



Formulation and Evaluation of Osmotic Pumps: An Overview

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Abstract

The tablets were prepared by wet granulation technique. Drug was uniformly mixed with mannitol and lactose in a high shear mixer granulator. The dry blend was granulated with povidone, which was dissolved in isopropyl alcohol. The mass was dried at 50°C and sized through American Society of Testing and Materials (ASTM) 20 mesh and mixed with talc and colloidal silicon dioxide. The granules were lubricated with magnesium stearate and compressed into round tablets with standard concave punches (diameter, 9.52 mm) using 27-station rotary compression machine.

Keywords: mannitol, wet granulation, compression machine, shear mixer.

Introduction

Osmotic systems utilize the principle of osmotic pressure for the delivery of drugs. Drug release from these systems is independent of pH and other physiological parameter to a large extent and it is possible to modulate the release characteristic by optimizing the properties of drug and system[1-2]. Pressure generated by the osmotic flow of water through a semi permeable membrane in to an aqueous compartment containing solute at higher concentration[3-4].

Basic Component of Osmotic Pumps[4]

Drugs ·Short biological half-life {2-6hr} ·highly potent drug ·required for prolonged treatment e.g. nifedipine, glipizide, verapamil.

A number of design options are available to control or modulate the drug release from a dosage form. Majority of per oral dosage form fall in the category of matrix, reservoir or osmotic system. In matrix system, the drug is embedded in polymer matrix and the release takes place by partitioning of drug into the polymer matrix and the release medium.

Osmotic agents Osmotic agents are essential ingredient of the osmotid formulation. They include inorganic salts and carbohydrates. Generally combinations of osmotic agents are used

to achieve optimum osmotic pressure inside the system.

Semi permeable membrane Cellulose acetate is commonly used for semi permeable membrane. It is available in different acetyl content like 32%, 38% are widely used.

Formulation[1] General Considerations and material used. Semi permeable membrane, Hydrophilic and hydrophobic polymer, Wicking agent, solubilizing agent. Osmogens, Surfactants, Coating solvents, Plasticizers, Flux regulators, Pore forming agent.

Semi permeable membrane: Cellulose acetate is commonly used for semi permeable membrane. It is available in different acetyl content like 32%, 38% are widely used. e.g. agaracetate, Betaglucan acetate, Polyether copolymer, Olyacetals, Polyglycolic acid, poly lactic acid.

Hydrophilic and hydrophobic polymers: These polymers are used for making drug containing matrix core. Mainly two types of polymers-swellaable & nonswellaable.

Hydrophilic materials: HPMC, Hydroxyl ethyl cellulose, Carboxy methyl cellulose (which has high molecular weight) *Hydrophobic materials:* ethyl cellulose and wax materials.

Wicking agent: It is defined as materials with the ability to draw water in to porous network of delivery device. The function of wicking at is to carry water to surface inside the concentration of water. Materials, which suitable for act as wicking agent, include colloidal silicon dioxide, kaolin, Titanium dioxide, alumina, niaciamide, SLS, etc. Solubility at, non swellaable agent classified into 3 groups:

1. At that inhibit crystal formation at the drug.
2. A high HLB micelle forming surfactant particular anionic surfactant (tween 20, 80, polyoxyethelene/ SLS)
3. Citrate esters & their combination with anionic surfactant.

Osmogens [2]: Osmogens used for fabrication of osmotic dispensing device are inorganic or organic in nature a water soluble drug by itself can serve the purpose of an osmogen. Inorganic water-soluble osmogens, Magnesium sulphate, Sodium chloride, Sodium sulphate, Potassium chloride, Sodium bicarbonate, Organic polymer osmogens: Sodium carboxymethyl cellulose, Hydroxypropylmethyl cellulose.

