HPLC (high performance liquid chromatography) studies showed no interaction in freshly prepared physical blends containing excipients and glipizide. The physical blends were also exposed to 105°C for 6h (hot air oven), 121°C for 30 min (autoclave), 25°C at 60%RH (four weeks) or 40°C at 75%RH (four weeks). The DSC (differential scanning calorimetry) thermograms revealed a sharp endothermic peak of glipizide. Only a slight variation in peak endothermic temperature of glipizide was observed in the presence of excipients. The presence of excipients is known to lower the purity of drug samples. Hence, the observed slight variation in peak endothermic temperature does not indicate any potential interaction between glipizide and excipients. However, significant shift in peak endothermic temperature of GP was observed in the presence of sodium chloride, cellulose acetate and polyethylene glycol. These thermograms also recorded a reduction in ΔHf. The physical mixtures yielded single max unknown and total impurities within the limits prescribed by ICH guidelines. Overall, the results of thermal and HPLC impurity analysis did not suggest the generation of any potential degradation products / incompatibility between glipizide and the selected excipients.

Percentage of fines was highest in granules prepared by direct compression (F1 and F2). High content of fines is known to retard the flow of powder blend from the hopper to the turret of the compression machine. In addition, high content of fines were found to be associated with high friability of the tablets prepared by the direct compression method. Similarly, granules manufactured by direct compression exhibited greater angle of repose which is known to reduce flowability of the granules. Granules manufactured by wet granulation (F3 & F4) exhibited lesser angle of repose with better flowability of the granules. As osmotic tablets contain water soluble excipients, it was decided to use solvent free granulation. Therefore, hot melt extrusion method was
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selected for manufacturing of glipizide. Granules prepared by effervescent technique (F5) exhibited better flowability of granules but tablets were highly prone to moisture uptake and in vitro release of stored tablets was faster than the freshly prepared tablets.

The results of granule characterization and tablet dissolution studies suggested the superiority of the granules produced by hot melt technique over those prepared by direct compression and wet granulation. The XRD (X-Ray Diffraction) profile of pure glipizide illustrated its crystallinity. The highest crystalline peaks of glipizide were observed at 2θ angles at 18.0. No change in crystallinity was observed in melted granules and after compressing hot melt granulates containing glipizide into tablets as demonstrated in the XRD diffractograms.

The use of sodium chloride, sodium carbonate or combination of sodium chloride and sodium carbonate as tools for modifying osmotic behavior, solubility or combination of both processes respectively, could not provide dissolution rate enhancement of glipizide comparable to that of Glucotrol XL tablets.

The tablets containing combination of sodium chloride (20% w/w), sodium carbonate (8% w/w) and carboxymethylcellulose sodium (50% w/w) followed by coating with cellulose acetate-hydroxypropyl methylcellulose solution mixture and subsequently drilled with 0.6 mm pore (F10) by laser beam yielded dissolution profile significantly comparable to that of Glucotrol XL (f2 value of 70.2). Further, the release of GP from the optimized formulation was observed to follow zero order kinetics over 16 h, independent of the pH of the dissolution media.

Formulations were also prepared by using magnesium hydroxide instead of sodium carbonate and polyethylene oxide instead of carboxymethylcellulose sodium. The results of dissolution studies revealed that none of these excipients when used alone in the uncoated tablet was able to release glipizide at a rate comparable to the marketed extended release tablet (Glucotrol XL) tablet. However, the tablets containing combination of sodium chloride (14.28 %w/w), magnesium hydroxide (8.56 %w/w) and polyethylene oxide (57.16 %w/w) followed by coating with cellulose acetate-polyethylene glycol mixture (4% w/w) solution prepared in acetone:water (9:1) and subsequently drilled with 0.6 mm pore by high energy laser beam yielded dissolution profile significantly comparable to that of Glucotrol XL tablet with f2 (similarity factor)
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of 74.7. F25C formulation was selected and tablets were drilled with high intensity laser beam (0.4, 0.5, 0.6, 0.7 or 0.8 mm diameters). The release of glipizide from tablets of batch F25CCC (drilled with 0.6mm) exhibited release comparable to glucotrol XL tablets with similarity factor 74.7(f2).

The release of glipizide from the optimized formulation (F25CCC) was observed to follow zero order kinetics upto 16 h, independent of the pH of the dissolution media. The investigated technique of preparing granules by hot melt granulation process is a simple one step process avoiding the use of water or solvents thus, being ideally suitable for water sensitive drugs. Further, the developed formulation is a hydrophilic matrix system, which minimizes the processing steps in designing an oral elementary osmotic release system.

The bioequivalence studies in healthy human beings revealed pharmacokinetic parameters for both rate and extent of glipizide absorption following oral administration of the optimized tablets (F25CCC) to be within the 80 – 125% range of those obtained after oral administration of Glucotrol XL tablets.

Hence, the results of this investigation demonstrate that a single oral 10mg dose of F25CCC tablets and Glucotrol XL tablets was bioequivalent in terms of pharmacokinetic parameters. Furthermore, none of the subjects experienced significant side effects during the study, indicating that both products were well tolerated.

In conclusion, hot melt granulation technique was found to offer a new approach for formulating osmotic release tablets of glipizide. The core tablets containing glipzide (2.86% w/w), microcrystalline cellulose (14.00% w/w), polyethylene glycol 6000 (2.86%), polyox WSR 303 (57.16% w/w), sodium chloride (14.28% w/w), magnesium hydroxide (8.56% w/w), coated with cellulose acetate-polyethylene glycol 6000 (4.28:0.86) mixture and subsequently laser drilled with 0.6 mm pore were found to yield in vitro and in vivo release profiles similar to that of Glucotrol XL tablets.