SUMMARY  
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Oral administration of drugs has been the most common and preferred route for delivery of most therapeutic agents. It remains the preferred route of administration investigated in the discovery and development of new drug candidates and formulations. The popularity of oral route is attributed to patient acceptance, ease of administration, accurate dosing, cost-effective manufacturing methods, and generally improved shelf-life of the product. For many drugs and therapeutic indications, conventional multiple dosing of immediate release formulations provides satisfactory clinical performance with an appropriate balance of efficacy and safety. The rationale for development of an extended-release formulation of a drug is to enhance its therapeutic benefits, minimizing its side effects while improving the management of the diseased condition. Besides its clinical advantages, an innovative extended-release formulation provides an opportunity for a pharmaceutical company to manage its product life-cycle. The dearth of new chemical entities is forcing many pharmaceutical companies to reformulate an existing conventional formulation to an extended-release product as a strategy of life-cycle management and retaining market share.

Thus it was observed that as the dissolution studies were carried out on matrix tablet formulations with PEO WSR301 and PEO WSR303 with an objective of achieving linear controlled release of Verapamil Hydrochloride and Losartan Potassium. PEO WSR301 and PEO WSR303 were reported to have better controlled release of drugs from the matrix tablet dosage forms. Earlier these polymers were used alone as matrix forming agents and there were no studies were performed on the influence of pharmaceutically acceptable electrolytes on these polymers. In the present study comparative evaluation of controlled drug release from PEO WSR301 and PEO WSR303 matrix tablets with and without electrolytes were carried out. The electrolytes employed in the study were aluminum hydroxide, aluminum sulphate, calcium carbonate, magnesium carbonate, sodium carbonate and sodium bicarbonate. The powder blend were sent for the evaluation of flow properties like carr’s index and angle of repose. The matrix tablets formulations prepared were evaluated for weight uniformity, hardness, friability and drug content.

The matrix tablet formulations were then evaluated for in vitro drug release studies. Influence of electrolytes on drug release from matrix, mechanism of drug release
from the matrix tablets, changes in matrix and gel structure with the incorporation of electrolytes by IR spectroscopic studies and swelling index properties by using dissolution of the drug release studies.

The selected matrix tablets were subjected to in vivo pharmacokinetics studies. These studies were carried out in rabbit (n=4). The pharmacokinetic parameters such as $C_{\text{max}}$, $t_{\text{max}}$, $t_{1/2}$, MRT, AUC $\text{O-\infty}$ were determined form the plasma concentration of drug versus time profiles and by using model independent computer program P.K.Solutions. The plasma concentration curve Verapamil Hydrochloride and Losartan Potassium were determined by HPLC method.

The Verapamil Hydrochloride and Losartan Potassium matrix tablet formulations subjected to in vivo studies were also subjected to accelerated stability studies. These formulations were stored at different storage conditions such as $25\pm2^\circ\text{C}$, $60\pm5\%\text{RH}$ for 12 months and $40\pm2^\circ\text{C}$, $75\pm5\%\text{RH}$ for 6 months. Then after storage, these formulations were evaluated for their physical parameters such as weight uniformity, hardness, friability and drug content and finally drug release studies were carried out.

The following conclusions were drawn from the results:

1. Verapamil Hydrochloride and Losartan Potassium were freely water soluble drugs and were suitable for direct compression as controlled release matrix tablets with PEO WSR301 and PEO WSR303 respectively.

2. The powder blends prepared for direct compression (both drug, polymer and electrolytes) were having good flow properties and hence suitable for direct compression.

3. Weight uniformity of matrix tablet formulations were uniform in all the cases and were maintained with in I.P specified limits.
4. Hardness of the matrix tablet formulations were constant in all the batches and maintained at $6.5\pm0.4\text{Kg/cm}^2$. Friability loss was negligible (<0.2%) in all the batches of matrix tablet formulations.

5. The drug content was uniform in all the batches of matrix tablet formulations. The drug content was also the same in case of matrix tablets containing electrolytes. The drug content in the matrix tablets of all batches were found to be within U.S.P specified range of Verapamil Hydrochloride extended release tablets.

6. The matrix tablet formulations prepared with PEO WSR301 at a drug and polymer ratio of 1:1.5 found suitable for extending the drug release up to 12hrs, whereas the tablets prepared with PEO WSR303 at a drug and polymer ratio of 1:1 was suitable for extending the drug release up to 12hrs.

7. The matrix tablet formulations (without electrolytes), gave slow release of drugs upto 12hrs. Drug release from all the tablets followed both diffusion and dissolution mechanisms.