Surfactant [1] Surfactants are particularly useful when added to wall forming material e.g. sorbitan trioleate (1.8), Poltoxyethylene sorbital, Bees wax (2.0), Sorbitan tristearate (2.1), Polyoxyethylene sorbital hexastearate (2.6), Ethylene glycol fatty acid ester (2.7), Propylene glycol fatty acid ester (3.4), Propylene glycol monostearate (3.4), Glycerol monostearate (3.8), Sorbitan monooleate (4.3).

Coating solvent solvent suitable for making polymeric solution that is used for manufacturing the wall of the osmotic device include inert inorganic and organic solvents, that don't adversely harm the core solvents, wall and other materials. e.g. ethylene chloride, Acetone, Methanol, Isopropyl alcohol, Butyl alcohol, Ethyl alcohol,

Plasticizers: It lowers the temperature of the second order phase transition of the wall or the

elastic modules of the wall and also increases the workability. e.g. dialkylphthalate, Trioctylphosphate, Alkyl adipates, Triethyl citrated, Acetate, Propionate, Glycolate.

Flux regulators Flux regulators are added to the wall forming material. This agent can be preselected to increase or decrease the liquid flux. agents that produce marked increase in permeability to fluid such as water are essentially hydrophilic while those produce a marked decrease in permeability to fluid are essential hydrophobic. Polyhydric alcohol such as polyalkylene glycols & low molecular weight glycols such as poly propylene, polybutyrene etc. usually 0.001 parts to 5 parts or higher weight fraction of flux regulators can be used to achieve the desired.

Pore forming agents This is used for pouring water soluble drug and development at controlled porosity or multiparticulate osmotic pumps. Pore forming agent makes a micro porous membrane. The micro porous wall may be formed in situ by a pore former by its leaching during the operation of the system. Pore formers can be inorganic or organic and solid or liquid in nature. For e.g. alkaline metal salts. Such as NaCl, NaBr, KCl, potassium sulfate, potassium phosphate etc. alkaline earth metal like CaCl₂, calcium nitrate. Carbohydrate such as sucrose, glucose, fructose, mannose, lactose, sorbitol, mannitol, and diols and polyols. It should be non toxic, and on their removal, channels should be formed.

Table 1: Specification for controlled porosity osmotic pumps

Material	Specification
Plasticizers and flux regulating agents	0 to 50, preferably 0.001 to 50 parts per 100 parts of wall material
Surfactants	0 to 40, preferably 0.001 to 40 parts per 100 parts of wall material
Wall thickness	1 to 100, preferably 20 to 500 mm
Micro porous nature	5 to 95 % pores between 10 A to 100 mc.m diameter
Pore forming additives	0.1 to 60 % , preferably 0.1 to 50%, by weight, based on the total weight of pore forming additive and polymer pH insensitive pore forming additive (solid or liquid) preferably 0.1 to 40 % by weight

Table 2: Specification for core of controlled porosity osmotic pumps

Property	Specification
Core loading (size)	0.05 g to 5 g or more (including dosage forms for humans and animals)
Osmotic pressure developed by a solution of core	8 to 500 atm typically, with commonly encountered water soluble drugs and excipients
Core solubility	To get continuous, uniform release of 90% or greater of the initially loaded core mass density, ρ , that is s/ρ , must be 0.1 or lower. Typically this occurs when 10% of the initially loaded core mass saturates a volume of external fluid equal to the total volume of the initial core mass.

Formulation of Core Tablets [5, 6 7] the tablets were prepared by wet granulation technique. Drug was uniformly mixed with mannitol and lactose in a high shear mixer granulator. The dry blend was granulated with povidone, which was dissolved in isopropyl alcohol. The mass was dried at 50°C and sized through American Society of Testing and Materials (ASTM) 20 mesh and mixed with talc and colloidal silicon dioxide. The granules were lubricated with magnesium stearate and compressed into round tablets with standard concave punches (diameter, 9.52 mm) using 27-station rotary compression machine Table 2 lists the composition of different formulations prepared using varying amounts of osmogents.

