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NOTE

Formulation and Characterization of Size Reduced Oral Extended Release Metformin Tablets

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The present study describes the newer cost-effective formulation of metformin extended release tablets. Metformin is one of the widely used drugs for the management of type-II diabetes and is a large dose drug. The total average weight of the commercially available tablets was more than 750 mg. Size reduced oral extended release tablets were meant to increase patient compliance particularly for use in geriatrics. The aim of the present study is to formulate metformin extended release tablets of lower weight and size. Size reduced tablets of metformin extended release, were prepared by incorporating newer combination of pH dependent polymers like Keltone HVCR and EPO 100 in small quantities so as to reduce the size of the tablet and at the same time extending the drug release to the maximum duration of time. Dissolution profiles were studied using basket model according USP XXIV. Different medium of buffer pH 1.2, pH 4.5 and pH 6.8 phosphate buffer were used. The release was found to be following zero-order, first-order, Higuchi and peppa's model.

Key Words: Eudragit, Size reduced, Metformin, Matrix tablet, pH Sensitive polymers.

Metformin comes under the group of biguanides widely used for blood glucose lowering properties. It is given by mouth in the treatment of type-II diabetes (non-insulin dependent). It is the first choice of type-II diabetes initial therapy. It enhances the activity of insulin by increasing the number of insulin receptors in human erythrocytes[1-3]. It has short biological half life (1.5-4.5 h) and thus frequent administration is required (3 times a day). Its high water solubility makes it potential candidate for extended release preparations. Various polymers have been extensively used for the developing extended release tablets. In order to increase patient compliance and cost effectiveness of the tablets, newer polymers are available in the market, which will control the release of drug when formulated using other polymers thus the pH dependent concentration of these newer polymers have an enormous effect

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on the kinetics and release mechanism of the formulation. Polymers like Keltone HVCR, EPO 100 and Eudragit L100 are having excellent properties in controlling the release of drug over an extended period of time.

The following materials were used as received. Metformin hydrochloride (MF.HCl) (CFL Pharm, Goa), Eudragit E 100 (EPO 100) (Rohm Pharm, Mumbai), Keltone HVCR (Kelco Pharm), PVP K-30, Microcrystalline cellulose (zydus-recon, Bangalore). The excipients like starch, magnesium stearate and talc obtained from SD Fine Chemicals, Mumbai.

Preformulation studies: Calibration curves of metformin HCl were prepared in distilled water in the concentration range of 1-10 µg/mL. The drug was analyzed spectrophotometrically (UV-240 Shimadzu, Japan) at 233 nm (regression coefficient, $r^2 = 0.9997$ in distilled water).

Selected excipients were checked for any changes when thoroughly mixed with drug in fixed proportions and checked at various temperatures like 25 ºC/60 % RH (relative humidity) and 30 ºC/65 % RH and 40 ºC/75 % RH and it was observed that there were no changes in the physical properties like appearance, colour, *etc*.

Methods: Metformin hydrochloride tablets were prepared by wet granulation method. Accurately weighed quantity of drug (Metformin HCl), EPO 100 powder, Keltone HVCR and excipients were passed through sieve no. 80. The materials were dry mixed (geometrically) for 15 min thoroughly. Required quantity of solvent mixture (ethanol:water) in the ratio 1:1 was added to the dry mixed materials to form granules. The dough mass was added through sieve no. 16 to obtain granules which were then dried between 50-60 ºC for 1 h. Dried granules were passed through sieve no. 20 under which sieve no. 40 was placed. The granules, which remained on sieve no. 40, were collected (considered as granules). Granules, which were passing through sieve no. 40, were considered as fines. The granules, which were retained over sieve no. 40, weighed and 15 % of the fines were added, magnesium stearate and talc (which were passed previously through sieve no. 80) were added and mixed with the granules. Then lubricant was added to the granules and mixed thoroughly. Different ratios of drug: polymers were used in different batches like F-I, F -II, F -III, F -IV and P-I, P-II, P-III, P-IV in different ratio's. The tablets of the above formulation were compressed using Cadmach compression machine.

The various characteristics of granules like bulk density, tapped density, angle of repose, Carr's index and housner's ratio were studied. The tablets were evaluated for hardness. Thickness, friability, uniformity of weight and drug content[4-6]. The *in vitro* dissolution profile of each formulation was determined on a USP XXIV dissolution apparatus type II.

Release models: Zero order and the first order, Higuchi's and peppa's equation were used in order to study the release form prepared by using different drug: polymer ratio.

Stability studies: Stability studies of tablets carried out at different conditions and tablets were evaluated for release study for 4 weeks.

Size reduced matrix tablets of metformin HCl were evaluated for hardness, friability, uniformity of the weight, thickness, drug content, drug release and stability studies were also carried out. Drug-excipients compatibility studies were carried out and no change was observed. In the current study the tablets were prepared with flat-faced punches with a hardness of 4.1-4.5 kg/cm^2. Friability of 0.094-0.428 was observed. The *in vitro* release studies were performed for all the formulated tablets including commercial formulation using USP XXIV tablet dissolution test acidic and alkaline buffer as dissolution medium. Evaluation results showed that for F-IV was found to be best formulation accordingly. The stabilities were performed on formulation F-4 (best formulation) and marketed tablets at 25 ºC ± 2 ºC/60 % RH ± 5 % RH and 30 ºC ± 2 ºC/65 % RH ± 5 % RH for 3 months. No significant difference was observed for the above parameters details are given in Table-1.

TABLE-1
STABILITY STUDIES FOR FORMULATION F-IV AND COMPARE WITH MARKETED BRAND GLYCOMET SR 500 Mg

Time (h)	Cumulative % drug released±SD							
	F-IV (Best formulation)				Marketed SR			
	At 25 ºC		At 30 ºC		At 25 ºC		At 30 ºC	
	1st Day	3 month	1st Day	3 month	1st Day	3 month	1st Day	3 month
1	20.35± 0.58	20.31±0.33	20.35±0.58	20.22±1.31	19.99±0.69	19.96±0.77	19.99±0.69	20.01±0.51
2	28.70±0.97	28.67±0.45	28.70±0.97	28.53±1.54	27.36±0.82	27.33±0.52	27.36±0.82	27.38±0.69
3	37.31±1.10	37.26±0.78	37.31±1.10	37.29±1.20	34.98±0.35	34.66±0.36	34.98±0.35	34.88±0.32
4	42.46±0.39	42.41±1.01	42.46±0.39	42.48±0.25	41.00±1.27	39.96±0.42	41.00±1.27	40.76±0.45
5	49.67±1.25	49.61±0.63	49.67±1.25	49.63±0.48	48.61±1.37	47.79±1.06	48.61±1.37	48.89±1.13
6	59.70±1.62	59.68±1.25	59.70±1.62	59.65±0.68	58.78±0.75	58.73±1.12	58.78±0.75	58.75±1.26
7	66.24±1.45	66.28±2.01	66.24±1.45	66.21±2.01	65.75±1.93	65.71±0.12	65.75±1.93	65.73±0.58
8	74.02±1.28	73.97±1.53	74.02±1.28	73.99±1.78	73.63±0.85	73.58±1.45	73.63±0.85	73.64±1.78
9	82.38±1.26	82.40±1.24	82.38±1.26	82.35±1.65	81.30±1.15	81.29±0.11	81.30±1.15	81.28±2.11
10	90.01±1.33	90.10±0.89	90.01±1.33	90.12±0.89	88.52±1.78	88.49±0.37	88.52±1.78	88.51±0.39

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