Buccal delivery became recently under spotlight in drug delivery research. This is because of the advantages of avoiding the first pass effect on the orally delivered drugs, and the high vascularity of the oral cavity. Buccal mucoadhesive gels are one of the strategies to deliver the actives through the buccal mucosa which utilize the advantage of the presence of the drugs in a solubilized state within the gel matrix. The aim of this research is formulate mucoadhesive buccal gels of two low bioavailable drugs; domperidone and mosapride citrate. The thesis focuses on the effect of solvents on the buccal mucosa and trying to find a correlation between two buccal models (i.e. porcine and tissue culture models). The work in this thesis is divided into:

I- Formulation and evaluation of domperidone buccal gels:

The study was designed to formulate a buccal mucoadhesive dosage form of domperidone with good bioavailability for pediatrics use. The gel formulation step was based on studying the solubility of domperidone in different organic solvents which can be used as cosolvent. Transcutol P, PEG 200 and PEG 400 were chosen as it achieved the highest domperidone solubility (22.94 ± 0.014, 7.37 ± 0.027 and 7.92 ± 0.027 mg/ml respectively) and due to their water miscibility. Transcutol P gave the highest flux (2.328 µg. cm^{-2} .hr^{-1}) among the selected cosolvents due to it permeation enhancing properties. Mixing Transcutol P with water gave exceptional results as the binary mixture of 60% Transcutol in water gave a higher flux than pure Transcutol P. The mixture Transcutol: water (40:60) was used to formulate the gel formulations with two levels of drug loading (3.5mg/ml and 5mg/ml) with two levels of polymer concentrations which act as stabilizing anti-nucleating agents for the prepared supersaturated systems of domperidone.

The stable gel formulations were evaluated for rheological mucoadhesive, drug release and permeation properties. The gels in general gave a lower flux values than the binary mixture alone. In addition, the permeation profiles were of infinite dose type with a straight steady-state flux line. The formulation D29 were chosen to be compared with the commercial Motilium® tablets in a bioequivalence in vivo study in human volunteers. The gel formula gave an $AUC_{0-\infty}$ (41.62±5.2 ng.hr/ml) higher than the one form the tablet product (40.54±3.02 ng.hr/ml). And the relative bioavailability of the buccal gel was 202% to the oral tablet product. Surprisingly, the gel formulation gave a sustained concentration of domperidone over a period of 5 hours. Combining these findings with the permeation data, it can be assumed that supersaturation and Transcutol P helped in the formation of domperidone depot sites inside the buccal mucosa. This could help in the future to formulate dosage forms that can form drug depot sites inside buccal mucosa for sustained drug action.

II- Formulation and evaluation of mosapride citrate buccal gels:

In this chapter, mosapride citrate was incorporated into mucoadhesive buccal gels utilizing mixed solvent approach. Mosapride citrate showed the highest solubility in PG, PEG200 and PEG400 among the solvents used in the solubility study (39.57±4.57, 12.53±0.028 and 17.09±0.0084 mg/ml respectively). From the permeation studies using dose approach, it was found that saturated solutions of the drug in PG achieved highest values of flux and cumulative amount permeated (0.0113±0.0025 µg. cm^{-2}. h^{-1} and 6.75±1.91 µg. cm^{-2} respectively). From these data, PG was chosen for

making binary mixtures with water (20%, 40% and 60% v/v) for further investigation. The system PG: water (40:60 v/v) was chosen formulation of buccal gels. The gels were formulated using different polymers and were inspected for any signs of crystallization within 24 hours. Six formulations were carried out for further characterization (Rheology, release, mucoadhesion and permeation studies). All the formulations showed shear thinning pattern with considerable yield values. Mucoadhesion studies showed high mucoadhesive characteristics of gels formed of chitosan (M30) and xanthan gum (M9 and M10) than gels from polyacrylic acid (M22 and M26) and Pluronic F-127 (M14) gels. Gels made of xanthan gum (M9) and chitosan (M30) achieved the highest amount released of drug (100% and 65% respectively). All gels showed a diffusion release pattern. The surprising results came from the permeation studies of the gels. The flux values from xanthan gum (M9) and chitosan (M30) gels were higher than the saturated solution of mosapride citrate in the same solvent system although the drug level in the gels was in the subsaturated region. These findings were combined with the results from Theramal and DVS analysis on the drug that revealed a polymorphism phenomenon. It was concluded that mosapride transforms to a less soluble form which will affect the overall thermodynamic activity of the drug in the donor side and in turn, will affect the flux through the barrier membrane. Storing the gel formulations at 4^{o} C for 12 weeks did not significantly affect the chemical and physical stability of the gels. Formula M9 was chosen to

be a candidate in the in vivo bioequivalence study against the commercial oral tablet of mosapride citrate (Fluxpride™ 5 mg tablet). The study was performed in a cross over design using 12 volunteers. M9 used in a dose of 2.5mg/volunteer while the commercial formula was used in a dose of 5mg/volunteer. The study showed no significant difference between the two formulations in term of AUC_{0-24} (60.2± 4.3 and 59.97± 5.82 ng.hr/ml for the oral tablet and the buccal gel respectively). The overall relative bioavailability of M9 was about 160%, which was a good sign of using the buccal route to increase the bioavailability of the drug.

III- Characterization of the buccal mucosa:

The work in this chapter was divided into two experiments, the uptake of different solvents to the buccal mucosa, and infinite dose permeation study of domperidone from different solvent systems through porcine and EpiOral™ tissue culture models to find a correlation between the two models. The solvent uptake experiment revealed a superb uptake of water by the dried mucosa (>300% increase in weight). There was high uptake of solvents with high solubility parameter (24.8 and 16.6% in case of PG and PEG200 respectively). Negative percent increase in weight was observed in case of transcutol P and IPM which suggests the lipid extraction effect of these solvents. The increase of weight of dried buccal mucosa by hydrophilic solvents was mainly due to the high level of total phospholipids and low percent of lipophilic ceramides.

