CHAPTER - 8

SUMMARY, CONCLUSION AND RECOMMENDATIONS

Design of controlled release drug delivery systems for highly soluble drugs is challenging to pharmaceutical scientists. Various techniques have been proposed in the design of controlled release systems of these moites. Matrix tablets have gained the popularity in the designing of controlled drug delivery systems. But it is difficult to control the release of high soluble drugs by simple matrix system. Hence in the present work it is planned to design matrix tablets by using natural polymer (i.e. Guar gum), synthetic polymers (i.e. HPMC K100 M, HPC HF, Eudragit RSPO & Eudragit RLPO) alone and in combination for the controlling drug release.

Alfuzosin is an antagonist for 1-adrenergic receptors in the lower urinary tract, which is used for the treatment of BPH.

Citicoline is used for the treatment of ischemic stroke and head trauma. Controlled release systems for these selected drugs to improve the efficacy, reduces the frequency of administration and also reduces the toxicity and adverse effects.

8.1 ALFUZOSIN EXTENDED RELEASE TABLET

Standard calibration cure of Alfuzosin was constructed in 0.01N HCl and the linearity of the standard curve was good with correlation coefficient 1.000.

Solubility study indicated that the Alfuzosin is highly soluble in 0.01N HCl (192 mg/mL) than other media like 4.5 Acetate buffer (172
mg/mL), 6.8 phosphate buffer (159mg/mL), pH10 phosphate buffer (123 mg/mL) and Purified water (123mg/mL). Therefore Alfuzosin is considered a highly soluble drug according biopharmaceutical classification system.

The preformulation studies for the selection of suitable polymers has performed by DSC & FT-IR. The endothermic peaks in differential scanning calorimetry scan of Alfuzosin with hydroxypropylmethyl Cellulose, (HPMC K100M), Guar gum 8000cP, Eudragit RLPO shows with the melting range of the pure drug. This indicates there is no interaction between the selected polymers and drug substance.

FTIR characteristic peaks between the drug substance and selected polymers (i.e. Guar gum 8000 cP, HPMCK100M, Eudragit RLPO) showed that no interaction between the selected polymers and drug substance.

The preparation of matrix tablets was planned with wet granulation method. Bulk properties like Carr’s index, Hausner’s ratio and angle of repose of the prepared granule were in the range of 21.13 – 33.60%, 1.267 – 1.506 and 41.8° – 56.7° respectively. The results indicated poor flow but the finalized batch ALF/10 was showed good flow properties15.28%, 1.180 and 33.6 ° for Carr’s index, Hausner’s ratio and angle of repose respectively.

The Alfuzosin extended release tablets are compressed with 8.8 mm round punch. The tablets were prepared with different concentration of Eudragit RLPO, Guar gum and HPMC K100 M alone
and the tablets were prepared with combination of Guar gum, HPMC K100M. The results showed good physical characters such as hardness (9-12.2 kp), thickness, average weight, weight variation and friability are comply as per the pharmacopeial standards.

The drug content of the prepared formulations were in the range of (99.2 % -100.1 %) and were per the pharmacopeial limits.

Alfuzosin extended release tablets are prepared B.No: ALF/01 with (Eudragit RLPO - 40 % w/w), B.No: ALF/02, ALF/03 & ALF/04 with (Guar gum8000cP - 13.33, 26.67 & 60.00 % w/w) and B.No: ALF/05, ALF/06 with (HPMC K100M - 33.33, 50.00 % w/w) alone with different concentration were shows the in-vitro drug release 99.80 % at 3 hr., 98.20% at 3 hr., 99.20% at 6 hr. and 99.10% at 20 hr. and 96.20% at 6 hr, 95.40% at 12 hr. respectively. These results were showed when these polymers used alone unable to control the drug release.

By using the combination of HPMC K100M & Guar gum8000cP polymers (B. No: ALF/07, 08, 09, 10, 11 & 12) with different concentration are used in the preparation of Alfuzosin extended release tablets were showed the different in-vitro drug release profile over extended period of time. (i.e. 20 hr.) among various formulations B.No: ALF/10 (HPMC K100M & Guar gum 8000cP -31.42 &11.42 % w/w) showed better release (i.e. 91.20% at 20 hr) hence this formulation was compared with marketed formulation (UROXATRAL Lot.No: XG33) and the f1 & f2 values are 1.20 &72.05 respectively.
The drug release from the prepared tablets follows first order kinetics by diffusion.

