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A Review of Novel Drug Delivery Controlled Porosity Osmotic Pump Tablets Therapeutic Approach and Future Trend

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Abstract

The review work is comprised the enhancement of bioavailability and increase therapeutic efficacy. The porous osmotic pump tablets were designed using D-Optimal design and numerical optimization technique was applied to find out the best formulation. Another hand an osmotic pump (OP) were designed and evaluated with the aim to deliver drug in a controlled manner. Osmotic agent and pore former was considered as independent variables. Drug release rate at 2 h, 4 h, 8 h, 12 h, T50% and release exponent (n) were taken as responses. The increase in concentration of pore former and osmotic agent after a limit, changes the release was measured. The optimized formulation follows mechanism measured. The FT-IR and DSC studies revealed that no physicochemical interaction between excipients and drug. The influence of pH and agitation intensity on the release of drug was studied and the release mechanism was through osmosis. Stability studies revealed that optimized formulation was stable. The result of D- Optimal design and ANOVA studies reveals that osmotic agent and pore former have significant effect on the drug release up to 12 h. The observed independent variables were found to be very close to predicted values of most satisfactory formulation which demonstrates the feasibility.

Keywords: osmotic pump, pore former, bioavailability

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INTRODUCTION:

Oral ingestion is one of the oldest and most extensively used route of drug administration, providing a convenient method of effectively achieving both local and systemic effects. The drug release from oral controlled release dosage forms may be affected by pH, GI motility and presence of food in the GI tract. Drugs can be delivered in a controlled pattern over a long period of time by the process of osmosis. Drug delivery from this system is not influenced by the different physiological factors within the gut lumen and the release characteristics can be predicted easily from the known properties of the drug and the dosage form.[1]

The oral osmotic pump tablets have many advantages, such as reducing risk of adverse reactions, zero-order delivery rate, a high degree of *in vitro in vivo* correlation and improving patient compliance. [2]

Studies of the controlled release of drugs for their extended and safe use have recently become an important field of research.[3]

To maintain drug concentration within the therapeutic window the drug dose and dosing interval are optimized, thus ensuring efficacy while minimizing toxic effects. Oral controlled release system that provides greater effectiveness

in the treatment of chronic conditions, reduced side effects, and greater patient convenience due to simplified dosing schedule.[4]

An appropriately designed osmotically controlled oral drug delivery system (OCODDS) can be a major advance toward overcoming some of these problems. Drug delivery from these systems is not influenced by the different physiological factors within the gut lumen, and the release characteristics can be predicted easily from the known properties of the drug and the dosage form.[5]

Drug delivery from these systems is not influenced by the different physiological factors within the gut lumen, and the release characteristics can be predicted easily from the known properties of the drug and the dosage form. Osmotically controlled drug delivery systems deliver the drug in a large extent and the delivery nature is independent of the physiological factors of the gastrointestinal tract and these systems can be utilized for systemic as well as targeted delivery of drugs. Osmotically controlled oral drug delivery systems utilize osmotic pressure for controlled delivery of active agents. Among the controlled release devices, osmotically controlled hold a stable place because of its reliability to deliver the API at predetermined zero order rate for prolonged period of time so these are used as the standard dosage forms for the constant delivery of contents. [6]

Recently, osmotic tablets have been developed the delivery orifice is formed by the incorporation of a leachable component in the coating. Once the tablet comes in contact with the aqueous environment, the water- soluble component dissolves and an osmotic pumping system results. Subsequently, water diffuses into the core through the microporous membrane, setting up an osmotic gradient and thereby controlling the release of drug. Osmotic pressure is a colligative property, which depends on concentration of solute that contributes to osmotic pressure. Solutions of different concentrations having the same solute and solvent system exhibit an osmotic pressure proportional to their concentrations. Thus a constant osmotic pressure, and thereby a constant influx of water can be achieved by an osmotic delivery system that results in a constant zero order release rate of drug. The rate of drug release from osmotic pump depends on the drug solubility and the osmotic pressure of the core. Hence, these systems are suitable for delivery of drugs with moderate water solubility. The drug shows linear pharmacokinetics, is suitable for oral controlled release tablets and it would be advantageous to slow down its release in GI tract not only to prolong its therapeutic action but also minimize possible side effects of drug. [6,7]

