CHAPTER 6

SUMMARY AND CONCLUSION

Drug delivery systems play a pivotal role in the therapeutic efficacy of any drug therapy. This work was executed with an aim to prepare and evaluate a novel drug delivery system of a therapeutically effective and proven drug.

Migraine, an acute illness may be treated using different drugs. Among the migraine specific therapy, sumatriptan succinate is a widely used drug of the triptan category and is available as tablets, injection, and suppository and unidose nasal spray. These forms have certain disadvantages.

Therefore the objective in this work was to develop a new drug delivery system of sumatriptan succinate (SS) which can be administered through the intranasal route, particularly to target the olfactory region, to achieve rapid relief by fast onset of action; to increase bioavailability; to avoid the second dose administration.

The hydrophilic sumatriptan succinate may have low bioavailability when administered through the nose. But once in the systemic circulation, hydrophilicity was required for effective distribution. Therefore it was proposed to use SS but modify its absorption by preparing nanoparticles using suitable polymer to achieve the result.

The decision for preparing nanoparticles were based on literature reports that transport of small particles was better across the nasal mucosa and also there was nose–to–brain transport via the olfactory region. The other approaches to improve
bioavailability, to name a few were by inclusion of penetration enhancers, chemical enhancers, enzymatic inhibitors. But all these suffer from disadvantage. The other way was to design specific drug delivery systems like microparticulate systems which for example may prevent rapid mucociliary clearance from nasal cavity. The limitation of adding enhancers was that they may lead to undesirable physiological effect or irritate the nasal mucosa. Enzyme inhibitors may have the capacity to alter the common physiology of the nasal environment. The microparticulate systems offers versatility in terms of size, mucoadhesiveness, a wide variety of matrix materials and this confers flexibility to the formulator to select the dosage form in a way which satisfied the final requirements

The amount of drug reaching the site of action is often only a small fraction of the administered dose. Accumulation at non target sites may lead to adverse reactions and undesirable side effects. A way of modifying the original biodistribution of substances is to entrap them in submicroscopic drug carriers. Among such particles, polymeric nanoparticles are receiving great attention in the present research scenario.

Considering the above factors, it was decided to prepare nanoparticles containing sumatriptan succinate for intranasal drug delivery for migraine treatment.

Poly (lactide-co-glycolide) (PLGA) was the polymer selected, which has the advantage of high purity and reproducibility; biocompatibility and biodegradability properties. In particular PLGA has been approved for human use by the Food and Drug Administration of United States of America. Among the numerous varieties of PLGA copolymers (Lactide: Glycolide 50:50) available, Resomer series, manufactured by Boehringer Ingelheim, Germany, especially Resomer RG 502 H (RsG), with the free carboxyl end group which was used in this work. RsG was reported to have the following advantages.
• RsG incorporated quantitatively higher amount of hydrophilic substances. This has been reported with proteins as candidate substance.

This may be due to favorable interaction of the water soluble protein with the more hydrophilic polymer.

• Presence of free carboxyl group significantly increased the degradation of the polymer. These hydrophilic groups allow better penetration of water molecules into the polymer matrix enabling faster release of the incorporated drug.

• The free carboxyl groups may also enhance adsorption of proteins which could be the reason for immediate release.

• This polymer was reported to have biphasic release pattern. The release pattern showed initial burst release followed by slow release. This was also reported to have the maximum entrapment for hydrophilic drugs.

The work started with the preformulation, followed by different methods of preparation. The compatibility study observations showed that chemically SS remained unaffected by RsG. There are different storage conditions recommended by ICH, FDA for evaluating stability. Among those, the accelerated and intermediate conditions may not suit the stability of RsG due to its hygroscopicity. Therefore the conditions of 30 +/- 2°C and 60 +/- 5 % RH and the conditions for refrigeration, that is 5 +/-3°C were followed in this study. From the results, it was determined that stability is unaffected when storage condition was around 5 +/- 3°C. Another option was to freeze dry the final formulation.

