SUMMARY AND CONCLUSIONS

Formulations research and development scientists design suitable and appropriate dosage forms for pharmaceutical active ingredients in order to achieve the best therapeutic efficacy in the human body. To formulate the dosage from, various materials other than the active ingredient, called excipients are necessary to fulfill the desired characteristics of the final product.

Awareness of properties and the roles of natural polymers as excipients in the development of versatile drug delivery systems have been increasing. This is because, these substances are abundant, non-toxic, economical and the development or synthesis of entirely new excipients is cumbersome, time consuming, involving tedious procedures and highly expensive. The main drawbacks of natural polymers are source variation, batch-to-batch variation, microbial contamination, purity etc. However, many natural polymers are yet to be exploited for their useful properties to compensate the emerging requirements.

Okra pods are fruits of the plant *Abelmoschus esculentus* L. moench, family *Malvaceae*. Okra gum, which is a natural polymer, has advantage over synthetic and semi-synthetic polymers, in that it is cheap and easily available, non-irritant, biodegradable, biocompatible, and eco-friendly. Okra gum has been investigated as a binding agent in tablet dosage forms, and has been shown to produce tablets with good hardness, friability and drug release profiles. The indigenous pharmaceutical manufacturers should therefore exploit this economic source of excellent pharmaceutical excipient that has been studied. Hence, the present work is undertaken to evaluate the properties and the applicability of Okra gum in the design of GRDDS.

In the present investigation the physico chemical, microbial and rheological properties of Okra gum powder were evaluated. Further Okra gum was subjected to accelerated
stability studies according to ICH guidelines. Physico chemical properties like particle size distribution, surface characteristics, bulk density, tapped density, compressibility, flow properties, moisture content, pH, volatile acidity, swelling and water absorption properties are carried out. DSC and Infrared spectroscopy are performed on Okra gum powder. To test the effect of region of collection and season on the above properties of Okra gum, samples were collected at different regions and seasons were evaluated.

The bulk density and compressibility index of Okra gum were 0.632 gm/cc and 10.45 respectively. The values of bulk density and compressibility index indicated that the Okra gum powder has good flow properties and compressibility. The static angle of repose value for Okra gum was $28^\circ.09$ conforming good flow properties. Moisture content of Okra gum was 14.96%.

The swelling index of Okra gum was 120%. High value of swelling index revealed the high swelling ability of Okra gum. The swelling ability of any polysaccharide depends upon its water retention capacity (or) water absorption capacity. The water absorption capacity of Okra gum was 19 ml/g.

The pH of the 1% w/v Okra gum solution was 4.8 indicating the gum is acidic in nature. Acidic nature of Okra gum may be due to the presence of carboxyl groups, which is confirmed by the determination of volatile acidity of Okra gum. The volatile acidity of Okra gum was 17.2%

Okra gum powder exhibited broad endothermic peak at 172°C. The principal absorption peaks of Okra gum at 1599 cm$^{-1}$ (ether group absorbance) 3453 cm$^{-1}$ (stretching of hydroxyl group of carboxylic acid) were observed. Rheological properties of Okra gum powder in various concentrations like 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0% w/v were evaluated,
showed that the Okra gum possess pseudo plasticity, obeys power law with correlation coefficient values ranging 98.8 to 99.6 and it should not have thixotropic phenomena.

The results of the analysis of the properties of the Okra gum for the different batches collected from three different regions and two seasons indicated that there was no significant difference between these samples indicating the uniformity in the properties of the gum irrespective of the source.

The results of accelerated stability studies on Okra gum powder showed that there was no significant difference between the initial and the samples withdrawn at different time intervals like 1, 2, 3 and 6 months. Very slight decrease in volatile acidity and corresponding increase in the pH values resulted in slight fluctuations in the viscosity of the aged samples. These studies proved that the Okra gum was stable over a long period of time.

The development of a successful GRDDS was strictly dependent on the selection of an appropriate carrier that was able to control the drug release. As Okra gum has good flow & compatability, high swelling index, lack of variations in properties of Okra gum due to source & time of collection and stability of Okra gum, the present investigation was aimed to evaluate Okra gum as a carrier in the design of GRDDS.

The applicability of any excipient can be suitably tested by formulating different dosage forms using suitable drugs. The formulated dosage forms are then evaluated for their physico-chemical properties, drug release studies comparing with Xanthan gum and then the promising formulation was subjected to in vivo evaluation. Therefore, to test the applicability of Okra gum in the design of Ofloxacin, Glipizide GRDDS tablets.

