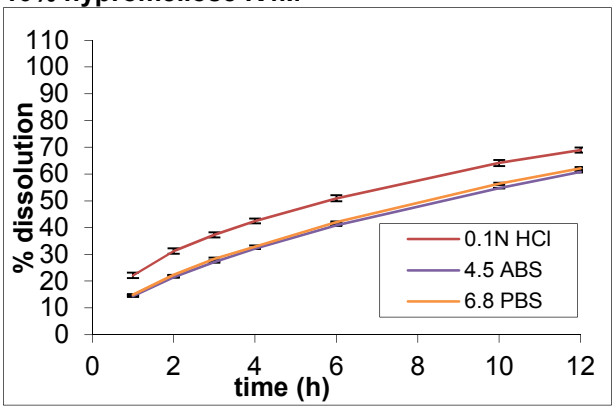
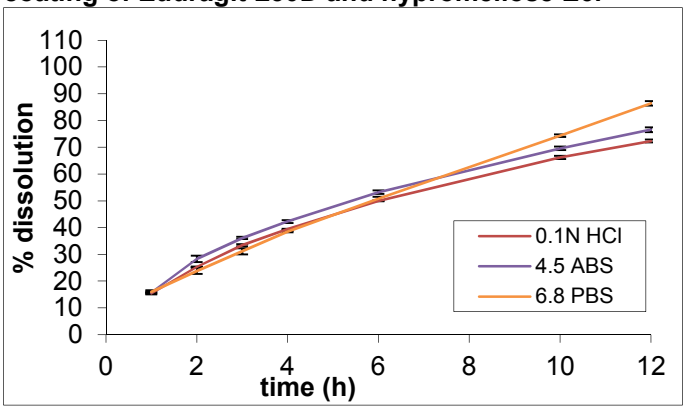


Figure 10: Guaifenesin with 10% Carbopol with coating of Eudragit L30D and hypromellose E6.



Guaifenesin 600 mg ER tablets with 20% Carbopol 971P NF polymer

Guaifenesin release from tablets formulated with 20% Carbopol and coexcipients is shown in Fig. 11-13 Combinations of Carbopol polymers with following coexcipients extended the release of guaifenesin and provided multimedia compliant dissolution with calculated F2 factor above 50

- hypromellose K100 LVCR and hypromellose K4M (Figure 11 and Figure 12)
- Sodium alginate low viscosity (Figure 13)

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. While comparing the dissolution profiles in 0.1N HCl, combination of Carbopol with hypromellose K100 LVCR showed slower release compared to combination with hypromellose K4M and sodium alginate low viscosity (Figure 14).

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Figure 11: Guaifenesin with 20% Carbopol and 10% hypromellose K100 LVCR

