Guaifenesin Extended Release Tablets Formulated with Carbopol® Polymers

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OBJECTIVE

Develop Guaifenesin tablets using Carbopol® polymers as intra- and/or extra-granular extended release excipients.

INTRODUCTION

Carbopol® polymers are efficient gel matrix formers for extended release dosage forms. The main phenomena governing the drug release from carbomer matrix tablets are water penetration, polymer swelling, drug dissolution and diffusion and matrix erosion. The polymers can be processed by direct compression, wet or dry granulation or mixed processing (intra- and extra-granular addition).

The current study focused on the applications of Carbopol® 971P NF polymer (powder grade) and Carbopol® 71G NF polymer (granular grade) as matrix excipients for extended release Guaifenesin 600 mg tablets.

METHODOLOGY

Materials

Guaifenesin, (Tianjin Xin Xin Pharmaceutical Corporation, China), Carbopol® 971P NF polymer (Lubrizol Advanced Materials, Inc., Cleveland, OH) - 971P NF, Carbopol® 71G NF polymer (Lubrizol Advanced Materials, Inc., Cleveland, OH) – 71G NF, Avicel® PH 102 (FMC Biopolymer, Philadelphia, PA) - MCC PH 102, Lactose 200 mesh (Lactose New Zealand), Cab-O-Sil® M5 Fumed Silica (Cabot Corp, Billerica, MA), Synpro® Magnesium Stearate NF (Ferro Corporation, Walton Hills, OH)

Methods

Guaifenesin 600 mg extended release tablets were manufactured by wet granulation.

The formulations were determined according to a central composite inscribed design, using Carbopol® 971P NF polymer and Carbopol® 71G NF polymer as independent variables: 971P NF (0 – 10% of the tablet weight) and 71G NF level (0 – 15% of the tablet weight) – Table 1.

For each formulation, the intra-granular (IG) components were granulated with deionized water and the resulting granules blended with the extra-granular (EG) excipients. The formulations were compressed on an automated Korsch PH100/DMS Rotary Press, using 0.32x0.67-inch capsule shape punches to tablet target weight (824.74 mg) and hardness (10 kP). The resulting tablets were evaluated for physical properties (weight, thickness, hardness, friability) and drug release in 0.1N HCl and pH=6.8 USP phosphate buffer.

Cumulative percentage of drug released in 0.1N HCl at various time intervals (1, 2, 4, 6, 8, 10 and 12 hours) were selected as response variables to generate regression models for characterization of the drug release profile (JMP® 7.0, SAS Institute, Inc). Results at 1, 4, 8 and 12 h are presented here. These time points were selected to ensure full description of the release profile: the initial phase of drug release to detect any dose dumping, intermediate phase, and terminal phase to determine that most of the drug was released from the tablets.

Two checkpoints were selected to validate the developed models. The corresponding formulations were prepared and evaluated for responses. Subsequently, the experimental data were compared to predicted values.

Table 1.
Composition (%w/w) of Guaifenesin 600 mg ER tablets – central composite design (G1 – G10) and checkpoint (GPA1 and GPA2) formulations

Formulation	G1	G2	G3	G4	G5	G6	G7	G8	G9	G10	GPA1	GPA2
intragranular Guaifenesin	72.75	72.75	72.75	72.75	72.75	72.75	72.75	72.75	72.75	72.75	72.75	72.75
971P NF	1.50	5.00	8.50	1.50	0.00	10.00	5.00	5.00	8.50	5.00	8.75	7.00
MCC PH102	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
Lactose	7.00	8.75	10.50	17.50	13.75	3.75	1.25	16.25	0.00	8.75	9.25	0.25
extragranular	12.75	7.50	2.25	2.25	7.50	7.50	15.00	0.00	12.75	7.50	3.25	14.00
71G NF	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Fumed silica	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
Mg. stearate	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
Total												
Design/levels	–+	00	+–	––	a0	A0	0A	0a	++	00		

G10 – replicate of G2

RESULTS

Tablet properties and drug release

All formulations, except for G5, showed good tablet properties – Table 2. Formulation G5, without 971P NF, resulted in tablets with low hardness (<5 kP) and high friability (tablets broke during testing).