The stability studies of B. No: ALF/10 showed there is no significant difference between the initial and final results with respect to the physical and chemical stability.

The selected formulation B. No: ALF/10 further in-vivo studied was performed in the health rabbits. The study was approved by the Institute Animal Ethical Committee (IAEC) with 1243/BC/08/ CPCSEA

The plasma samples were collected after administration of dosage form over a period of 48 hr, the pharmacokinetic data was estimated by non-compartmental method using WinNonlin version 5.1 (Pharsight Corporation, Mountain View, CA).

The overall pharmacokinetic parameters i.e. Cmax, Tmax, AUC0-t, AUC0- INF, Kel and elimination half-life of the reference product (Uroxatral) (2.197µg/mL, 6hr, 33.64µg.hr/mL, 35.852 µg.hr/mL, 0.069h⁻¹ & 11.86hr respectively) and test formulation (ALF/10)(i.e 2.140µg/mL, 6.667hr, 34.619µg.hr/mL, 37.602µg.hr/mL, 0.048h⁻¹ & 14.941hr respectively). These results showed that B.No: ALF/10 was in comparison with reference product.

The results showed that no significant difference in pharmacokinetic parameters between test and reference product. Hence the further B. No: ALF/10 is comparable with reference product.
8.2 CITICOLINE CONTROLLED RELEASE TABLETS

Standard calibration cure of citicoline was prepared in 6.8 phosphate buffer and the linearity of the standard curve was good with correlation coefficient 1.000.

Solubility study indicates that the citicoline was freely soluble in the pH range 1-7. (i.e 0.1N HCl 100 mg/mL, 4.5 Acetate buffer 100 mg/mL, 6.8 phosphate buffer 100 mg/mL and Purified water 100 mg/mL. Therefore Citicoline is considered a highly soluble drug according biopharmaceutical classification system.

The preformulation studies for the selection of suitable polymers has performed by DSC & FT-IR. The exothermic peaks in differential scanning calorimetry scan of citicoline with hydroxypropylmethyl Cellulose, (HPMC K100M), Hydroxypropyl Cellulose (HPC HF), Eudragit RLPO and Eudragit RSPO shows with the melting range of the pure drug. This indicates there is no interaction between the selected polymers and drug substance.

FT-IR characteristic peaks between the citicoline and selected polymers (i.e. HPMC K100M, HPC HF, Eudragit RLPO & Eudragit RSPO) shows that no major change peaks between the mixtures of drug – polymers.

The preparation of controlled tablets was planned with non-aqueous granulation method. The granules are evaluated for their bulk properties by using compressibility index, Hausner’s ratio and angle of repose 12.40% – 36.60 %, 1.14 – 1.57 and 31.6° – 56.5°.
respectively. The bulk properties of B. No: CTC/14 was showed flow properties. (20.80 %, 1.260 and 37.20° respectively).

The results clearly indicate that the prepared blends have fair flowability and compressibility.

The preparation of controlled tablets was planned with non–aqueous wet granulation method. The controlled release tablets were compressed with 22 x 10 mm & 20 x 10 mm oval shape punches (i.e. based on tablet weight). The tablets were prepared with different concentration of HPMC K100M, HPC HF, Eudragit RLPO and Eudragit RSPO alone and then all batches were coated with Eudragit RLPO by non-aqueous coating process; these core and coated tablets were showed good physical parameters as per the pharmacopeial standards.

The drug content of the all prepared formulations was found within the pharmacopeia limits. (99.1 – 100.8 %). Citicoline controlled release coated tablets were prepared with B. No: CTC/01, CTC/02, CTC/03 & CTC/04 (HPMC K100M-7.8, 12.5, 21.12 & 28.48%w/w) and B. No: CTC/05, CTC/06, CTC/07 & CTC/08 (HPC HF– 7.8, 12.5, 21.12 & 28.48% w/w) alone with different concentration were showed the drug release 85.6% at 3 hr., 80.50% at 3 hr., 75.50% at 3 hr. and 99.10% at 20 hr. and 96.20% at 6 hr, 95.40% at 12 hr. respectively. These results were showed that high amount of polymers are required to retard the drug release rate and also increase the size of the tablet respectively, which was difficult to swallow the patient.
The coated tablets are prepared B.No: CTC/09, CTC/10, CTC/11 and CTC/12 (Eudragit RLPO – 7.8 %, 12.5 %, 21.12 % and 28.48 % w/w) are showed 50 % drug release within 1 hr. even at higher concentration, hence the eudragit RLPO unable to control the drug release.

