Lubrizol LifeSciences

Development of Compendial and Multimedia Compliant Metoprolol Succinate Extended Release Tablets Using Carbopol® Polymers

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Objective

To develop multimedia compliant metoprolol succinate extended release tablets 25mg and 50mg to meet USP dissolution specifications, using Carbopol® polymers in a matrix technology that allows easy processing.

Methodology

Materials:
Metoprolol succinate USP (Polydrug Laboratories Pvt. Ltd., India), carbomer homopolymer type A (Carbopol® 971P NF and 71G NF polymers, Lubrizol Advanced Material Inc., USA), microcrystalline cellulose (Avicel® PH 101), methacrylic acid copolymer type C USP NF (Eudragit® L30D 55, Evonik Industries, Germany), colloidal silicon dioxide USP NF (Aerosil® 200 fumed silica, Evonik Industries, Germany), magnesium stearate USP (Ferro Inc., USA), hypromellose USP (Metolose® 90SH-4000SR, Shin-Etsu Chemical Co. Ltd., Japan), lactose monohydrate (Kerry Bio-Science, USA), triethyl citrate (Alfa Aesar, England), talc (Luzenac Pharma, Italy).

Methods:
Metoprolol succinate extended release tablets 25 and 50 mg were formulated using Carbopol polymers and hypromellose as matrix forming agents – **Tables 1 and 2**. The tablets were manufactured by aqueous high shear granulation.

Metoprolol succinate, Carbopol 971P NF polymer, lactose and microcrystalline cellulose were granulated. The dried granules were blended with Carbopol 71G NF and 971P NF polymers, hypromellose K4M, glidant and lubricant. The blend was evaluated for density, particle size distribution and flow characteristics. The lubricated blend was compressed into tablets on a rotary tablet press, using plain round standard concave punches (7.5 mm for 25 mg and 10.5 mm for 50 mg). The tablets were evaluated for physical parameters and dissolution as per USP 38/NF 33 test 1 monograph for metoprolol succinate extended release tablets in pH 6.8 phosphate buffer solution, type 2 apparatus at 50 rpm.

For multimedia compliant release, the tablet cores were coated with enteric coating dispersion of Eudragit® L30D 55 and lactose as pore former. The coated tablets were evaluated for physical parameters and multimedia dissolution properties (in 0.1N hydrochloric acid, pH 4.5 acetate buffer USP and pH 6.8 phosphate buffer USP). Reproducibility studies were carried out to ascertain the robustness of the formulation.

Table 1: Metoprolol Succinate Extended Release Tablets 25mg

Ingredients	%w/w
Intragranular	
Metoprolol succinate	15.08
Carbopol 971P NF polymer	4.76
Lactose monohydrate	14.76
Microcrystalline cellulose (Avicel PH 101)	28.57
Water	*q.s.*
Extragranular	
Hypromellose K4M (Metolose 90SH 4000SR)	4.44
Carbopol 71G NF polymer	19.04
Carbopol 971P NF polymer	6.67
Colloidal anhydrous silica	0.95
Magnesium stearate	0.95
Coating Dispersion	
Methacrylic acid copolymer dispersion (Eudragit L30D 55)*	3.07
Lactose monohydrate	0.86
Triethyl citrate	0.32
Talc	0.53
Water	*q.s.*
Total	**100.00**
Tablet weight (mg)	***157.5***

* Weight of dry polymer in Eudragit L30D dispersion (Amount of polymer dispersion = 10.22)

Table 2: Metoprolol Succinate Extended Release Tablets 50mg

Ingredients	%w/w
Intragranular	
Metoprolol succinate	15.22
Carbopol 971P NF polymer	4.81
Lactose monohydrate	14.90
Microcrystalline cellulose (Avicel PH 101)	28.84
Water	*q.s.*
Extragranular	
Hypromellose K4M (Metolose 90SH 4000SR)	12.82
Carbopol 71G NF polymer	9.61
Carbopol 971P NF polymer	4.81
Microcrystalline cellulose (Avicel PH 101)	3.20
Colloidal anhydrous silica	0.96
Magnesium stearate	0.96
Coating Dispersion	
Methacrylic acid copolymer dispersion (Eudragit L30D 55)*	2.54
Lactose monohydrate	0.64
Triethyl citrate	0.26
Talc	0.43
Water	*q.s.*
Total	**100.00**
Tablet weight (mg)	***312.00***

