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Formulation of Glimepiride Immediate Release for Anti-diabetes Bilayer Tablets Using Design of Experiments

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PURPOSE

Anti-diabetes bilayer tablets were designed with:

- An extended release layer of Metformin HCl 500 mg in a Carbopol® polymer-based hydrophilic matrix
- An immediate release layer of Glimepiride 2 mg.

OBJECTIVE

The objective of the present work was to formulate the Glimepiride immediate release layer (2 mg) to be used in the design of anti-diabetes bilayer tablets containing Metformin HCl 500 mg as the extended release layer.

METHODS

A constrained mixture design was used to formulate the immediate release Glimepiride layer with disintegrant level (sodium starch glycolate) and binder type/amount (pregelatinized starch and polyvinylpyrrolidone PVP K-30) as independent variables – Table 1. Lactose monohydrate was varied to achieve 100% w/w of the formulation. Output variables were the % drug release at 15 and 30 minutes, and assay. The target ranges were not less than 70% drug release in 30 minutes and assay of 90% to 110% of the label claim.

Table 1: Glimepiride layer composition for design of experiment (DoE) study

Factor type	Ingredient	Input variable range % w/w
Intra-granular		
Constant	Glimepiride	0.61
Mixture variable	Lactose monohydrate	67.55 – 79.55
Mixture variable	Sodium starch glycolate (Primojel®)	2.24 – 10.24
Mixture variable	Pregelatinized starch (Lycatab®)	1.45 – 9.45
Mixture variable	Polyvinylpyrrolidone (PVP) K-30	0 – 3.00
Constant	Red iron oxide	0.30
Extra-granular		
Constant	Microcrystalline cellulose	11.50
Constant	Magnesium stearate	0.79
Total		100.0
Weight		165.0 mg

The design was suitable to estimate the linear effect of the three variables and curvature effects of sodium starch glycolate and PVP K-30 on drug release. In addition, interaction effects between sodium starch glycolate and the binders were used to explore how disintegrant and binder work together to influence drug release.

METHODS

The range of the total amount of binder necessary for compression and dissolution places restrictions on the formulation concentrations of sodium starch glycolate and PVP K-30. Too little binder may create a problem with compression; too much binder may affect dissolution. The experiments were designed to avoid these issues while still gaining an understanding of the relationships between binder and Glimepiride release and assay – Figure 1. Eleven different Glimepiride (2 mg) layer formulations in the above ranges were manufactured. Glimepiride granules were prepared by high shear aqueous granulation, blended with microcrystalline cellulose, lubricated, and compressed into tablets using 14.0 x 9.0 mm capsule shaped punches to achieve bilayer tablets of total target tablet weight 815 mg (Metformin HCl extended release layer weight 650 mg and Glimepiride immediate release layer weight 165 mg) and hardness 20 kP.

Glimepiride dissolution studies were conducted for all formulations: USP apparatus 2 (Paddle), 75 RPM, 900 mL pH 7.8 phosphate buffer.

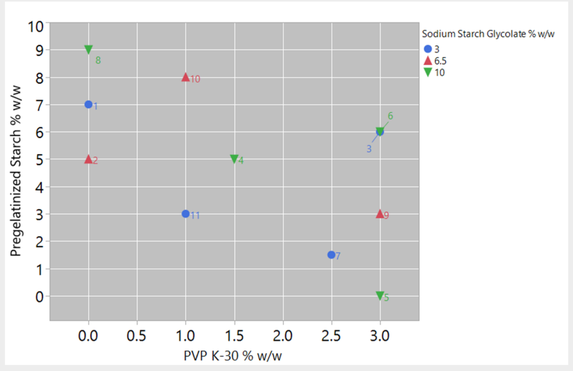

Fig. 1. Interaction effects between sodium starch glycolate and binders

RESULTS

The physical properties of the bilayer tablets were satisfactory.

The assay and 30-minute dissolution of all batches were within limits – Table 2. As the polymers from the extended layer may interfere with the release of Glimepiride during stability, formulations with >95% drug dissolved were selected for further studies.

A broader dissolution range was observed at 15 minutes compared to 30 minutes as shown in Figure 2.