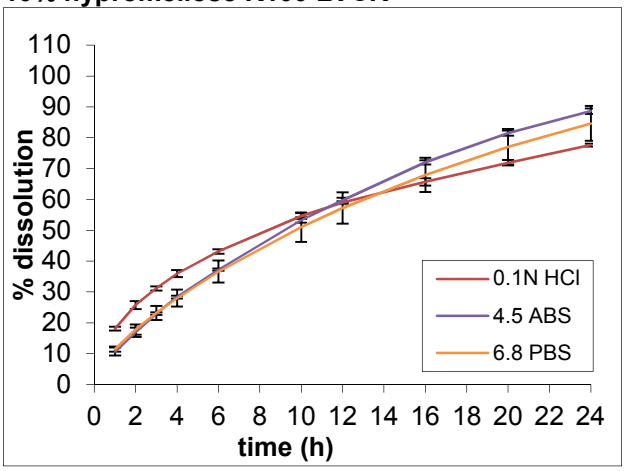


Figure 12: Guaifenesin with 20% Carbopol and 10% hypromellose K4M

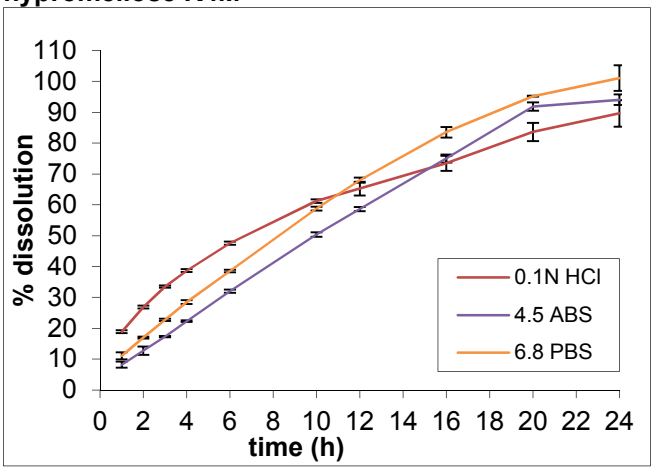


Figure 13: Guaifenesin with 20% Carbopol and 10% sodium alginate low viscosity

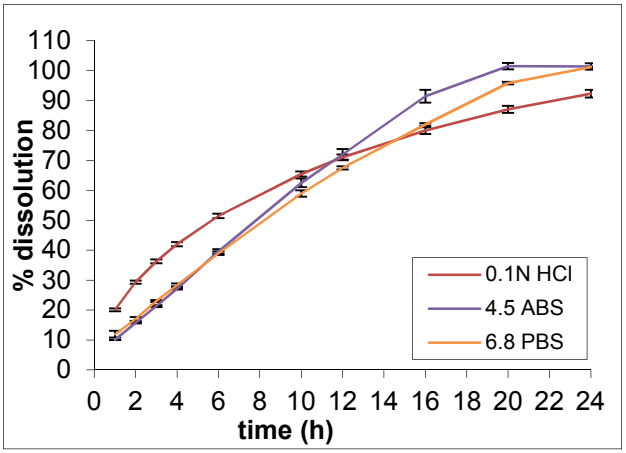
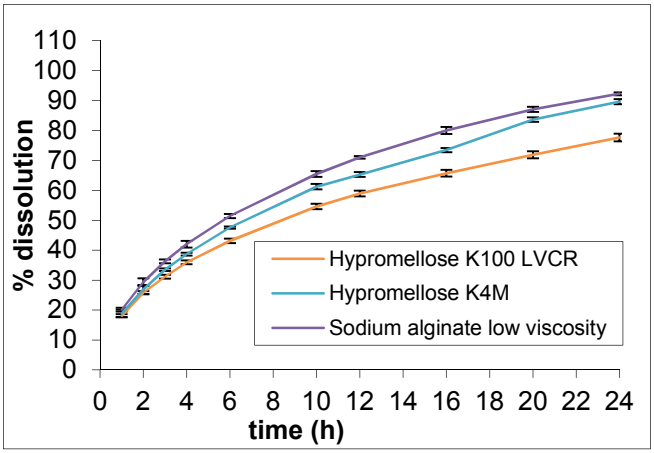


Figure 14: Comparative release of Guaifenesin with 20% Carbopol and other polymeric excipients in 0.1N HCl



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Conclusion:

Both metformin HCl and guaifenesin, Carbopol polymers have shown good synergy with the following low-medium viscosity grades of hydrophilic cellulosic and non-cellulosic polymers allowing for extended release multimedia compliance.

- Hypromellose K100 LVCR
- Hypromellose K4M
- Sodium alginate low viscosity

In case of metformin HCl combinations of Carbopol with sodium citrate at 4:1 and maize starch at 1:1 inclusion levels and in case of guaifenesin the additional strategy of porous enteric coating also has helped to significantly improve the f2 factor. The same coating technique is also likely to work with metformin HCl.
Other beneficial approaches are:

- Use porous enteric coating applied on Carbopol cores and as this has been demonstrated in case of guaifenesin. It may potentially be applied to metformin.
- Use of Carbopol in combination with sodium citrate and maize starch

All these techniques used have contributed slower release in 0.1N HCl release (without affecting pH 6.8 and pH 4.5 buffer release). These techniques not only lowered the 0.1N HCl release but also improved the f2 factor to above 60.
Lubrizol studies have resulted in formulation of multimedia compliant extended release matrix tablets containing Carbopol 971P NF polymer for both metformin HCl (ionic drug) and guaifenesin (non-ionic drug). The drugs selected represent the spectrum of highly water soluble and high dose category and for other categories of drugs; the learnings of this study can be extended on a case to case basis.

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