Gastric retention systems are such systems, which increase the gastric retention time of the dosage form at the stomach and upper parts of the small intestine and suitable for the
drugs having site-specific absorption from the above sites. The controlled release of the drug from these systems at the preferred absorption site optimizes delivery of the drug, maximizing its therapeutic benefits and reduces side effects by permitting a large portion of the drug to be absorbed before passing through the lower G.I. tract.

Ofloxacin is an oral fluoroquinolone antibacterial which acts by inhibiting the subunit of DNA gyrase (topoisomerase) which is essential in the reproduction of the bacterial DNA. As it is mainly absorbed at the stomach with short biological half life, there is a need for gastric retention systems for Ofloxacin to improve its bioavailability. There are very few reports on the formulation of gastric retention systems of Ofloxacin.

Glipizide is a Second generation sulfonylurea, pyrazine derivative, medium-to-long acting oral Antidiabetic Agent. As it is mainly absorbed at the stomach with short biological half life, there is a need for gastric retention systems for Glipizide to improve its bioavailability.

Hence, in the present investigation, GRDDS of Ofloxacin, Glipizide were developed with hydrophilic polymers like Xanthan gum, Okra gum to deliver the Ofloxacin and Glipizide at the stomach in a controlled manner to improve its bioavailability. The GRDDS were developed in the form of tablets comprises an effervescent agent, swellable polymer and optionally a binding agent.

The GRDDS prepared from these polymers were found to be of good quality fulfilling all the official and other requirements of compressed tablets. The effect of different formulation parameters such as concentrations of effervescent agent and viscosity of the polymer on floating properties and drug release kinetics were studied and optimized the formulations. The effervescent agent present in the system provided the buoyancy to the system. When comes in contact with water or gastric fluid, effervescent agent generates
carbon dioxide that gets entrapped within the hydrated gel matrix. The density of the dosage form decreases due to the entrapped gas. This produces an upward motion of the dosage form and maintains its buoyancy. The concentration of the effervescent agent greatly influenced the floating lag time. By increasing the concentration of effervescent agent, decreased lag times were obtained.

Effervescent agent played a major role in bringing up buoyancy, a significant change in the lag time was observed. All the optimized formulations were having a floating lag time of less than 30sec and floated up to more than 24 hrs (floating time). The GRDDS prepared from Xanthan gum lost the compactness after 4-6 hrs of in vitro dissolution rate studies. IR spectras clearly indicated that there is no interaction between Ofloxacin and the excipients used in the formulation of GRDDS. It was found that the drug release from the GRDDS mainly depended upon the concentration of polymer present in the GRDDS for both the polymers. By increasing the concentration of the polymer, decreased dissolution rates were obtained. The slow rate of polymer hydration and the presence of effervescent agent caused a burst release initially. Hence, all the GRDDS were formulated without addition of the loading dose. Although the release rate mainly depended on the proportion of the polymer, the entrapped gas within the hydro gel also influenced the rate of drug release from the GRDDS. By increasing the proportion of the effervescent agent, the porosity produced by the entrapped gas increased and dissolution rate was increased.

The dissolution data were fitted to five popular release models such as zero-order, first-order, diffusion, erosion and exponential equations to determine the release mechanism. The correlation coefficients of the slopes and slope values indicated that the release mechanism followed non-fickian diffusion with first order kinetics in case of EF6, GEF6. Where as in case of EFX6 and GEX6 the release mechanism followed non-fickian diffusion with zero order kinetics.
The promising formulations of GRDDS were selected on the basis of the release profile similar to the commercial extended release formulation. Similarity factor f2 was calculated for the EF6 and EFX6. It was found 85 and 69; similarly difference factor f1 was also calculated it was found to be 4 and 5. Where as the f2 and f1 factors for GEF6 and GEX6 were 84, 69 and 4, 5. From these f2 and f1 factors it was concluded that EF6 (Ofloxacin + Okra gum) and GEF6 (Glipizide + Okra gum) were selected for stability studies.

To these formulations stability studies were performed according to ICH guidelines. No visible physical changes were observed in the all formulations. Lag time and floating time have not been changed significantly. Ofloxacin, Glipizide release from GRDDS has not changed significantly after storage at various conditions. These formulations were used to perform an *in vivo* study.