8. The incorporation of electrolytes in the matrix tablet formulations has significant influence on drug release.

9. The matrix tablet formulations (with electrolytes), gave slow release of drugs and extended the release over 12hrs. Drug release from all the tablets followed both diffusion and dissolution mechanisms. Drug release from the tablets depends on the composition of electrolytes employed. Good linear relationships were observed between drug release and electrolyte concentration.

10. Electrolytes such as aluminum hydroxide, calcium carbonate, magnesium carbonate, and sodium carbonate have high influence on extending the drug release over a prolonged period, while aluminum sulphate and sodium bicarbonate have mild influence on extending the drug release.
11. Log percentage drug undissolved versus time plots for first order release rate constant of all the prepared matrix tablets were found to be linear with $R^2$ values of 0.91-0.97.

12. The cumulative amount of drug released versus square root of time plots for Higuchi’s dissolution rate constant of all the matrix tablet formulations were found to be linear with $R^2$ values of 0.90-0.98.

13. Log $M_t$/ Log $M_{0t}$ versus log time for Korsermeyer peppas constant were found to be linear with ‘n’ values ranging from 0.45-0.9 indicating the mechanism of drug release from all the matrix tablet formulations by both combinations of dissolution and diffusion controlled mechanisms.

14. FTIR spectral studies of selected formulations of Verapamil Hydrochloride (VP3, VPA6 and VPC44) and for Losartan Potassium (LP3, LPA6 and LPS55) exhibited no major interactions between the drug, polymer and electrolytes during dissolution process.

15. Swelling index studies on selected formulations of Verapamil Hydrochloride (VP3, VPA6 and VPC44) and Losartan Potassium (LP3, LPA6 and LPS55) indicated the influence of electrolytes on the swelling behavior of matrix tablet formulations by altering the matrix and gel structure during the drug release process. The formulations (VP3, VPA6, VPC44, LP3, LPA6 and LPS55) containing electrolytes such as aluminum hydroxide, calcium carbonate, magnesium carbonate, and sodium carbonate exhibited low swelling during 2 to 6hrs of dissolution period.

16. The pharmacokinetic evaluation of Verapamil Hydrochloride and it's matrix tablets were carried out in rabbits indicated very rapid absorption of Verapamil Hydrochloride oral solution form. The peak plasma concentration was observed at 2.0±0.1 hrs after oral administration and later the concentration decreased rapidly. Whereas when Verapamil Hydrochloride matrix tablets prepared were administered, the peak plasma concentrations were observed at 4.0±0.1 hrs and maintained the
concentrations within a narrow range over a prolonged period. The MRT was increased from 1.9±0.2hrs for Verapamil Hydrochloride oral solution to 10.2±0.4hr with matrix tablet formulations. The matrix tablet formulations containing electrolytes were found suitable for once a day administration.

17. The pharmacokinetic evaluation of Losartan Potassium and it’s matrix tablets were carried out in rabbits indicated very rapid absorption of Losartan Potassium oral solution form. The peak plasma concentration was observed at 2.0±0.1 hrs after oral administration and later the concentration decreased rapidly. Whereas when Losartan Potassium matrix tablets prepared were administered, the peak plasma concentrations were observed at 4.0±0.1hrs and maintained the concentrations within a narrow range over a prolonged period. The MRT was increased from 3.4±0.3 for Losartan Potassium oral solution to 13.6±0.34hrs with matrix tablet formulations. The matrix tablet formulations containing electrolytes were found suitable for once a day administration.

18. Accelerated stability studies were carried out for some selected matrix tablets, indicated no significant change in physical parameters such as weight uniformity, hardness, friability and drug content. The drug release from the matrix tablets after storage at different conditions, remain unaltered and was quiet stable.

Thus the present studies clearly indicated that the incorporation of electrolytes in the matrix tablet formulations had greatly influenced the drug release properties. The electrolytes such as aluminum hydroxide, calcium carbonate, magnesium carbonate, and sodium carbonate were found to be ideal electrolytes for incorporation into the matrix tablets for extending the drug release. These matrix tablets with the said electrolytes exhibited good controlled release characteristics by both in vitro and in vivo studies, Thus the present study was found suitable for preparation of matrix tablets employing the electrolytes for oral control release of Verapamil Hydrochloride and Losartan Potassium along with PEO WSR301 and PEO WSR303 fulfilling the major objective by extending the drug release up to 24hrs. Hence these formulations were found to be suitable for once a day matrix tablet administration for treating the angina patients.