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In recent years, oral controlled release (CR) system is most adequate dosage form by the patients. Drugs having short biological half-life and poor water solubility are the suitable candidate for development of CR system. Research revealed that conventional matrix or reservoir type formulations exhibits bioavailability issues due to gastric pH variations and is also affected by the hydrodynamic conditions of the body. Introduction of Osmotically controlled oral drug delivery systems (OCDDS) overcome these issues. OCDDS exploit osmotic pressure for controlled delivery of active agent(s). Drug delivery from these systems is independent of the hydrodynamic conditions of the body and these systems can be utilized for systemic as well as targeted delivery of drugs. The release of drug(s) from osmotic systems follows zero order.

Flurbiprofen (FL) and Nicardipine Hydrochloride (NH) were selected as they have short half-life and requires more frequency of administration. Identification was done using FT-IR and DSC study and estimation of drug was done using UV visible spectrophotometer for both the drugs. These drugs fall under category of BCS class-II drugs so it requires solubility enhancement. Various formulation strategies are available to enhance the dissolution of sparingly soluble drugs. In order to enhance the dissolution of selected sparingly soluble drugs, inclusion complex approach was used. Instrumental analysis like FT-IR, DSC and XRD can help in identifying the physicochemical interaction as well as state of the drug in the formulation. These methods were utilized in present investigations to evaluate the formation of complex with β-CD. Inclusion complex based tablet formulations shows better drug release compared to conventional tablet formulations. In the present study, attempts were made to develop inclusion complex based osmotic pump tablets for selected drugs using various technologies which provides 15-20% drug release in first 120 min and more than 80% drug release in 540 min in zero order drug release pattern.

Controlled Porosity Osmotic Pump Tablets of Flurbiprofen

- Initially preliminary studies were carried out using different osmotic agent and wicking agent. Tablets were prepared by direct compression method and coated with a cellulose acetate as a semipermeable membrane containing sorbitol as a poreformer. From the results, Sodium chloride as an osmotic agent and sorbitol as a poreformer gives better drug release. So, they were selected and used in further formulation.
A Box-Behnken design was used to evaluate the effect of independent variables, percentage of cellulose acetate ($X_1$), % weight gain ($X_2$) and amount of osmotic agent ($X_3$) on %CDR at 120 min and 540 min. Various feasibility and grid searches were conducted to find the optimum parameters.

Batch FC19 which contained 28.57 mg of sodium chloride, 60.82% of cellulose acetate and 2.98% of weight gain has shown desired release criteria. The observed response was in good agreement with the predicted values.

Optimized formulations were also evaluated to study the effect of pH, agitational intensity and fitting of kinetic model was done. It was observed that drug release was independent of pH and hydrodynamic conditions of the body. The drug release kinetic of optimized formulation was well fitted with Zero order drug release model and also indicated diffusion type of drug release. The short term stability study of the CPOP tablet of FL results in satisfactory stability.

**Elementary Osmotic Pump Tablets of Flurbiprofen**

Another approach containing osmotic agent and orifice in place of poreforming agent in the semipermeable membrane to release the drug was adopted.

Preliminary investigations were made to identify the osmotic agent and osmopolymers that gives better drug release. Studies were also done using different size of orifice. Fructose and osmopolymer as an osmotic agent and osmopolymer were selected for optimization.

Process parameters were optimized and effect of variables like osmotic agent ($X_1$) and size of delivery orifice ($X_2$) on %CDR at 120min and 540min were systematically optimized using $3^2$ factorial design.

Characterization study demonstrated that as the concentration of osmotic agent increased, amount of drug release found to be increased.

The optimized batch was obtained based on overlay plot and it was further evaluated for the effect of pH and agitational intensity and found to be independent of these parameters. The drug release kinetics of optimized batch was fitted well with Zero order kinetic model and short term stability study provided satisfactory stability for 6 months storage at accelerated conditions.
Push Pull Osmotic Pump Tablets of Flurbiprofen

- Another formulation of FL i.e. PPOP tablets were formulated for the selection osmotic agent, different concentration as well as using various osmopolymers to push the drug compartment.