The coated tablets are prepared B.No: CTC/13, CTC/14, CTC/15 and CTC/16 with (Eudragit RSPO – 7.8 %, 12.5 %, 21.12 % and 28.48 % w/w) are showed controlled the drug release over a period of 12Hr.

Among all prepared coated formulations B.No: CTC/14 (Eudragit RSPO -12.5 %w/w) showed better release hence this formulation was compared with marketed formulation (STROLIN- OD) the f1 & f2 values are 4.96 & 67.91 respectively.

The drug release from the prepared controlled matrix tablets follows first order kinetics by diffusion.

The stability studies of B.No: CTC/14 showed there is no significant difference between the initial and final results with respect to the physical and chemical stability.

The selected formulation B.No: CTC/14 further in–vivo studied was performed in the health rabbits. The study was approved by the Institute Animal Ethical Committee (IAEC) with 1243/ BC/08/ CPCSEA.

The plasma samples were collected after administration of dosage form over a period of 12hr, the pharmacokinetic data was estimated by non-compartmental method using WinNonlin version 5.1 (Pharsight Corporation, Mountain View, CA).
The overall pharmacokinetic parameters i.e. Cmax, Tmax, AUC Last, AUCINF _OBS, Kel and elimination half life of uridine (i.e. metabolite of citicoline) the pure drug (Reference) (6.392 µg/mL, 0.5 hrs, 29.70 µg.hr/mL, 31.480 µg.hr/mL, 0.30h⁻¹ and 2.343hrs respectively) and test formulation (T) (i.e. 4.493µg/mL, 3.5hrs, 39.40 µg.hr/mL, 41.37 µg.hr/mL, 0.38 h⁻¹ and 1.851hrs respectively). These results showed that test formulation(T) having controlled release property showed over an extended period of time.

8.3 CONCLUSION

The present study clearly indicated the usefulness of matrix tablets contains combination of polymers could control the release of highly soluble drugs like alfuzosin and citicoline. The drug release in case of alfuzosin was extended over a period of 20 hrs. The drug release in case of citicoline over a period of 12hrs. The polymer are used in the present study is biocompatible. This study can be scaled up for commercial exploitation of these polymers combination in the development of controlled released drug delivery systems.

The present research work is useful for the pharmaceutical industry in terms of simple technology, easy to manufacture, time saving, finally less cost of the product development can be achieved.

8.4 RECOMMENDATIONS FOR ALFUZOSIN EXTENDED RELEASE TABLETS

The present research work was a adequate study in development and evaluation of Alfuzosin monolithic extended release
matrix tablets by using the combination of natural (i.e. Guar gum 8000cP) and synthetic polymers (i.e. Hydroxypropylmethyl cellulose) (HPMC K100M) to control the drug release over an extended period of time.

In further the work can be extended as:

- To establish the validation of mixing time at dry mix stage, granulation fluid qty, total granulation time, drying time, blending time & speed and compression parameters (i.e. Low speed, optimum speed & High speed, Low & High thickness of tablets and hopper studies at scale-up batch stage.

- Further detailed long term stability studies to be performed on scale-up batches to decide the shelf-life and storage conditions of the finished product.

- To establish in vitro in vivo correlation to guarantee the efficacy and bioavailability of extended release tablets.

- Further detailed in vivo bioequivalence studies to be performed on healthy human volunteers.

8.5 RECOMMENDATIONS FOR CITICOLINE CONTROLLED RELEASE TABLETS

The present research work was a satisfactory study in development and evaluation of citicoline controlled release matrix tablets by using the hydrophobic polymes of Eudragit RSPO and Eudragit RLPO to control the drug release over an extended period of time.
In further the work can be extended as:

- Further to establish the Process validation data on larger batch sizes.
- Further to establish the expiry date and storage conditions of the controlled release tablets.
- To establish in vitro in vivo correlation to guarantee the efficacy and bioavailability of controlled release tablets.
- Further detailed in vivo bioequivalence studies to be performed on healthy human volunteers.