CHAPTER 9

SUMMARY & CONCLUSIONS

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The objective here was to provide an extended release pharmaceutical composition of lornoxicam and butorphanol tartrate, which upon ingestion results in blood plasma levels having pharmacological effect for an extended period of time_equivalent to the multiple dosing of the immediate release formulations. It is needed to produce a pharmaceutical composition which releases drugs in predetermined manner. The use of high viscosity grade hydrophilic and the hydrophobic polymers to produce extended or controlled release pharmaceutical composition is very well known. For extending the release, the tablet comprising the drug also comprises of high viscosity grade hydrophilic polymer. In some cases the core is coated with hydrophobic coating membrane with hydrophilic pore formers incorporated in it. On contact with gastric fluid, fluid enters the tablet core and results into the hydration of the polymer which also controls the release of the drug. In case of coated system fluid on contact with osmotically active core exerts osmotic pressure and because of positive pressure in the system drug gets release in constant fashion from the osmotic Control of the rate of release benefits therapy by producing constant blood plasma levels of the active ingredient and by decreasing the frequency of administration, thereby improving the patient compliance to the dosage regimen.

Butorphanol was developed as osmotic drug delivery system to have constant drug release irrespective of food effect, agitation intensity and pH. Lactose, mannitol and sodium chloride and combination thereof were verified as core components besides it was also considered that Butorphanol tartrate being water soluble salt it may exert some osmotic pressure. UV-Visible Spectrophotometric analytical method for characterization of drug for Assay (%) Content Uniformity, in different dissolution media was developed. And HPLC analytical methods for characterization of Controlled porosity osmotic pump of Butorphanol tartrate in different media and animal plasma was developed.

Drug excipient compatibility study was done at an early stage of proposed drug product development by mixing drug with Lactose and mannitol in Drug to Excipient ratio of 1:5 W/W and Other excipients in Drug to Excipient ratio of 5:1 proportion and exposed to 40°C /75 % RH temperatures for 4 weeks to accelerate drug degradation. The blend exposed to

stress conditions was compared with their respective initial blend stored at controlled condition by physical observation. The samples are then characterized for the drug content, which were determined quantitatively using analytical method. Selected excipients were compatible with Butorphanol tartrate and do not produce any potential degradation products. During differential scanning colorimetric (DSC) evaluation no specific interaction between the drug and excipients used in the formulation were observed.

For development of the formulation target release profile which can produce effective plasma concentration for extended period of time was predicted using Wagner nelson de-convolution.

Core tablets were prepared by wet granulation the powdered blend was characterized for Assay, Blend uniformity, LOD, Bulk Density, Tapped Density.

Granules were compressed on 8 Station rotary tablet compression machine from general machinery company. Compressed core was characterized for Description, Uniformity of Weight (mg), Hardness (kg/cm2), Friability (% wt loss), Thickness (mm), Diameter (mm), Disintegration Time (min.), % drug Dissolution, % drug Assay and % drug Content Uniformity. During core finalizing Lactose, mannitol and sodium chloride separately and in combination with each other in equal ratio were used as osmogen and its effect on drug release was determined keeping coating & compression parameters constant.

Compressed core were coated on 6" perforated coating machine. Cellulose Acetate 398-10 was used as coating polymer which will be forming semi-permeable membrane. PEG 400 was incorporated as water soluble plasticizer and D-sorbitol as pore forming agent. Water and acetone were used as a solvent. Solid content in the coating formula has immense impact on uniformity of coating. Some trial of coating was done on dummy tablet to have idea of solid content in the coating solution and based on literature after 4% solid content was confirmed.

Machine parameters like Fluid nozzle diameter (mm), Spray pan size (Inch), Baffles (Nos.), Inlet air CFM, Outlet air CFM, Inlet air temperature (°C), Out let air temperature (°C), Pre-warm tablet bed (°C), Tablet surface bed temp (°C) and Atomizing air pressure (kg/cm2) were fixed on the basis of previous experience and Gun-to-bed distance, Spray Rate / Peristaltic Pump RPM, Perforated Coating pan Speed, Tablet Surface bed Temperature,