* Weight of dry polymer in Eudragit L30D dispersion (Amount of polymer dispersion = 10.22)

Results

Metoprolol succinate extended release tablet cores were successfully developed by matrix technology in an aqueous granulation process to meet compendial requirements. Quantitative formula for aqueous granulation part of both the strengths (25 mg and 50 mg) was kept linear with 5% intragranular Carbopol 971P NF along with other excipients. The tablet core weight was 150 mg and 300 mg for the doses of 25 mg and 50 mg respectively of metoprolol succinate. The developed formulations showed consistent and acceptable physical parameters - **Table 3**.

The cumulative drug release profiles in pH 6.8 phosphate buffer solution of core tablets complied with USP specifications and showed low intra-batch variability. The robustness of the formulation was proven with three reproducibility batches of each strength - **Fig 1 and 2**.

Coating of the tablet cores with the dispersion of Eudragit L30D 55 and lactose was conducted to achieve a 5% weight gain for the 25 mg dose and 4% for the 50 mg dose. Multimedia dissolution profiles of the developed formulations were within the pharmacopoeial limits - **Fig. 3**.

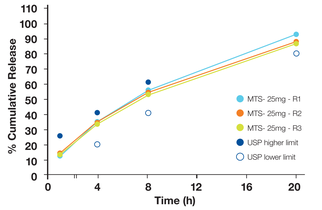

Figure 1. Metoprolol succinate ER core tablets 25mg reproducibility batches - dissolution in pH 6.8 phosphate buffer (n=6 ± SD)

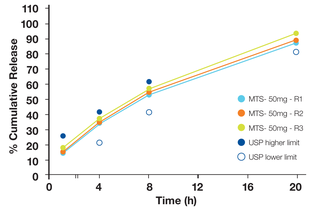

Figure 2. Metoprolol succinate ER core tablets 50mg reproducibility batches - dissolution in pH 6.8 phosphate buffer (n=6 ± SD)

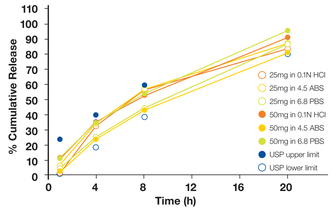

Figure 3. Metoprolol succinate extended release film coated tablets - multimedia drug release (n=6 ± SD)

Table 3: Physical properties of metoprolol succinate ER tablets 25 and 50 mg

	Metoprolol succinate ER tablets 25 mg	Metoprolol succinate ER tablets 50mg
Description	White circular biconvex film coated tablets plain on both sides	White circular biconvex film coated tablets plain on both sides
Average weight (mg)	157.50	312.00
SD	0.675	0.738
Diameter (mm)	7.50	10.50
SD	1.027	0.974
Thickness (mm)	3.50	3.90
SD	1.322	0.308
Breaking strength (kP)	17.82	16.42
SD	1.651	1.525

SD: standard deviation

Conclusion

Metoprolol succinate extended release tablets USP 25 mg and 50 mg containing Carbopol polymers have been developed by matrix technology. Coating of the tablet cores with an aqueous dispersion of enteric polymer and film former resulted in multimedia compliant release profile. Aqueous process was used for granulation and coating of the formulation. The technology used allowed for simpler manufacture process compared to coated beads technology. The reproducibility of the formulations was demonstrated in terms of physical properties and drug release.

Value proposition of the formulations:
- Easy aqueous processing (granulation and coating)
- Potential manufacturing cost saving compared to multi-unit particulate system compression technology
- Multimedia dissolution compliance