Rationale for the Investigation

CHAPTER 3

RATIONALE FOR THE INVESTIGATION

Drug delivery systems consisting of a drug-containing core, coated with a semi-permeable membrane and with one or more delivery ports, have been previously developed and commercialized. The elementary osmotic pump is an example of such a delivery system with a laser drilled delivery port. Other formulations of the osmotic coatings include those that consist of dense membranes containing a water-soluble ingredient which is leached out of the membrane to form the delivery ports in situ. The asymmetric membrane coated tablets and capsules is also an example of a single core osmotic delivery system consisting of a drug-containing core surrounded by an asymmetric membrane. One of the advantages of the asymmetric membrane capsule is the higher rate of water influx, allowing the release of drugs with a lower osmotic pressure or lower solubility. In spite of this advantage, there are many instances where the solubility of the drug is too low to provide a reasonable driving force. In such situations, solubilizer for the drug are included in the core formulation. It is also possible that the drug is soluble and the water flux is too great to provide sustained release. In this case the core can include a component that suppresses the solubility of the active agent. In both the above-mentioned cases, the rate of release of the solubility-controlling component relative to the rate of drug release is important. If the solubility controlling component is depleted from the core of the osmotic device before all the drug is released, then control over the solubility of the drug is lost and the release rate may revert back to being too slow in the case of poorly soluble drugs or to being too fast in the case of highly water soluble drugs. Increasing the amount of excipient in the core so that it lasts longer can be considered but this approach is not practical because, depending on the solubility ratio of drug to excipient, it can require an unacceptably large quantity of the excipient. Two-compartment osmotic tablets
which contain an osmotic layer and an expandable layer are more complex but they can deliver either a solution or a suspension of drug.

In order to maintain the solubility modifying component in the core over the entire drug delivery duration, the component itself can be encapsulated along with the drug in a rate controlling membrane. By optimizing the rate of release of the solubility modifying agent into the osmotic core of a delivery device, it is possible to extend its availability in the core to provide an osmotic driving force or solubilization over the entire delivery period, so that the desired profile can be achieved for an active agent that has sub-optimal solubility characteristics. This strategy is illustrated in Figure 3.1.

Glipizide, an oral hypoglycemic agent, is one of the most commonly prescribed drugs for the treatment of patients with type II diabetes mellitus [4]. It is practically water-insoluble, but the absolute bioavailability is close to 1. Thus, it belongs to Class II of Biopharmaceutic Classification System (BCS). Glipizide has a relatively short elimination half-life (2–4 h), thereby requiring twice daily dosing in a large number of patients, which often leads to non-compliance. Thus, there is a strong clinical need and market potential for a dosage form that will deliver glipizide in a controlled manner to a patient needing this therapy, thereby resulting in a better patient compliance (Verma and Garg, 2004).

Drug substances with a poor aqueous solubility are released at very low rates. This limitation can be overcome for a drug such as glipizide, which has a pH-dependent solubility, by including a solubility modifying excipient in the core. In order to avoid depletion of the excipient from the core before complete drug release, the excipient can be encapsulated in a rate-controlling membrane (Thombre et al, 1999).
Hot melt extrusion (HME) offers several advantages over conventionally available pharmaceutical processing techniques including: (a) increased solubility and bioavailability of water insoluble compounds, (b) solvent free non ambient process, (c) economical process with reduced production time, fewer processing steps, and a continuous operation, (d) capabilities of sustained, modified and targeted release, (e) better content uniformity in extrudates, (f) no requirements on the compressibility of active ingredients, (g) uniform dispersion of fine particles, (h) reduced number of unit operations and production of a wide range of performance dosage forms.
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(Maniruzzaman M et al., 2012). The major advantage of HME is preparation of granules without the use of water. As the formulation contains water soluble excipients where polyethylene oxide is more prone to oxidation, it was decided to granulate the excipients using HME technique to prevent the granules from degradation.

On the basis of the above facts, this investigation was aimed at formulating tablets for osmotic release of glipizide by granulation through hot melt granulation and coating them with a semipermeable coat with cellulose acetate (rigid coat) by mixing with polyethylene glycol as pore performer (channelizer). Coating of the glipizide core tablets with a combination of cellulose acetate and polyethylene glycol can be hypothesized to release glipizide over an extended period of time by slowly releasing glipizide throughout the gastrointestinal tract. In addition, biodegradable nature of these polymers could be expected to ensure complete release of glipizide throughout the gastrointestinal tract.

The main objectives of this study are:

1. To screen few matrices for their effect on glipizide release rate.
2. To study the influence of sodium chloride as the osmotic agent to release the drug from the core.
3. To study the influence of sodium bicarbonate -- citric acid complex on glipizide release.
4. To study the in-vitro release of glipizide from formulated core matrices containing suitable concentration of cellulose acetate and ethyl cellulose in the coating membrane.
5. To study the in vitro release of glipizide from formulated osmotic systems.
6. To study the pharmacokinetics of glipizide and its hypoglycemic effect in appropriate animal model using optimized formulation.