Atomization air pressure, Spray rate and air volume for optimum spray pattern were fixed on dummy tablet. Effect of osmogen and combination thereof in the core on drug release, Effect of level of pore former in the coating membranes and Effect of coating thickness on drug release (Weight gain) was determined. Optimised formulation was characterized for Description, Uniformity of Weight (mg), Thickness (mm), Diameter (mm), Assay (%) Content Uniformity (%) and degradation. The stability studies were carried out in accordance with the ICH guidelines for stability. The samples were subjected to stability in HDPE bottles with induction seal. The samples were subjected to stability at 40° C/75 % RH (accelerated stability) for 1, 2, 3, 6months and at 25° C/60 % RH (controlled room temperature) at 3, 6, 9, 12months. The parameters studied are the drug content (Assay), average weight, dissolution studies, description and water by KF. During and after the completion of the stability studies, all the studied parameters like description, assay, water by KF, average weight were found to be within the predefined limits. It was also observed that the drug release studies showed no significant change in the dissolution (with respect to the initial dissolution). The dissolution studies were compared using the similarity factor (f2). The f2 values > 50 clearly indicate a similar dissolution profile as compared to the initial drug release. Surface electron microscopy of the exhausted cell after coating was done to confirm the drug release through pore formed through osmotic mechanism. In order to study the effect of alcohol on drug release or to verify weather alcohol leads to dose dumping 4 % V/V, 20 % V/V and 40 %V/V alcohol was added in the release media and drug release was verified against control (without alcohol).

Mini tab dose proportionate formulation with similarity factor 89.01 with optimised formula made and the pharmacokinetic parameters verified after oral delivery in rat model with N = 12 Wistar rat weighing between **250-300 gm** were selected for PK studies. The extended release 510 mcg formulation and immediate release solution 170 mcg triplicate at of 0 hr, 9 hr and 17 Hr administration of Butorphanol Tartrate were evaluated for similarity in pharmacokinetic studies in rat for 48 hrs after oral administration. Pharmacokinetic parameters lice C_{max}, T_{max}, AUC (t) and AUC $_{0->inf}$ were determined and compared by ratio of % ref, Lower and higher confidence interval.

Non-Compartmental analysis of plasma data after extravascular input was evaluated using PK Solver Software Ver. 2.0 with Linear Trapezoidal method.

Significant improvement in plasma butorphanol concentration was observed following administration of extended release formulation 510 mcg formulation compared to typical saw tooth pattern was observed following immediate release solution 170 mcg triplicate at of 0 hr, 8.5 hr and 17 Hr administration of Butorphanol Tartrate.

The major problem associated with the formulation and effectiveness of the lornoxicam is its variable oral absorption due to insufficient aqueous solubility at gastrointestinal pH, thus making solubility the rate-determining step in the gastric absorption to solve this issue micronized lornoxicam was used and pH modifier Meglumine and NaOH were added pH modifier and alkalizing agent in the lornocxicam formulation. The use of high viscosity grade hydrophilic and the hydrophobic polymers to produce extended or controlled release pharmaceutical composition is very well known and was used to have extended effect.

Lornoxicam was developed as oral matrix drug delivery system to have constant drug release. Reduce the dosing frequency and increase the patient compliance. UV-Visible Spectrophotometric analytical method for characterization of drug for Assay (%) Content Uniformity, in different dissolution media was developed. And HPLC analytical methods for characterization of oral matrix tablet of Lornoxicam in release media and animal plasma was developed.

Drug excipient compatibility study was done at an early stage of proposed drug product development by mixing drug with Excipient and exposed to 40°C /75 % RH temperatures for 4 weeks to accelerate drug degradation. The blend exposed to stress conditions was compared with their respective initial blend stored at controlled condition by physical observation. The samples are then characterized for the drug content, which were determined quantitatively using analytical method. Selected excipients were compatible with Lornoxicam and do not produce any potential degradation products. During differential scanning colorimetric (DSC) evaluation no specific interaction between the drug and excipients used in the formulation were observed.

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For that drug was dissolved in solution of NaOH & meglumine in water and using that solution as a for binder followed dry mix of Lactose Monihydrate & MCC in wruster coater. The above granules further mixed with extra granular matrix forming agent followed by addition of lubrication, antiadherant & glident.

Palm Glatt Wuruster coating machine was used for making granules. Machine parameters like Fluid nozzle (mm), Inlet air temperature (°C), Out let air temperature (°C), Product Temp (°C), Atomizing air pressure (kg/cm2), Inlet Opening ,Spray rate (g/min), Peristaltic Pump RPM, Purging Time were fixed on the basis of previous experience and Gun-to-bed distance, Spray Rate / Paristaltic Pump RPM, Perforated Coating pan Speed, Tablet Surface bed Temperature, Atomization air pressure, Spray rate and air volume for optimum spray pattern were fixed on dummy tablet. Optimised formulation was characterized for Description, Uniformity of Weight (mg), Thickness (mm), Diameter (mm), Assay (%) Content Uniformity (%) and Degradation. The stability studies were carried out in accordance with the ICH guidelines for stability. The samples were subjected to stability in HDPE bottles with