FACTORS AFFECTING THE DESIGN OF OSMOTIC CONTROLLED DRUG DELIVERY SYSTEMS:

1. **Solubility:** The delivery rate of a drug from an osmotic pump depends to a large extent on the solubility of drug at saturation. Candidate drugs for osmotic delivery have water solubility in the different range. However, by modulating the solubility of these drugs within the core, effective release patterns may be obtained for the drugs, which might otherwise appear to be poor candidates for an OCODDS. Some of examples are co-compression of the drug with excipients, which modulate the solubility of the drug within the core.[8,9,10]

2. **Thickness:** Thickness of the core tablets and coated tablets were measured by using screw gauge. Ten tablets from each formulation were randomly selected and used. Thickness is expressed in millimeters.

3. **Hardness:** The hardness of the core tablets and coated tables were measured using the Pfizer hardness tester. Six tablets from each formulation were randomly selected and used. The average hardness and the standard deviation were calculated. It is expressed in Kg/cm^2.

4. **Friability:** Friability of the matrix tablets and core tablets of porous osmotic pump tablets were determined. 10 tablets were randomly selected, weighed and placed in the Roche Friabilator. The apparatus was rotated at 25 rpm for 4 min. After revolutions the tablets were dedusted and weighed again. The percentage friability was measured using the formula,

$$\% \text{ Friability} = \frac{\text{Initial wt. of tablets} - \text{Final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100$$

5. **Weight uniformity:** Ten tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated.[11]

6. **Size of delivery orifice**: Some of the methods to create a delivery orifice in the osmotic tablet coating are use of a mechanical dril, laser drilling, use of an apparatus with slidable punches, indentation that is not covered during the coating process, and use of leachable substances in the coating. The size of the delivery orifice must be smaller than the maximum size Amax to minimize the solute diffusion through the orifice. Also, it must be sufficiently large, above a minimum size a min, to minimize hydrostatic pressure inside the system that would affect the zero-order release rate. Large hydrostatic pressure can also lead to the deformation of the device, thereby resulting in unpredictable drug delivery.[12,13,14]

7. **Orifice size:** The orifice must be smaller than a maximum size to minimize drug delivery by diffusion through the orifice. Furthermore, the area must be sufficiently large, above a minimum size to minimize hydrostatic pressure buildup in the system. Therefore, the cross-sectional area of the orifice should be maintained between the minimum and maximum values. This technology is well established for producing sub-millimeter size hole in tablets. Use of leachable substances in the semipermeable coating: e.g. controlled porosity osmotic pump. [15]

8. **Osmotic pressure:** The osmotic pressure π directly affects the release rate. To achieve a zero-order release rate, it is essential to keep π constant by maintaining a saturated solute solution. In this case, other osmotic agents are added that enhance osmotic pressure. For example, addition of bicarbonate salt not only provides the necessary osmotic gradient but also prevents clogging of the orifice by precipitated drug through producing an effervescent action in acidic media. [15]

9. **Semipermeable membrane:** Since the semipermeable membrane is permeable to water and not to ions, the release rate is essentially independent of the pH of the environment. Additionally, the drug dissolution process takes place inside the delivery system, completely separated from the environment. [16,17]

10. **Osmotic agents:** Osmotic agents maintain a concentration gradient across the membrane. They also generate a driving force for the uptake of water and assist in maintaining drug uniformity in the hydrated formulation. Osmotic components usually are ionic compounds consisting of either inorganic salts or hydrophilic polymers. Osmotic agents can be any salt such as sodium chloride, potassium chloride, or sulfates of sodium or potassium and lithium.[18]