The preparation of formulations were carried out by the three different methods, namely multiple emulsion-solvent evaporation, spray drying and
nanoprecipitation. Ratio of SS to RsG was adopted from previous literature reports and for each method of preparation, six different ratios were followed. A total of thirty-six (36) preparations were prepared by w/o/w method. The drawback of the multiple emulsion method was the leakage of the hydrophilic drug out of the polymer phase to the outer dispersion medium which was water. When organic solvents of low water solubility were used, polymer precipitation was slow leading to complete partitioning of the drug into the aqueous phase. But when a water miscible organic solvent was added to the organic phase of the system, higher drug loading has been reported. Therefore, the novelty introduced in the preparation method followed in this work, was using a combination of dichloromethane (DCM) and methanol (90:10), as solvent for RsG. This has not been reported in literature till date, for NPs preparation, using RsG and a hydrophilic drug. The success of the method followed in this work, has been proved by the evaluation test results. Different methods of harvesting, namely, centrifugation and membrane filtration, followed by rotary vacuum evaporation or lyophilization for drying. Harvesting of the particles was important because process efficiency was the parameter used for further selection.

After evaluating process efficiency, the samples were subjected to SS content determination. The further selection was based on the maximum SS content observed in each type of preparation. Based on SS content, few formulations were selected to evaluate SS loading and encapsulation efficiency. All the formulations evaluated for SS loading and encapsulation efficiency were subjected to SS release study. Biphasic release pattern were observed in few formulations. The formulation exhibiting initial burst release followed by slow, but extended release with maximum release after 2 h were selected. Diffusion study of the selected formulation was executed. The best formulation was selected for characterization.
Formulation FHCL- 4 (F-IV) performed as per requirements in all the evaluation tests hence was selected for further analysis. Histological study also showed that the formulation did not affect the nasal mucosa (porcine nasal mucosa) used in the diffusion study. The evaluation tests executed until now have proved that the preparation F-IV was suitable to achieve the aim of the work. Therefore, further evaluations were executed on F-IV only.

The surface morphology was studied by obtaining the SEM. The particles were spherical in shape and were in the nano size range. Analysis of the particle size showed that the size ranged from 50 nm to 900 nm. In this observation, the particles with highest distribution were in the range between 320 nm and 389 nm. This proved the size of the particles to be in the nanorange and the method adopted resulted in the formation of NPs.

The FT-IR spectral analysis and thermal analysis proved that chemically there was no interaction between SS and RsG polymer matrix. Therefore the therapeutic effect of SS may remain unaffected in F-IV.

Stability studies were executed on F-IV. It was proved that F-IV was stable when stored at recommended conditions.

After evaluating the pharmaceutical parameters, the ex-vivo, in situ and in – vivo evaluations were performed.

The nasal perfusion study was performed and from its results, it can be concluded that SS from reference and test (F-IV), has been absorbed through the nasal region of the test animals. The absorption was depended on the concentration administered and it increased with increase in SS concentration. This study was included to have an idea whether the NPs were able to cross the nasal barrier in
animals and that F-IV had been absorbed at a quantitatively higher concentration than
the reference standard.

Following the nasal perfusion test, to verify where exactly the SS has been
distributed, brain tissue sampling was followed. The olfactory lobes were selected
because theoretically, the concentration must be high in that region as the route of
administration was nasal. The result of this study unequivocally proved that SS has
been absorbed both from reference solution and from F-IV through the nose into the
brain tissue and group administered with F-IV showed higher amounts of SS to the
brain tissue (particularly the olfactory lobes).

This was followed by pharmacokinetic study, to evaluate the bioavailability.
In this work, rabbits were used as models. The data were analyzed by using the pK
summit solutions. The pharmacokinetic analysis proved the faster, quantitatively
better action of F-IV NPs.

Pharmacodynamic study was executed to ascertain the results observed in the
pharmacokinetic test and to evaluate the therapeutic effect of the dosage form which
had been characterized. This study showed that SS was effective when administered
nasally but it takes longer time for onset of action and F-IV showed faster onset of
action. The observed values, showed significant difference (p<0.001), and proved that
the treatment with F-IV, which contains NPs of SS was effective and that their action
started rapidly on the animals. Two different tests were executed and both confirmed
the F-IV [NPs of SS], was absorbed faster, released SS faster and provided faster
relief from the hyperalgesia which simulates the migraine pain.
To conclude,

- Nanoparticles of sumatriptan succinate may be successfully prepared by multiple emulsion solvent evaporation method.

- Evaluation of the NPs of SS by *in–vitro, ex-vivo, in situ and in-vivo* methods proved the fast onset of action in animal models used.