induction seal. The samples were subjected to stability at 40° C/75 % RH (accelerated stability) for 1, 2, 3, 6months and at 25° C/60 % RH (controlled room temperature) at 3, 6, 9, 12months. The parameters studied are the drug content (Assay), average weight, dissolution studies, description and water by KF. During and after the completion of the stability studies , all the studied parameters like description, assay, water by KF, average weight were found to be within the predefined limits. It was also observed that the drug release studies showed no significant change in the dissolution (with respect to the initial dissolution). The dissolution studies were compared using the similarity factor (f2). The f2 values > 50 clearly indicate a similar dissolution profile as compared to the initial drug release. Surface electron microscopy of the exhausted cell after coating was done to confirm the drug release through pore formed through osmotic mechanism. In order to study the effect of alcohol on drug release or to verify weather alcohol leads to dose dumping 4 % V/V, 20 % V/V and 40 %V/V alcohol was added in the release media and drug release was verified against control (without alcohol).

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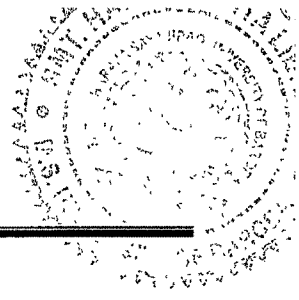


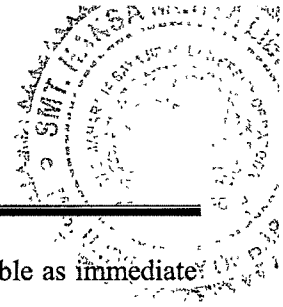
Conclusion

The scope of this development is to extended release formulation of analgesic drugs. Butorphanol tartrate and Lornoxicam are drugs with shorter half-life.

Butorphanol is not available in market as oral formulation due to higher first pass metabolism which is addressed by developing Controlled porosity osmotic Pump tablet. It is verified that excipients used for developing formulation do not have any incompatibility with the drug. Developed formulation releases the drug independent of pH of the release media and agitation intensity. Formulation is optimised for core composition, percentage weight gain during coating (thickness of the coating membrane) and concentration of pore-former in the coating. Surface characteristic observation of exhausted shell after coating through SEM analysis confirms formation of micropores in the coating during dissolution. Cellulose acetate serves as an excellent semipermeable membrane and drug release is driven by osmotic mechanism also confirmed though observation of CPOP tablet before and after dissolution. Formulation is subjected to ethanol induced dose dumping study which confirmed no possibility of alcohol induced dose dumping.

Prepared formulation is characterised for description, uniformity of weight (mg), thickness (mm), diameter (mm), assay (%) content uniformity (%), degradation and stability studies. Developed formulation is stable as per ICH guidelines at 40° C/75 % RH (accelerated stability) for 1, 2, 3, 6 months and at 25° C/60 % RH (controlled room temperature) at 3, 6, 9, 12 months.

Dose proportionate formulation with established similarity with developed formulation is proven to be bio equivalent in-vivo in rat model same one third dose of immediate relase solution give three time orally. Pharmacokinetic parameters like C_{max}, T_{max}, AUC (t) and AUC $_{0\text{->}\ inf}$ are determined and compared by ratio of % reference, Lower and higher confidence interval. Non-Compartmental analysis of plasma data after extravascular input is evaluated using PK Solver Software Ver. 2.0 with Linear Trapezoidal method confirming developed extended release formulation of butorphanol Tartrate.



Once daily formulation of lornoxicam is not available in market it is available as immediate release oral formulation twice daily. It is drug with shorter half life with very less solubility which is addressed by dissolving drug in solution of alkalizing agent sodium hydroxide and meglumine and using that solution as binding solution. It is verified that excipients used for developing formulation do not have any incompatibility with the drug. Formulation is subjected to ethanol induced dose dumping study which confirmed no possibility of alcohol induced dose dumping.

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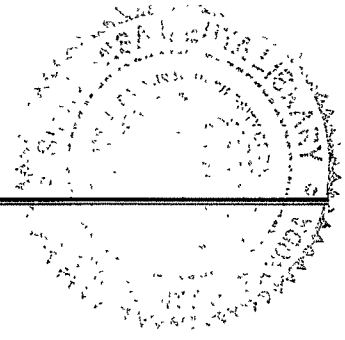

SUMMARY

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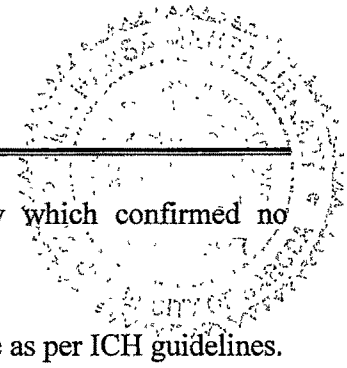

Formulation is subjected to ethanol induced dose dumping study which confirmed no possibility of alcohol induced dose dumping.

Prepared formulation is characterised. Developed formulation is stable as per ICH guidelines.

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