- Cumulative guaifenesin release profiles in pH=6.8 buffer and 0.1N HCl are shown in Fig. 1 and 2.
- Medium or high concentrations of powder grade polymer were able to extend the release for over 12 h in acid or buffer, even in the absence of the granular form of polymer.
- Formulations having low amount of total polymers or no/low amount of 971P NF and medium amount of granular grade (71G NF) led to fast release in both dissolution media: G4 and G5. The fast release in the case of formulation G5 - 0% 971P NF (IG) & 7.5% 71G NF (EG) correlated well with tablet properties: low hardness and high friability (these properties determined a fast disintegration and thus rapid dissolution).
- In the case of the formulations which successfully extended the drug release, no major impact of the dissolution media was observed.

Table 2. Properties of Guaifenesin 600 mg ER tablets – central composite design (G1 – G10) and checkpoint (GPA1 and GPA2) formulations

	G1	G2	G3	G4	G5	G6	G7	G8	G9	G10	GPA1	GPA2
971P NF (%) - IG	1.50	5.00	8.50	1.50	0.00	10.00	5.00	5.00	8.50	5.00	8.75	7.00
71G NF (%) - EG	12.75	7.50	2.25	2.25	7.50	7.50	15.00	0.00	12.75	7.50	3.25	14.00
Weight (mg)	825.89	824.48	824.24	822.97	819.43	827.02	826.31	827.40	824.98	827.97	826.17	826.43
SD	5.12	13.55	8.52	8.07	8.27	7.41	10.12	7.38	5.60	11.66	6.38	5.87
Thickness (mm)	7.88	7.85	7.81	7.51	6.89	8.01	8.13	7.90	8.10	7.94	7.95	8.16
SD	0.03	0.03	0.01	0.01	0.07	0.03	0.03	0.04	0.04	0.04	0.02	0.02
Hardness (kP)	11.35	11.05	12.30	12.07	4.91	12.55	12.07	11.02	12.35	12.12	11.82	11.80
SD	0.63	1.25	1.23	1.00	1.46	1.49	1.45	1.09	1.78	1.38	0.50	0.67
Friability (@100rot)	0.21	0.16	0.22	0.23	failed	0.22	0.16	0.23	0.18	0.16	0.13	0.04

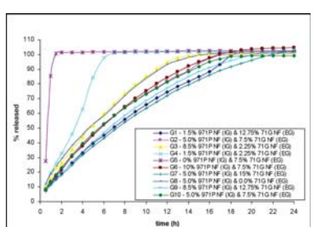

Fig. 1. Cumulative Guaifenesin release (%) in pH=6.8 buffer from central composite design formulations

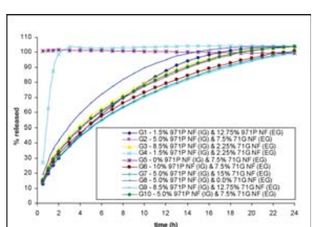

Fig. 2. Cumulative Guaifenesin release (%) in 0.1N HCl from central composite design formulations

Table 3. Model parameters affecting Guaifenesin release

Parameter/ Response	Intercept		971P NF		71G NF		(971P NF) * (71G NF)		(971P NF)2		Model fit		
	Estimate	Prob>|t|	Estimate	Prob>|t|	Estimate	Prob>|t|	Estimate	Prob>|t|	Estimate	Prob>|t|	P value	RSq	RMSE
1 h	112.285	0.0029	-23.216	0.0126	-4.004	0.1375	0.522	0.2553	1.395	0.0401	0.0384	0.83	14.944
4 h	137.026	0.0001	-18.860	0.0021	-5.397	0.0065	0.676	0.0261	0.915	0.0193	0.0039	0.93	7.949
8 h	123.485	<.0001	-10.442	0.0007	-3.283	0.0015	0.333	0.0163	0.483	0.0090	0.0005	0.97	3.442
12 h	113.245	<.0001	-4.730	0.0002	-1.646	0.0002	0.087	0.0360	0.198	0.0036	<.0001	0.99	1.128

