

# The Influence of Polymer Concentration, Particle Size, Compression Force and Film Coating on Drug Release

## from Polyethylene Oxide Extended Release Matrices

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### Purpose

To investigate the influence of polymer concentration, particle size, compression force and film coating on the release of metformin hydrochloride, a highly water soluble drug, from an extended release (ER) directly compressible matrix formulation, containing polyethylene oxide (PEO) as the rate controlling polymer.

### Methods

Formulations containing 50% w/w of metformin HCl (AMRI, India), an oral antidiabetic drug with aqueous solubility of 300 mg/mL; 5%-49% w/w PEO (POLYOX™, water soluble resins, WSR-1105, Dow Chemical Co., USA), 0%-44% w/w of microcrystalline cellulose (Microcel 102, Blanver, Brazil), 0.5% w/w of fumed silica (Aerosil 200, Evonik, Germany) and 0.5% w/w magnesium stearate (Peter Greven, UK) were prepared.

An ER formulation of metformin HCl containing 30% w/w POLYOX was selected to study the effect of polymer particle size, compression force and film coating. To demonstrate the effect of particle size of PEO on the rate of drug release, various sieve cuts were used in the matrix formulation. Tablets were manufactured by direct compression with a target weight of 1000 mg using a 10-station rotary press (Piccola, Riva, Argentina), fitted with 7x18 mm caplet tooling; and operated at 20 rpm and 20 kN. To investigate the effect of compression force on drug release, additional tableting trials were conducted at 5 kN and 10 kN. Tablet coating was conducted in a side-vented 15" machine (Labcoat II, O'Hara, Canada) using Opadry® II, high performance film coating system, (85-Series, Colorcon) to a 4% theoretical weight gain. 20% w/w aqueous dispersion of the Opadry II was prepared and continuously stirred throughout the process using a propeller mixer (IKA Labortechnik, Germany). Coating process parameters are listed in **Table 1**.

### Methods

Table 1. Coating Process Parameters

Parameter	Values
Batch size (kg)	1
Pan speed (rpm)	20
Inlet air temperature (°C)	65-69
Exhaust air temperature (°C)	48-53
Product temperature (°C)	42-45
Fluidizing airflow (m <sup>3</sup> /hour)	250
Atomization/fan air pressure (bar)	1.5
Spray rate (g/min)	10-21
Process duration (min)	17

Drug release was measured in an AT7 dissolution bath (Sotax, UK) using 8-mesh (2.38 mm) quadrangular baskets (QLA, US) positioned within the dissolution vessel perpendicular to the shaft of the paddle, 3 cm above the paddle operated at 100 rpm.<sup>1</sup> The dissolution medium was purified water at 37.0 ± 0.5°C. Samples were analyzed using 0.1 mm quartz cells. A dual beam spectrophotometer (Perkin Elmer, USA) was used for the drug detection at a wavelength of 233 nm. Measurements at each time point were performed in triplicate, and mean and standard deviation (SD) values were calculated. The dissolution profiles were compared using the *f*<sub>2</sub> factor.<sup>2,3</sup> An *f*<sub>2</sub> value between 50 and 100 indicates that the two dissolution profiles are similar.

To investigate the kinetics of drug release from the matrices containing various amounts of PEO, the dissolution results between 5% - 60% were fitted to Eq. (1):

$$Q = k t^n \text{ (Equation 1)}$$

Where Q is the percentage of drug released at time *t*, *k* is the kinetic constant representing structural and geometric characteristic of the tablet and *n* is the release exponent indicative of the drug release mechanism. For matrix tablets, an *n* value of approximately 0.5 indicates diffusion control, and an *n* value of approximately 1.0 indicates erosion control. Intermediate values suggest that erosion and diffusion each contribute to the overall release mechanism.<sup>4</sup> The values of *n* and *k* are inversely related, ie, it can be expected that with a decrease in *n* value, *k* value is expected to increase. A very high *k* value may suggest a burst drug release from the matrix.<sup>5</sup>

### Results

For all formulations, robust tablet matrices were produced with low weight variation of less than 2%, mechanical strength values of 21 kp – 33 kp (1.0 MPa - 1.6 MPa) and friability ≤0.02%. Reproducible first-order drug release profiles were obtained for different polymer concentrations, a wide range of PEO particle sizes and at all compression forces used in this study (**Figures 1-4**). Metformin HCl release was not controlled beyond one hour when POLYOX concentration was less than 15% w/w; matrices containing 5% and 10% w/w PEO resulted in rapid drug dissolution. With a further increase in polymer concentration (≥15% w/w), drug release rate decreased significantly (**Figure 1** and **Table 2**).