11. **Flux regulators:** Delivery systems can be designed to regulate the permeability of the fluid by incorporating flux regulating agents in the layer. Hydrophilic substances such as poly ethylene glycols (300 to 6000 Da), polyhydric alcohols, poly alkylene glycols, and the like improve the flux. [19]

Pore forming agent: These pore forming agents cause the formation of microporous membrane. The microporous wall may be formed in situ by a pore-former by its leaching during the operation of the system. The pore formers can be inorganic or organic and solid or liquid in nature. For example, alkaline metal salts such as sodium chloride, sodium bromide, potassium chloride, potassium sulphate, potassium phosphate etc polyols such as poly hydric alcohols and polyvinyl pyrrolidone can be used as pore forming agents. [20]

Coating solvent: Solvents suitable for making polymeric solution that is used for manufacturing the wall of the osmotic device include inert inorganic and organic solvents that do not adversely harm the core, wall and other

materials. The typical solvents include methylene chloride, acetone, methanol, ethanol, water etc. [20,21,22]

Plasticizer: Different types and amount of plasticizers used in coating membrane also have a significant importance in the formulation of osmotic systems. They can change visco-elastic behavior of polymers and these changes may affect the permeability of the polymeric films. Some of the plasticizers used are as: Diethyl tartarate or Diacetin- for more permeable film. [22]

TYPES OF OSMOTIC PUMPS:

1. Elementary osmotic pump (EOP):

2. Push pull osmotic pump (PPOP):

3. Osmotic pumps with non-expanding second chamber:

4. Controlled porosity osmotic pumps (CPOP):

5. Modified osmotic pump for insoluble drugs:

6. Modified osmotic pump for highly soluble drugs:

7. Osmo matrix system:

8. Osmotic pumps for two or more drugs:

9. Microbially activated colon targeted osmotic pump:

10. Floating osmotic drug delivery system (FODDS):

11. Osmotic system for controlled delivery of liquid drug:

PREPARATION OF OSMOTIC PUMP TABLET:

1. **Preparation of core tablets:** Core tablets of were prepared by wet granulation method. All the ingredients except lubrication and talc were accurately weighted and mixed in mortar with a pestle for 10 minutes to get the uniform mix. The dry blend was granulated with sufficient quantity of solution which was dissolved in alcohol. The powder mass was dried at 55-60 °C in hot air oven for 6 h and passed through sieve. The dried granules were mixed with lubrication and talc. The blended powder was compressed in to round tablets by using punch in Rimek mini press-I compression machine.

2. **Coating of the core tablets:** Coating was performed by using spray pan coating machine. The cellulose containing different levels of pore formers was used as coating solution. Total components in the coating solution. The coating conditions were as follows: pan, inch circular; speed of pan, rev./min; nozzle diameter, mm; spray rate, ml/min; spray pressure, lb/sq.in.; drying temperature, 55-60 °C. Weight gain of all the formulations was maintained to 3%[10].

EVALUATION OF POROUS OSMOTIC PUMP TABLETS

1. **Preformulation Study**

a) **Powder flow properties/Angle of repose:** The angle of repose of the mixture of the drug and excipients was determined by fixed funnel method. The values are used in the following equation to get the angle of repose. Tan θ = h/r Where, h, r and θ are the height, radius and angle of repose of the powder pile.

b) **Bulk density:** Accurately weighed 3 g of the sample was transferred to the measuring cylinder of bulk density apparatus. The apparatus was adjusted for 100 tapping and noted the final volume as tapped volume.

c) **Porosity:** Porosity of the powder was determined by using formula: Porosity = [(Vb – Vp)/ Vb] ×100. Where Vb is the bulk volume and Vp is the true volume

d) **Carr's index:** The Carr's index of the powder was determined by using formula: Carr's index (%) = [(TBD – LBD) × 100]/TBD

Where, TBD is the total bulk density and LBD is the loose bulk density.

