SUMMARY

Within the oral mucosal cavity, the buccal region offers an adorable route of administration for systemic drug delivery. Among the various transmucosal sites available, mucosa of the buccal cavity was found to be the most convenient and easily approachable site for the delivery of therapeutic agents for both local and systemic delivery as retentive dosage forms.

The main objective of this study was to studied chitosan based buccal mucoadhesive devices for systemic delivery of cardiovascular drugs (metoprolol succinate-MS and carvedilol-CR) with special reference to percentage inhibition of isoprenaline induced tachycardia. Both metoprolol succinate and carvedilol undergo first pass metabolism and hence, oral bioavailability is 50% and 25% for metoprolol succinate and carvedilol. The plasma half life of metoprolol succinate and carvedilol are 3-7 hrs and 6-10 hrs respectively. These said factors make metoprolol succinate and carvedilol more suitable candidate for administration via buccal route.

The mucoadhesive buccal patches of metoprolol succinate and carvedilol were prepared using chitosan, NaCMC & PVA as polymer and glycerol as plasticizer by solvent casting method. The prepared patches were evaluated for content uniformity, patch thickness, weight variation, % swelling, folding endurance, residence time, mechanical properties, bioadhesion study, in vitro permeation & release study, pharmacodynamic & pharmacokinetic study and the effect of ageing on patches.

The interaction between the drug and polymer was analysed by FTIR and DSC study, and found that there was no any interaction between drug and polymer molecules. The crystalline nature of the drug was analysed by x-ray diffraction pattern. X-ray diffractometer (XRD) equipped with a Ni-filtered Cu radiation, under the voltage of 30kV and 15 mA current. The dried samples were mounted on a sample holder and XRD scans were recorded upto 20 plane in the angle range of 1° to 50° at a scan speed of 1°/min to estimate the crystallinity of the samples. For the morphology of the prepared patch was determined with the help of scanning electron microscopy (SEM) method. The SEM photograph indicates the uniform dispersion of polymeric solution with drug molecules.

A good physical characteristic was found for the buccal patches prepared using chitosan; NaCMC and PVA. The patch thickness and weight was patches increased with an increase in the amount of polymer percent. The surface pH plays an important role in the mucosal irritation, and it was found that the pH of prepared patches was
almost neutral (5.5-7.0) so that no irritation was observed after application on mucosa. Folding endurance is an important parameter for the determination of elastic nature of the patch, and it was found more than 300 for all the patches, shows goog elastic behaviour of the patches. The % swelling was determined on agar plate and as the concentration of the polymer increases the value of % swelling decreases. In vitro residence time was determined by a locally modified USP disintegration apparatus using phosphate buffer of pH 6.8 using a segment of pig intestinal mucosa which was glued to the surface of glass slab, vertically attached to the apparatus. Residence time was increased as the concentration of the polymer increased, and found maximum in case of CM-3 (12.0±0.80 hrs) and PC-3 (13.5±0.58 hrs). The mechanical properties (tensile strength-TS and elongation at break-E/B) were determined to check the flexibility and elasticity of the patches. The TS was maximum for SM-3 (12.7±1.10 kg mm$^{-2}$) and minimum for CM-1 (3.30±1.91 kg mm$^{-2}$), while E/B was maximum for PM-1 (110.22±0.28 % mm$^{-2}$) and minimum for SM-3 (80.75±4.20 % mm$^{-2}$) in case of patches containing MS. For CR patches TS was maximum for PC-3 (13.47±0.10 kg mm$^{-2}$) and minimum for CC-1 (5.08±1.48 kg mm$^{-2}$), while E/B was maximum for CC-1 (131.65±5.46 % mm$^{-2}$) and minimum for SC-3 (82.80±1.55 % mm$^{-2}$). The bioadhesion was determines as Peak detachment force and In-vivo bioadhesion time, and found that the bioadhesion time was maximum in case of CM-3 & CC-3 (6.0 hrs). Permeation of drug through porcine buccal mucosa was determined for 8 hrs and found that the MS permeated 91% and CR permeated 82% in 8 hrs. Drug release from the buccal patches was studied using USP type I dissolution test apparatus. The release study of patches containing MS shows that the maximum release was found from CM-2 (97.11±2.80%), SM-3 (84.10±2.80%) and PM-3 (92.45±1.20%) patches, and in case of patches containing CR maximum release was from CC-2 (94.75±0.70%), SC-3 (85.50±0.20%) and PC-2 (89.65±3.30%) patches. The release kinetic parameters were determined for zero order, first order. Highuchi model and Korsmeyer- Peppas model. For release kinetic of MS patches, the Korsmeyer-Peppas model equation was used, and the $n$ values were obtained between 0.2316 and 0.5000 for all formulations. These values are characteristic of Fickian diffusion. In this context, the results obtained from the fitting the data in Koresmeyer-Peppas and zero order kinetics also supported the theory that the release of the drug from the patches was by a diffusion dominated. For CR patches the $n$ values were obtained between 0.2960 and 0.5287 for all formulations. These values are characteristic of Non-Fickian
or anomalous diffusion. In this context, the results obtained from the fitting the data in Koresmeyer-Peppas and zero order kinetics also supported the theory that the release of the drug from the patches was by a diffusion dominated.

On the bases of in vitro release study CM-2, SM-3, PM-3 (MS containing patches) and CC-2, SC-3, PC-2 (CR containing patches) patches were found suitable for further study.

Pharmacodynamic study was performed on animal rabbit, and determined the inhibitory effect of MS and CR on isoprenaline induced tachycardia by giving through intravenous, oral and buccal route. The patches achieved a good prolonged and steady inhibitory effect of isoprenaline in rabbits with minimal quantity of drug as compared with the inhibitory effect produced by high oral dose. Pharmacokinetic study was performed on the optimized patches, and determined $C_{\text{max}}$, $T_{\text{max}}$ and AUC. The AUC$_{\text{total}}$ for the buccal patch was significantly ($p < 0.005$) higher than that of the oral solution, indicating improved bioavailability for the buccal patch. The patches were stored for 6 months at $37 \pm 0.5 ^\circ\text{C}$ and $75 \pm 0.5 \text{ RH}$, and found that no any changes in physical appearance, no any major difference in residence time of patches. The release of drug from the patches was slightly decreases and the decrease in release during storage may be a direct consequence of the reduced erosion rate of the patches.

Buccal patches of chitosan, NaCMC and PVA containing MS and CR are well accepted and produce no side effect at contact surface. This route is suitable for the administration of MS and CR, because it bypass the extensive hepatic first pass metabolism, avoid the loss of drug into the saliva and increase bioavailability. On the above results this system proved to be potential candidate for the delivery of metoprolol succinate and carvedilol.