Assessing buccal delivery was previously tested using porcine buccal model due to its similarity to human buccal mucosa. Recently, tissue cultures from the buccal mucosa of healthy human volunteers have been used in assessing drug delivery through buccal mucosa. The aim of this study is to find a correlation in the permeation parameters between the two models. The study was based on permeation studies of domperidone (as model drug) through both models from single and binary solvent systems using Franz diffusion cells. Transcutol® P (TC), polyethylene glycol 200 (PEG 200) and polyethylene glycol 400 (PEG 400) were used as single solvent systems. Binary solvent systems were done using binary mixtures of Transcutol® P and water at three different ratios (20, 40 and 60%). The flux (J) of domperidone from different solvent systems through both models showed the same system rank where 60% TC > 40% TC> TC > PEG 200> PEG 400> 20% TC. By plotting the values of flux (J) and permeability coefficient (k_p) of domperidone form different system in porcine buccal model against tissue culture model showed a correlation coefficient (r^2) more than 0.8. The study opens the door for more trials with different model drugs to establish the correlation.

Assessing buccal delivery was previously tested using porcine buccal model due to its similarity to human buccal mucosa. Recently, tissue cultures from the buccal mucosa of healthy human volunteers have been used in assessing drug delivery through buccal mucosa. The aim of this study is to find a correlation in the permeation parameters between the two models. The study was based on permeation studies

of domperidone (as model drug) through both models from single and binary solvent systems using Franz diffusion cells. Transcutol® P (TC), polyethylene glycol 200 (PEG 200) and polyethylene glycol 400 (PEG 400) were used as single solvent systems. Binary solvent systems were done using binary mixtures of Transcutol® P and water at three different ratios (20, 40 and 60%). The flux (J) of domperidone from different solvent systems through both models showed the same system rank where 60% TC > 40% TC> TC > PEG 200> PEG 400> 20% TC. By plotting the values of flux (*J*) and permeability coefficient (k_p) of domperidone form different system in porcine buccal model against tissue culture model showed a correlation coefficient (r^2) more than 0.8. The study opens the door for more trials with different model drugs to establish the correlation.

Assessing buccal delivery was previously tested using porcine buccal model due to its similarity to human buccal mucosa. Recently, tissue cultures from the buccal mucosa of healthy human volunteers have been used in assessing drug delivery through buccal mucosa. The aim of this study is to find a correlation in the permeation parameters between the two models. The study was based on permeation studies of domperidone (as model drug) through both models from single and binary solvent systems using Franz diffusion cells. Transcutol® P (TC), polyethylene glycol 200 (PEG 200) and polyethylene glycol 400 (PEG 400) were used as single solvent systems. Binary solvent systems were done using binary mixtures of Transcutol® P and water at three different ratios (20, 40 and 60%). The flux (J) of domperidone from

different solvent systems through both models showed the same system rank where 60% TC > 40% TC> TC > PEG 200> PEG 400> 20% TC. By plotting the values of flux (*J*) and permeability coefficient (k_p) of domperidone form different system in porcine buccal model against tissue culture model showed a correlation coefficient (r^2) more than 0.8. The study opens the door for more trials with different model drugs to establish the correlation.

IV- Effect of cyclodextrins on the solubility and permeability of mosapride citrate:

The aim of this work was to investigate the inclusion complexation between mosapride citrate (a sparingly soluble gastrointestinal prokinetic agent), and SBE7 β-cyclodextrin (SBE7 β-CD) in comparison with the natural β-cyclodextrin (β-CD) in order to improve the solubility and the dissolution rate of the drug in an attempt to enhance its bioavailability. The phase solubility profiles indicated that drug solubility increases linearly as a function of CD concentrations. The complexation efficiency values (CE) of SBE7 β-CD was higher than that for β-CD reflecting the higher solubilizing power of the SBE7 β-CD towards the drug. Solid binary systems of mosapride citrate with CDs were prepared by physical mixing, kneading and freeze-drying techniques at molar ratio of 1:1(drug to CD). Physicochemical characterization of the prepared systems was studied using differential scanning calorimetry, X-ray diffractometry, and Fourier-transform infrared spectroscopy. Permeation studies have been conducted using saturated solution on mosapride inclusion complexes with β-CD and

SBE7 β-CD prepared by freeze drying. The results showed the formation of true inclusion complexes between the drug and both SBE7 β-CD and β-CD using the freeze-drying and kneading methods. Amorphous drug was detectable to large extent in inclusion complexes prepared using the freeze-drying. The dissolution of different inclusion complexes was carried out in simulated saliva solution (pH 6.8) to determine the most appropriate CD type and preparation technique to prepare inclusion complexes. Irrespective of the preparation technique, the systems prepared using SBE7 β-CD yielded better performance than the corresponding ones prepared using β-CD. In addition, the freeze-drying technique showed superior dissolution enhancement than other methods especially when combined with the SBE7 β-CD. In case of permeation studies, inclusion complex of mosapride citrate with β-CD achieved the highest flux values, higher than the flux values recorded in case of complex with SBE7 β-CD. This could be attributed to the fact that complex with β-CD deliver more free drug on the surface of the biological barrier than the more stable complex of SBE7 β-CD. These findings show that increasing drug solubility and dissolution using cyclodextrins does not always results in increasing the drug permeability through mucosal barriers.