2. **Determination of drug content:** Ten tablets were accurately weighed and powdered. A quantity of the powder equivalent to 100 mg of Diclofenac sodium was weighed accurately and extracted in 100 ml methanol by shaking for 20 min. After filtration through whatmann filter paper no.1 and sufficient dilution with methanol, samples were analyzed spectrophotometrically at 283 nm. Amount of drug present was determined from the calibration curve of Diclofenac sodium in methanol.

3. *In vitro* **dissolution studies:** Drug release studies were carried out using USP dissolution test apparatus (Apparatus I basket type). The dissolution medium was 900 ml of phosphate buffer pH 7.5. The release was performed at 37 ± 0.5°C, with a rotation speed of 100 rpm. 10 ml samples were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through whatmann filter paper and analyzed after appropriate dilution by UV spectrophotometer.

4. **In vivo** *studies: In vivo* studies were performed following the standard protocols in six healthy human volunteers of either sex weighing 55–75 kg and 24–29 years old in a cross-over design. Volunteers agreed in writing to participate in the study after being informed about the experimental protocol. All subjects were in good health according their medical history and complete physical examination. The volunteers neither smoked nor were on any kind of medication before or during the experiment. The experiment protocol was approved by the Ethical Committee, BHU, India.

5. **Curve fitting Analysis:** For the determination of the drug release kinetics from the porous osmotic pump tablet, the *in vitro* release data were analyzed by zero order, first order, Higuchi and Korsmeyer and Peppas equations.

a) **Zero order release kinetic:** To study the zero order release kinetics the release data was fitted into the following equation: $dQ/dt = K_0$ Where, 'Q' is the amount of drug release, 'K_0' is the zero order release rate constant and 't' is the release time. The graph is plotted percentage cumulative drug release (% CDR) verse time.

b) **First order release kinetic:** To study the first order release kinetics the release rate data are fitted into the following equation: $dQ/dt = K_1 Q$ Where, 'Q' is the fraction of drug release, 'K_1' is the first order release rate constant and 't' is the release time. The graph is plotted log % CDR remaining verse time.

c) **Higuchi release model:** To study the Higuchi release model the release rate data are fitted into the following equation: $Q = K_H t^{1/2}$ Where, 'Q' is the fraction of drug release, 'K_H' is the release rate constant and 't' is the release time. The graph is plotted % CDR verses square root of time.

d) **Korsmeyer and Peppas kinetics:** To study the Korsmeyer and Peppas release kinetics the release rate data are fitted in to following equation: $M_t/M_\infty = K_{KP} t^n$

Where, Mt/M∞ is the fraction of drug release, 'KKP' is the release rate constant and 't' is the release time and 'n' is the diffusion exponent related to mechanism of drug release. The graph is plotted log %CDR verses log time.

6. *Statistical analysis:* Experimental results were expressed as mean SD values. Student's *t* test was performed to determine the level of significance. Differences were considered to be statistically significant at $p < 0.05$.

7. **ANOVA:** In porous osmotic pump tablets the result of ANOVA demonstrate all the independent variables (Factors) were found to be significant for response. The linear models were found to be significant.

8. **Stability studies:** After the 6 month's storage of formulation OP7, values of all parameters like hardness, diameter, thickness, % drug content, friability were checked periodically and found to be almost similar to the initial values. The drug dissolution and diffusion profile were similar to the initial profile. There was not any significant change in any value and also no changes in the physical appearance. So it can be said that formulation is stable.

CONCLUSION

The observed independent variables were found to be very close to predicted values of optimized formulation which demonstrates the feasibility of the optimization procedure in successful development of porous osmotic pump tablets containing drug with using osmotic agent and pore former. Stability studies revealed that optimized formulation is stable. This study suggests that the OP tablets of could perform therapeutically much better than the commercial conventional tablets, as potential prolonged and controlled release dosage forms, which may lead to improved efficacy and better patient compliance.

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