- Results of preliminary batches concluded that amount of osmotic agent ($X_1$), HPMC K-15M ($X_2$) and PEO-200K ($X_3$) had pronounced effect on drug release. %CDR at 120min and 540min were taken as responses for the optimization of variables using Box-Behnken design. This design was selected as it requires 13 runs compared to Full factorial design which needs 27 runs.

- The results were analyzed systematically by applying the ANOVA and generating the polynomial equations as well as 3D response surface plots and contour plot were generated for graphical interpretation and easy understanding of effect of critical factors on product characteristics.

Controlled Porosity Osmotic Pump Tablets of Nicardipine Hydrochloride

- CPOP tablets of NH were developed using different osmotic agents and different drug to osmotic agent ratio of selected osmotic agent in preliminary study. Mannitol containing 1:2 drug to polymer ratio was selected for further formulation of NH. Amount of poreformer also shown its influence on drug release. So, amount of osmotic agent and poreformer were taken as independent variables.

- Optimization of various factors was carried out using Central composite design using Design Expert software. Polynomial equation was generated that indicates the effect of variables on the %CDR. It was found that as the concentration of osmotic agent and poreformer increased, amount of drug release increased.

- Optimized batch revealed no effect of pH and agitational intensity on drug release, followed Zero order kinetics and found to be stable during short term stability studies.

Elementary Osmotic Pump Tablets of Nicardipine Hydrochloride

- EOP tablets are similar except delivery orifice is present in EOP in place of poreformer used in CPOP. Another formulation developed was EOP tablets and preliminary findings were done using different osmopolymers like PEO-200K, HPMC K100M and Sodium CMC and osmotic agents like potassium chloride, sodium chloride, mannitol and fructose. Fructose as an osmotic agent and PEO-200K were selected for further formulation
development. Batches having different size of delivery orifice tried. Amount of osmotic agent and size of delivery orifice shown major effect on drug release.

- A Central Composite Design was employed to optimize the independent variables using Design Expert software. ANOVA, contour and response surface plots generated using design expert software (8.0.5) has proved the effect of variables on drug release from the developed formulations of FL.
- Optimized batch was studied for various parameters and found satisfactory and within the acceptable limits.

**Push Pull Osmotic Pump Tablets of Nicardipine Hydrochloride**

- A novel approach for osmotic formulation of NH was used that contains bilayer tablet upper compartment having drug and lower compartment having osmopolymer that pushes the upper compartment and helps in releasing the drug. In preliminary study, different osmopolymers and osmotic agents were evaluated for better drug release. Various concentrations of osmopolymers and osmotic agents also studied and found that sodium chloride and PEO-7000K have major effect on drug release.
- $3^2$ full factorial design using amount of osmotic agent (sodium chloride, $X_1$) and osmopolymer (PEO-7000K, $X_2$) was applied and optimized for percentage cumulative drug at various time interval. Batch NP13 containing 60mg of osmotic agent and 75mg of osmopolymer delivered the drug in a zero order fashion upto 12hr. The formulation was found to be stable at accelerated condition.

The comparison of tablet made using CPOP, EOP and PPOP technologies were done to find the optimized formulation for selected drugs. In both the drugs, it was observed that all the three formulations could give desired drug release upto 12 hrs in zero order fashion. However, looking to the cost, expertise required, manufacturing consideration and process time, CPOP approached was considered as optimum and thus subjected to *in vivo* study. *In vivo* study revealed higher bioavailability of developed formulation of Flurbiprofen and Nicardipine Hydrochloride.

Compared to test formulations of FL and NH, Osmotic tablets of both drugs FL and NH formulations has shown an increase in the AUC 0-24 hr value for formulation, corresponding to a greater extent of oral absorption when compared with the drug alone. This increase in the AUC 0-24 hr may be due to a longer residence time of these formulations in the gastrointestinal tract, as was suggested by their larger MRT and Tmax values.