Figure 1. Metformin HCl Release from Matrices Containing Various Concentrations of PEO

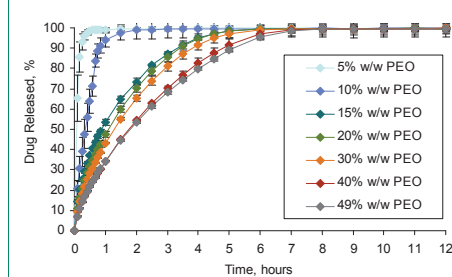


Table 2. Values of T<sub>20%</sub>, T<sub>50%</sub> and T<sub>80%</sub> for Metformin HCl Matrices Containing Various Concentrations of PEO

PEO concentration (% w/w)	T <sub>20%</sub> (min)	T <sub>50%</sub> (min)	T <sub>80%</sub> (min)
5	1 ± 0	4 ± 1	8 ± 1
10	5 ± 4	20 ± 7	40 ± 3
15	10 ± 1	50 ± 1	150 ± 1
20	15 ± 0	60 ± 2	150 ± 2
30	20 ± 0	90 ± 1	180 ± 2
40	25 ± 0	120 ± 0	240 ± 2
49	25 ± 0	120 ± 1	240 ± 1

For formulations where 10% w/w or more of PEO were used, the values of the kinetic constant (*k*), the release exponent (*n*) and correlation coefficient (*R*<sup>2</sup>) were determined and presented in **Table 3**. The correlation coefficients for the data were > 0.99. Since all *n* values were found to be in the range of 0.53-0.63, it may be suggested that the mechanism of metformin HCl release from these ER matrices was dominated by diffusion. For 10% w/w PEO formulation, a very high *k* value of 93.46 indicated a burst drug release from the matrix.

Table 3. Values of the Kinetic Constant (*k*), Diffusion Exponent (*n*) Derived from Equation 1 and Correlation Coefficient (*R*<sup>2</sup>) for Matrices Containing Various Concentrations of PEO

PEO concentration (% w/w)	<i>k</i>	<i>n</i>	<i>R</i> <sup>2</sup>
10	93.46	0.61	0.997
15	53.74	0.54	0.999
20	47.79	0.60	0.999
30	43.13	0.62	1.000
40	35.30	0.64	0.998
49	34.27	0.64	0.999

**Figure 2** shows that PEO particle size had no significant effect on metformin HCl release (*f*<sub>2</sub> = 55-87) when compared to release from tablets containing un-sieved PEO. It appeared that in all cases polymer particles hydrated fast enough and formed a protective gel layer, slowing both water penetration into the tablet and drug release out of the matrix.

Metformin HCl release from PEO matrices was not significantly affected by compression force (*f*<sub>2</sub> = 85, 90) in the range of 5 kN – 20 kN (**Figure 3**).

**Figure 4** shows that the drug release from tablets coated with Opadry II 85-Series remained similar to that from the uncoated matrices (*f*<sub>2</sub> = 91).

Figure 2. Metformin HCl Release from Matrices Containing Various Particle Size Fractions of PEO (30% PEO)

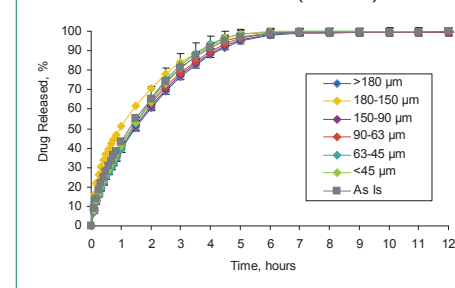


Figure 3. Metformin HCl Release from PEO Matrices Manufactured using Various Compression Forces (30% PEO)

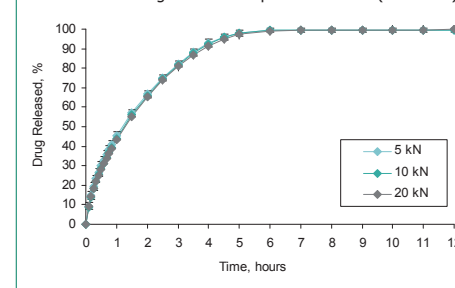
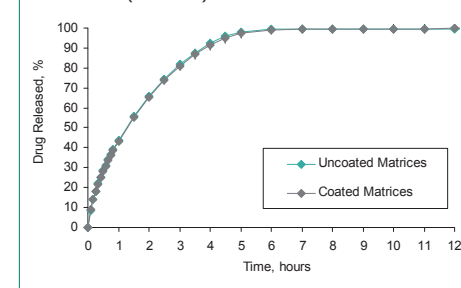


Figure 4. Metformin HCl Release from Uncoated and Coated PEO Matrices (30% PEO)



### Conclusions

- All manufactured PEO matrices had low weight variation of less than 2%, mechanical strength values of 21 kp – 33 kp (1.0 MPa - 1.6 MPa) and friability ≤0.02% indicating that robust directly compressible dosage forms were produced.
- Metformin HCl release was rapid when 5% or 10% w/w POLYOX was used in the formulations. Further increase in PEO concentration resulted in a significant decrease in drug release rate.
- Metformin HCl release from POLYOX ER matrices was unaffected by the polymer particle size, compression force or immediate release film coating.

### References

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