Chapter 5

Summary
and
Conclusions
5. Summary and Conclusions
Pharmacists have made important contributions in the field of pharmacy from the time of the early apothecaries, like in discovering or isolating new therapeutic agents that are more potent and having minimum side effects, developing stable and efficacious dosage forms and formulations for new drugs, developing novel and patient convenient formulations for existing drugs and by developing analytical methods for standardization and quality control of active ingredients alone as well as in dosage forms. Drug delivery systems (DDS) that can precisely modify the release rates of drugs have had an enormous impact on the healthcare system. In recent years, extensive research work has been carried out in academics and industries, for the development of new drug delivery systems by formulation and development scientists.

5.1 Sustained release DS tablets containing dried mucilage of *Hibiscus rosasinensis* Linn:
Sustained drug delivery systems are becoming popular in pharmaceutical product development. The major benefits include improved patient compliance and decreased side effects. Many sustained drug delivery systems are available commercially with various degrees of sophistication, including multiparticulates and osmotic pumps. Hydrophilic matrix dosage forms are very popular for oral drug delivery. Generally they consist of a compressed blend of hydrophilic polymer and drug. Natural materials are relatively inexpensive in nature, non toxic and are easily available as compared to semi-synthetic polymers. They have been used by researchers for the development of modified release dosage forms. In present study, attempt was done to explore the potential use of mucilage extracted from *Hibiscus rosasinensis* Linn in developing sustained release tablets of DS.

- Optimum % yield of mucilage extracted from leaves of *Hibiscus rosasinensis* Linn was 15% i.e., when 12.5 g of leaves were taken.
- Acute Oral Toxicity Test shows that LD$_{50}$ dose for dried mucilage was found to be 3000 mg/kg and 1 / 10$^{th}$ dose of LD$_{50}$ i.e., 300 mg/kg was considered safe for use as the metabolic rate in animals is be 5 to 10 times more than the human individual.
- Swelling ratio of dried mucilage was 9, 10 and 9 in distilled water, simulated gastric fluid (0.1N HCl) and phosphate buffer (pH 6.8). It was concluded that
swelling of mucilage is pH independent and mucilage may be considered as non-ionic.

- The dried mucilage powder shows excellent flow property and compressibility and was sufficient to prepare for direct compression tabletting.
- DSC study confirms that there was a no drug-excipient interaction.
- A preliminary trial of dried mucilage with DS tablets shows that all drug release within 9 to 11 hr. It was concluded that mucilage has capacity to sustain the drug action.
- A $3^2$ factorial design was selected for the systematic study. DS tablets were prepared containing different amount of mucilage and diluents (hydrophobic – DCP and hydrophilic – lactose) via direct compression method. In first design, the amount of mucilage ($X_1$) and amount of DCP ($X_2$) were taken as independent variables and in second design, the amount of mucilage ($X_1$) and amount of lactose ($X_2$) were selected as independent variables, while time required for 80% drug dissolution ($t_{80}$) and percentage drug released in 60 min ($Y_{60}$) and 300 min ($Y_{300}$) were selected as dependent variables. Batch HD8 and HL6 was found to be fulfilling all selected criteria as well as sustained drug release for 12 hr. The \textit{in-vitro} dissolution profile was not significantly altered in different dissolution medium like distilled water and phosphate buffer pH 6.8. There was an insignificant difference in the release profile of market product and batch HD8 and HL6 as revealed by the student t-test. The results of F-statistics revealed that the drug release pattern for both batches HD8 and HL6, fitted well to the zero order model.
- Water uptake and mass loss study was carried out using matrix tablets of dried mucilage (without drug and diluents) and tablets containing dried mucilage, DS and diluents (Batch HD8 and HL6) at two different agitation speeds (50 and 100 rpm) in distilled water for 6 hr. As the time progress there was increase in water uptake by all batches, this may be due to hydrophilic nature of mucilage. Similarly, as the time increases there was increase in mass loss, this may be due to drug and mucilage dissolution over a period of time. There was no significant effect of agitation speed on water uptake while mass loss was significantly affected by agitation speeds of prepared tablets.
The results of radial and axial swelling study of batch HD8 and HL6 show good correlation between time and normalized volume (Q). It was concluded that dried mucilage swelled more axially than radially.

It was concluded with the help of F-statistics that tablets of both batches (Batch HD8 and HL6) are stable after stability study. There was an insignificant difference in in vitro release profile before and after stability.

The dried mucilage can be further explored as disintegrating agent, gelling agent and modified release dosage form.

5.2 Modified gellan gum as disintegrant in tablet formulation:

Despite increasing interest in controlled-release drug delivery systems, the most common tablets are those intended to be swallowed whole and to disintegrate and release their medicaments rapidly in the GIT. The proper choice of disintegrant and its consistency of performance are of critical importance to the formulation development of such tablets.

Disintegrating agents are useful for conventional tablets and super-disintegrants are useful for the preparation of fast release tablets, mouth dissolving tablets and other tablets.

Gellan gum - a bacterial polysaccharide, due to its good rheological characteristics, it has great commercial potential for food, pharmaceuticals, and particularly environmental bioremediation.

- Physical modification of gellan gum was carried out using microwave energy.
  In $3^2$ full factorial design two independent variables – amount of water ($X_1$) and time of exposure in microwave ($X_2$), were selected, while swelling in distilled water, HCl buffer and phosphate buffer, respectively, were taken as dependent variables. High level of $X_1$ (amount of water in mL) and $X_2$ (time of exposure in microwave) gives maximum swelling in all three media.

