SUMMARY

In the present study fast disintegrating sublingual tablets of potent anti-migraine drugs of zolmitriptan (5mg/tablet) and rizatriptan (10mg/tablet) were prepared by the help of direct compression technique. The superdisintegrants used were sodium starch glycollate, croscarmellose sodium and crospovidone. Mannitol and avicel pH102 (microcrystalline cellulose) were used as diluents. Aspartame was used as a sweetener and magnesium stearate was selected as a lubricant.

The blend of all powder formulations were examined for angle of repose, Carr’s Compressibility Index and Hausner’s Ratio. Results showed that the angle of repose is <33° assuming good flow properties for formulations. Carr’s compressibility index and Hausner’s ratio were found to be <14 and <1.17 for zolmitriptan and ≤15 and ≤1.18 for rizatriptan powder formulations respectively, ensuring that all the preparations resulted in good mixing, flow ability and compressible characteristics. The formulated tablets were evaluated for physiochemical properties and dissolution efficiency. Good drug uniformity results were established among different batches of tablets and it was more than 97.5% (p<0.05) in zolmitriptan and more than 95.5% (p<0.05) in rizatriptan.

The wetting time and disintegration time for zolmitriptan sublingual tablets were found to be 66.0±1.0s to 5.0±1.0s and 84.3±0.58s to 7.7±0.58s respectively and 65.33±0.58s to 5.33±0.58s and 80.33±0.58s to 7.33±0.58s respectively in case of rizatriptan sublingual tablets. The tablets containing 6% crospovidone showed faster disintegration and more dissolution efficiency. The tablet disintegration was effected by the wicking and swelling nature of
the disintegrants. The crospovidone present in the tablets is responsible for the quick wicks of saliva into the tablet and volume expansion is generated and hydrostatic pressure, which provides quick disintegration in the mouth (Jinichi et al., 2006). Based on faster disintegration and dissolution efficiency the formulation nine (F9) was selected as optimised. The wetting and disintegration time for optimised formulation (F9) was found to be 5±1s and 7.7±0.58s for zolmitriptan tablets and 5.33±0.58s and 7.33±0.58s for rizatriptan tablets. The optimised formulation showed 100.34±1.19 dissolution efficiency for zolmitriptan sublingual tablets and 97.47±0.36 dissolution efficiency for rizatriptan sublingual tablets.

The optimized formulations were characterized with the help of Scanning Electron Microscopy (SEM), Differential Scanning Calorimetry (DSC), Powder X-ray Diffractometry (PXRD) and Fourier Transform Infrared Spectroscopy (FTIR); in both formulations the SEM pictures reveal that there was no segregation or deposition of particles on the surface of sublingual tablets. From DSC and PXRD studies, it was observed that in both optimised formulations the drug exists in crystalline form without having polymorphic change. FTIR studies revealed that the drug and excipients did not have interactions. Based on disintegration and dissolution studies, the optimized preparations were subjected to stability studies. These formulations were analysed for drug content, friability, hardness, wetting time and in vitro disintegration time for three months. Both the optimised formulations were stable and did not show much variation in any of the parameters.
Comparative pharmacokinetic studies of prepared zolmitriptan tablets (5mg/tablet) and intravenous injection (5mg/kg) were carried out using New Zealand rabbits. The $C_{\text{max}}$, $T_{1/2}$, $T_{\text{max}}$ and AUC were calculated.

Peak serum concentration attained by the test item zolmitriptan was 140.622ng/ml and 2500.846ng/ml following sublingual and intravenous administration respectively. The time needed to attain peak serum concentration by drug, following sublingual and intravenous administration was 1 hr and 0.083 hr respectively. The area under the curve $\text{AUC}_{(0-24)}$, was found to be 231.769 ng.hr/ml and 1712.739 ng.hr/ml for sublingual and intravenous administration respectively. $\text{AUC}_{(0-\infty)}$ was calculated and was found to be 295.131ng.hr/ml and 1750.454ng.hr/ml for sublingual and intravenous administration respectively. The $T_{1/2}$ was found to be 0.855 hr and 1.665 hr following sublingual and intravenous administration respectively.

Intravenous route gives 100% bioavailability where as oral or sublingual gives less bioavailability due to absorption, first-pass effect, receptor binding, rapid absorption etc. In the present market zolmitriptan oral and nasal formulations are available and the oral bioavailability of zolmitriptan is 25% (10mg/kg rabbit) suggesting significant first metabolism in rabbit. So sublingual route of administration helps the bioavailability and the maximum concentrations attained with zolmitriptan at 5mg tablet in rabbits elicits the pharmacological activity. The main object of this study is to show fast absorption of the drug and provide more consistent relief from migraine.

In conclusion, the average plasma concentration-time profiles for zolmitriptan 5 mg tablet by sublingual route show quite rapid initial drug
absorption, on normal reaching 80% of eventual Cmax within 1 hour and 5 mg/kg intravenous route show time to peak plasma concentration within 1 hour. Zolmitriptan 5 mg tablet by sublingual route in rabbits showed effective therapeutic Cmax (140.622 ng/ml) when compared to clinical dose by oral route (5.6 ng/ml).

Comparative pharmacokinetic studies of prepared rizatriptan sublingual tablets (10mg/tablet) and marketed oral tablets (10mg/tablet) were carried out using New Zealand rabbits. The C\text{max}, T\text{1/2}, T\text{max} and AUC were calculated.

Peak serum concentration attained by rizatriptan following sublingual and oral administration was 235.227ng/mL and 486.336ng/ml respectively. The time needed for reaching peak serum concentration by the drug, following sublingual and oral administration was 0.5 hr and 1.333 hr respectively. The area under the curve AUC\text{(0 - 24)}, was 475.488 and 1083.305 ng.hr/ml for sublingual and oral administration respectively. AUC\text{(0 - ∞)} was calculated and was 235.227 and 1298.551ng.hr/ml respectively for sublingual and oral administration. The time needed for a drug to decrease by half (i.e. T\text{1/2}) was found to be 1.335 and 1.024 hr respectively following sublingual and oral administration.

In the study even though the plasma concentrations of sublingual tablets were less compared to oral tablets, the Cmax (235 ng/ml) achieved with sublingual route elicits the pharmacological activity (Suzanne et al. 2006).

In conclusion, rizatriptan 10 mg tablet average plasma concentration-time profiles by sublingual and oral route show a comparable time to peak plasma concentration and the time of occurrence of T\text{max} was faster in
sublingual route of administration. Rizatriptan 10 mg tablet by sublingual route in rabbits show effective therapeutic Cmax when compared to clinical dose (Suzanne et al., 2006; Jun et al., 2005; Chen et al., 2005).
CONCLUSION

Fast dissolving zolmitriptan and rizatriptan sublingual tablets were prepared with the help of direct compression technique by using sodium starch glycollate, croscarmellose sodium and crospovidone as superdisintegrants. The formulae were optimized for zolmitriptan and rizatriptan sublingual tablets to give fast relief and increase the patient compliance. The unpleasant taste of these drugs was masked by aspartame (sweetener). The tablets containing 6% of crospovidone showed faster disintegration and more dissolution efficiency. The characterisation of optimised formulations was done and the result showed without any interaction among the drug and excipients. Optimized formulations were subjected to stability studies and studies confirmed that the tablets were stable. These optimised formulations were evaluated for in vivo release studies using rabbit model and showed effective therapeutic $C_{\text{max}}$ when compared to clinical dose. The study concludes that these formulated fast disintegrating sublingual tablets are promising alternative to oral administration route in acute management of migraine.