Table 2. Dissolution and assay of Glimepiride (2 mg) immediate release layer

Batch No.	Sodium Starch Glycolate % w/w	Pregelatinized Starch % w/w	PVP K-30 % w/w	Glimepiride Release at 15 min (%)	Glimepiride Release at 30 min (%)	Glimepiride Assay (%)
1	3.0	7.0	0.0	74.3	96.7	100.1
2	6.5	5.0	0.0	80.0	95.3	97.6
3	3.0	6.0	3.0	90.9	97.7	99.9
4	10.0	5.0	1.5	85.7	91.9	98.1
5	10.0	0.0	3.0	76.0	89.4	97.7
6	10.0	6.0	3.0	72.9	86.1	97.0
7	3.0	1.5	2.5	89.9	94.6	99.5
8	10.0	9.0	0.0	92.2	100.1	102.4
9	6.5	3.0	3.0	83.7	98.9	100.7
10	6.5	8.0	1.0	78.2	96.4	99.6
11	3.0	3.0	1.0	79.7	90.6	98.3

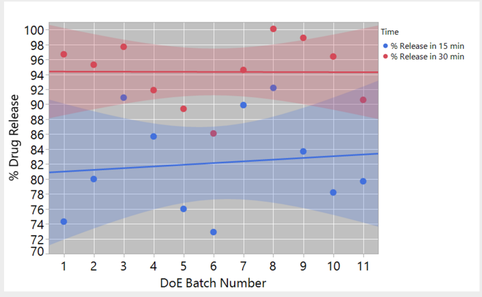

Fig. 2. Predicted Dissolution of Glimepiride in 15 minutes and 30 minutes based on DoE

Interactions between disintegrant and binder influenced the behavior of the drug release of the immediate release layer of the tablets. Nevertheless, the formulations were robust and not sensitive to changes in the levels of binders or in the disintegrant within the studied ranges.

One optimum formulation has been derived from DOE studies and was found to be stable when subjected to accelerated stability for six months in PVC/PVDC blister packaging. Stability studies were carried out as per Indian Pharmacopoeia (IP) monograph of Metformin Hydrochloride Prolonged Release and Glimepiride Tablets: dissolution (USP apparatus 2 paddle, 75 RPM, 900 mL pH 7.8 phosphate buffer in 1%SLS) and assay. Additional tests performed were LOD (loss on drying) and Related substances (RS limit as per IP monograph of Glimepiride monolayer tablets).

RESULTS

***Table 3**: Tablet properties of the optimum formulation*

Weight (mg)	815 ± 0.67
Hardness (kP)	19.9 ± 0.98
Friability (%) @ 100 revolutions	0.39
Friability (%) @ 300 revolutions	0.48

***Table 4**. Accelerated stability results for optimum formulation*

Property/ Specifications	Hardness (kP)	%LOD	Assay (As per IP Bilayer Monograph) **	RS (As per IP Monolayer Monograph)*			Dissolution (As per IP Monolayer Monograph) *			
	Report Results	Report Results	90%-110%	Glimepiride Related compound B NMT 2.5%	Any individual unspecified impurity NMT 0.5%	Total Impurity NMT 1.0%	NLT 75% in 30 Min			
							Average	%RSD	Min	Max
T=0	20.1	2.05	96.40	0.27	0.15	0.30	100.10	6.16	76.2	88.3
T=6Months 40C/75%RH-	20.5	2.36	97.90	0.91	0.14	0.23	95.76	2.71	93.1	100.3

*IP Monolayer Monograph: - Glimepiride tablets IP 2018 Monograph

**IP Bilayer Monograph: - Metformin Hydrochloride Prolonged release and Glimepiride Tablets IP 2018 Monograph

CONCLUSIONS

- Predictive models were derived based on the DoE approach, identifying the impact of binder and disintegrant on the drug release from the immediate release layer of the tablets.
- Interactions between disintegrant and binder drove the Glimepiride dissolution from the immediate release layer of the tablets. All formulations showed acceptable levels of Glimepiride release within 30 minutes.
- The immediate release layer can be extrapolated to various anti-diabetes bilayer compositions.
- The final formulation can also be adopted for other strengths of Glimepiride.
- Optimum formulation was stable when subjected to six-month accelerated stability testing.

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