- Confirmation of physical modification of gellan gum was confirmed by DSC, X-ray and FT-IR study. There was no chemical change or degradation in MGG after microwave treatment.

- Physical modification was also confirmed by change in its various physicochemical parameters like swelling ratio, flow property and compressibility. There was increase in swelling property but there was a change in its viscosity. There was remarkable decreased in viscosity of MGG. It was concluded that
there was excellent swelling, superior flow property and compressibility of modified gellan gum and can be useful in tablet formulation.

- Preliminary batches of lactose and DCP were prepared. It was observed that on addition of MGG in to tablets, there was a more reduction in DT. It was concluded that tablets containing MGG and DCP shows faster disintegration as compared to MGG and lactose tablets. So, DCP was used as diluents for further tablet formulation. Acceptable hardness and friability was observed.
- It was concluded that MGG is not sensitive to glidant and lubricant. There was a no significant change in DT and other parameters.
- DS tablets containing MGG were prepared using $3^2$ factorial designs. Mode of addition of disintegrant ($X_1$) (intra-granular, extra-granular and intra plus extra granular in ratio of 1:1) and amount of disintegrant ($X_2$) were selected as independent variables, while DT and drug release in 2 & 5 min were selected as dependent variables. It was concluded that higher amount of disintegrant and intra-granular mode of addition of disintegrant gives best results. Optimized batch (Batch II) shows lesser DT and faster drug release in 2 & 5 min. Intra-granular addition of disintegrant gives complete break down of tablets in to finer particles and faster disintegration.
- To check versatility of MGG with hydrophobic drug, aceclofenac tablets were prepared. It was concluded that a faster disintegration of aceclofenac tablets was observed as compared to hydrophilic drug – DS.
- MGG was compared with well accepted super-disintegrant SSG. It was concluded that MGG shows better results as compared to SSG.
- Dissolution profile of optimized batch (Batch II) was compared with market preparation (Voveran-50 tablet). Batch II shows complete drug release within 15 min, while market preparation takes 30 min. It was concluded that batch II is superior to conventional market preparation due to quick disintegration and dissolution of MGG.
- Stability study of optimized batch (batch II) was carried out for three months in humidity oven at 40°C and 75% RH. It was concluded that DS tablets were not affected by such environmental conditions and are stable.
It was concluded from study that MGG may be a good substitute for SSG and other super-disintegrant. Further, research can be explored by treating material in spray dryer, fluidized bed dryer and freeze dryer.

5.3 Mucilage extracted from *Blepharis edulis* Pers as disintegrant in tablet formulation:

Natural excipients are very popular for oral drug delivery. They are inexpensive in nature, non-toxic and easily available. They have been used by researchers for the development of fast release and other tablets. In present study, attempt was done to explore potential use of mucilage extracted from *Blepharis edulis* Pers as a disintegrant for tablets.

- Total and acid insoluble ash values are within limit, as per Herbal Pharmacopoeia.
- Optimum % yield of mucilage extracted from seeds of *Blepharis edulis* Pers was 14% i.e., when 10 g of seeds were taken.
- Swelling ratio of dried mucilage was 19, 18 and 19 in distilled water, simulated gastric fluid (0.1N HCl) and phosphate buffer (pH 6.8). It was concluded that swelling of mucilage is pH independent and mucilage may be considered as non-ionic.
- The dried mucilage powder (extracted from seeds of *Blepharis edulis* Pers.) shows good flow property and compressibility as compared to starch.
- DSC study confirms that there was no drug-excipient interaction.
- Preliminary batches of lactose and DCP were prepared containing DM. It was observed that on addition of DM in to tablets, there was a more reduction in DT. It was concluded that tablets containing DM and DCP shows faster disintegration as compared to DM and lactose tablets.
- Lubricant and glidant sensitivity test was performed for dried mucilage. Effect of addition of Mg-stearate (lubricant) and Cab-O-Sil (glidant) to DS tablets was studied on parameters like crushing strength, friability and DT. Mixing time was 2 and 5 min. It was concluded that DM is not sensitive to addition of lubricant and glidant. There was an acceptable difference in crushing strength, friability and DT after addition of lubricant and glidant.
- DS tablets containing DM and starch were prepared via wet granulation. In these experiments three parameters were studied, (a) amount of disintegrant,
(b) order of addition of disintegrant (internal, external and internal + external in ratio of 1:1), and (c) type of filler (DCP and lactose), respectively, on parameters like DT, crushing strength and friability. It was concluded that as the concentration of DM increased, there was a decreased in DT. These results were similar with different type of filler like DCP and lactose. It was also concluded that when mode of addition of disintegrating agent was external, it shows excellent results as compared internal and internal + external mode of addition. Finally, CSFR/DT ratio was used for the assessment of the disintegrant activity of DS tablet. It was concluded from CSFT/DT ratio, that when amount of disintegrant was at 10% level, hydrophobic filler – DCP taken and mode of addition was external, shows best results.

- Dissolution profile of market formulation (Tablet Voveran-50) and optimized batch (AD7) was carried out in distilled water. It was observed that batch AD7 shows faster dissolution profile as compared to market formulation. This may be due to quick disintegration and dissolution capacity of DM.

- Stability study of optimized batch (batch AD7) was carried out at 40°C and 75% RH for three months in humidity oven. The result shows that tablets are stable after stability study.

This work has revealed that, the tested disintegrant (dried mucilage) in the DS tablets could be useful as alternative disintegrants for tablet formulations. So, dried mucilage from *Blepharis edulis* Pers may be a good substitute for starch in a compressed tablet as a disintegrant.