In case of EF6, the mean peak plasma concentration of test (T) formulation $C_{\text{max}}$ 9112.8 ng/ml was gradually reached in 6 hr. In case of marketed formulation (R) the $C_{\text{max}}$ was 9221.3 ng/ml which was reached in 4 hr. The $C_{\text{max}}$ of the test formulation (T) was less when compared with reference (R) formulation. The increase in $T_{\text{max}}$ was clearly indicating the drug availability for prolonged period. The reference (R) formulation was rapidly absorbed and the $T_{\text{max}}$ reached in about 4 hr. After reaching the $T_{\text{max}}$ the drug starts elimination and the plasma concentration gradually decreased. In case of test (T) formulation the $T_{\text{max}}$ achieved slowly and the drug availability was found for long time. The $\text{AUC}_{0-t}$ of the reference (R) was found to be 41124 ng.min/ml. The increase in $\text{AUC}_{0-t}$ was observed in the test (T) formulation, which was around 52387.2 ng.min/ml. This clearly indicates the drug availability for long duration.

Decrease in elimination rate constant ($K_{\text{el}}$) from 0.215 hr$^{-1}$ (R) to 0.105 hr$^{-1}$ (T) indicates the slow release rate of the drug in the body. The plasma elimination half life
(t_{1/2}) of the reference (R) and test (T) formulations were 3.21 hr and 6.27 hr respectively, which were significantly different. Thus the prolonged t_{1/2} is another indication on the in vivo performance of the Ofloxacin floating tablets. There is a difference in T_{max} and C_{max} was observed when compared among individual subjects which may be due to the subjective variability. This was observed in both test and reference formulations. The overall C_{max}, T_{max}, AUC_{0-t}, K_{el} and t_{1/2} were completely different between both test and reference formulation. Therefore the prepared formulation was releasing the drug for a prolonged period of time.

Whereas in case of GEF6, the mean peak plasma concentration of test (T) formulation C_{max} 268.8 ng/ml was gradually reached in 8 hr. In case of marketed formulation (R) the C_{max} was 271.3 ng/ml which was reached in 7 hr. The C_{max} of the test formulation (T) was less when compared with reference (R) formulation. The increase in T_{max} was clearly indicating the drug availability for prolonged period. The reference (R) formulation reached the T_{max} in about 7 hr. After reaching the T_{max} the drug starts elimination and the plasma concentration gradually decreased. In case of test (T) formulation the T_{max} achieved slowly and the drug availability was found for long time. The AUC_{0-t}, of the reference (R) was found to be 2615.9 ng.min/ml. The increase in AUC_{0-t} was observed in the test (T) formulation, which was around 2662.3 ng.min/ml. This clearly indicates the drug availability for long duration.

Decrease in elimination rate constant (K_{el}) from 0.15 hr^{-1} (R) to 0.108 hr^{-1} (T) indicates the slow release rate of the drug in the body. The plasma elimination half life (t_{1/2}) of the reference (R) and test (T) formulations were 5.3 hr and 6.3 hr respectively, which were significantly different. Thus the prolonged t_{1/2} is another indication on the in vivo performance of the Glipizide floating tablets. There is a difference in T_{max} and
$C_{\text{max}}$ was observed when compared among individual subjects which may be due to the subjective variability. This was observed in both test and reference formulations. The overall $C_{\text{max}}$, $T_{\text{max}}$, AUC$_{0-t}$, $K_e$ and $t_{1/2}$ were completely different between both test and reference formulation. Therefore the prepared formulation was releasing the drug for a prolonged period of time.

From the results discussed above it was found that the in house formulation prepared with Okra gum had shown good in vivo properties and in order to find the type of correlation between in vitro and in vivo, graphs were plotted between cumulative percent drug dissolved and cumulative fraction of drug absorbed. Significant level of correlation was observed. Good quality of level A correlation has been established for both EF6 and GEF6. Thus the formulation has good potential to liberate Ofloxacin, Glipizide following non-fickian diffusion mechanism having good degree of in vitro-in vivo correlation.

The results of the present study thus clearly indicated that the Okra gum, a novel polysaccharide, could efficiently be used as a sustained release excipient.

The present investigation provides a novel slow release excipient, Okra gum, which provides a desired slow release profile for a wide variety of drugs. Thus once the excipient is admixed with an active medicament (and optional lubricant) in a ratio to the hydrophilic matrix in accordance with the present invention, the resulting mixture granulated or may be directly compressed into solid dosage forms.