STATISTICAL MODELS

- Regression models including the two polymers, their interaction and the 971P NF quadratic trend were generated to describe the release; statistical analysis using Analysis of Variance (ANOVA) revealed significant model fit with p-value < 0.05 – Table 3.
- ANOVA indicated that change in 971P NF level was the most significant factor affecting drug release, while 71G NF also significantly contributed to the release at later stages.
- Interaction effects between the variables studied were also found to be statistically significant: at low 971P NF level, 71G NF has a strong negative effect on the release (slower release), while at high 971P NF level, its contribution was marginal. Similarly, stronger effect of 971P NF was observed at low 71G NF levels (Fig. 3).
- Negative coefficient estimates indicated the percent of Guaifenesin released decreased as the 971P NF or 71G NF level in the tablet increased.
- Larger contribution of 971P NF to the response is in good agreement with Lubrizol's findings that carbomer in the powder form is **more efficient** in controlling the release than the granular form, due to the larger surface area.
- Three-dimension contour diagrams visualizing the simultaneous effect of the two polymers on the response at each time point were established – Fig. 4.

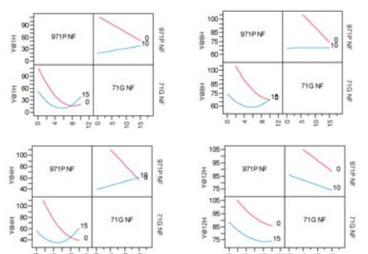

Fig. 3. Interaction profiles for Guaifenesin release (Y= % released)

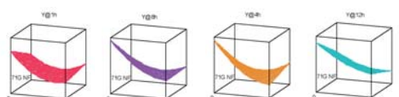

Fig. 4. Three-dimension contour diagrams for Guaifenesin release

MODEL VALIDATION

The model demonstrated acceptable predictability for checkpoint formulations GPA1 and GPA2 - Table 4, Fig. 5. The actual and predicted release profiles were compared using the FDA recommended similarity factor. The values F2 actual vs. predicted were above 50 at all the time points throughout the release process, which indicated equivalence of the release profile.

Table 4.
Guaifenesin release from GPA – predicted and actual responses

Time (h)	GPA1 - predicted	GPA1 - actual	F2 actual vs. predicted – GPA1	GPA2 - predicted	GPA2 - actual	F2 actual vs. predicted – GPA2
1	17.81	24.05	59.97	13.27	20.31	57.40
4	43.76	50.37	59.34	40.55	44.16	62.27
8	67.94	70.20	62.98	60.77	62.64	65.94
12	84.13	83.94	65.98	75.33	75.74	68.88

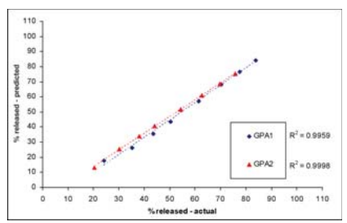

Fig. 5. Linear correlation plot between actual and predicted release values for GPA1 and GPA2

CONCLUSIONS

- Guaifenesin tablets were successfully formulated to release the drug over 12-24 h in both acidic and buffer media, by using Carbopol® polymers as intra- and/or extra-granular matrix forming excipients.
- The approach offered flexibility in achieving target release profiles by varying the total polymer level and the ratio of the intra- vs. extra-granular Carbopol® polymers.
- Drug release at various points was characterized by a mathematical model, which included 971P NF, 71G NF, their interaction and the 971P NF quadratic trend.
- The model predictability was demonstrated for checkpoint formulations.