Table 3: Composition of Core Oxybutynin Tablet

Ingredients (mg/tablet)	Formulation Code			
	OXY/F01	OXY/F02	OXY/F03	OXY/F04
Oxybutynin chloride	10	10	10	10
Mannitol	0	50	100	200
Lactose	212	162	112	12
Povidone K30	12	12	12	12
Magnesium stearate	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5
Colloidal silicon dioxide	1	1	1	1

Coating The coating solutions were prepared using a mixture of dichloromethane and methanol (80:20) as the coating solvent. All coating compositions were clear solutions. Coating was performed by spray pan coating in a perforated pan (GAC-205, Gansons Ltd, Mumbai, India). The laboratory scale batch size was 700 g (350 g core tablets mixed with equal quantity of dummy tablets). Initially, tablets were preheated by passing hot air through the tablet bed and by rotating at a lower speed of 5 to 8 rpm. Coating process was started with rotation speed of 10 to 12 rpm. The spray rate and atomizing air pressure were 4 to 6 mL/min and 1.75 kg/cm², respectively. Inlet and outlet air temperatures were 50°C and 40°C, respectively. Coated tablets were dried at 50°C for 12 hours and the percentage weight gain and thickness (Digimatic Caliper, Mitutoyo, Japan) of the coating membrane were measured.

Table 4: Coating Composition for Oxybutynin Tablets

Ingredients†	Coating Composition Code		
	C-I	C-II	C-III
Sorbitol	0	10	20
PEG-400	10	10	10

*PEG indicates polyethylene glycol, †Composition based on percentage wt/wt of cellulose acetate, Total solids in the coating composition is 4% wt/vol.

Evaluation:

Physical evaluation of asymmetric membrane capsule Color any imperfection, Texture and membrane size Height and radius, Scanning electron microscopy Drug content, Dissolution behavior Stability studies

In vivo evaluation In vivo evaluation carried out on dog, monkey (1983) studied of indomethacin from OROS pump in mongrel dogs .forty OROS systems of indomethacin were weighed and marketed divided in to four groups of 20 and used for evaluation.

In vitro evaluation oral osmotic system has been evaluated by the conventional USP paddle basket type apparatus. US patents describes use of commercial venkel standard dissolution apparatus and commercial applied analytical standard dissolution apparatus. The dissolution medium is generally distilled water, as well as gastric pH (For first 2-4 hrs) [3]

In Vitro Drug Release In vitro drug release of the formulations was performed using United States Pharmacopeia's (USP) type I apparatus (2100C, Distek Inc, North Brunswick, NJ) attached with auto-sampler, at 75 rpm. The dissolution medium consisted of 900 mL of degassed simulated gastric fluid (SGF, without enzymes) at $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$. The drug release at different time intervals was analyzed by high-performance liquid chromatography (HPLC). The release studies were conducted in triplicate and parameters such as percentage cumulative drug release and drug release rate were calculated.

HPLC Analysis Chromatographic separation of oxybutynin was performed on a Shimadzu LC-2010C_{HT} HPLC system using YMC-Pack-CN column (4.6 mm × 250 mm × 5 μm particle size; Shimadzu, Kyoto, Japan). Mobile phase used was mobile phase-A (water: methanol [800:200] + 0.2 mL triethylamine, with pH 3.5. Temperature of the column was maintained at 30°C . Standard solution and dissolution samples were analyzed at 203 nm using a UV detector.

Scanning Electron Microscopy Coating membranes of formulation obtained before and after complete dissolution of core contents were examined for their porous morphology by scanning electron microscope (XL30 ESEM TMP+EDAX, Philips, Eindhoven, The Netherlands). Membranes were dried at 45°C for 12 hours and stored between sheets of wax paper in a dessicator until examination.

Effect of pH To study the effect of pH and to assure a reliable performance of the developed formulations independent of pH, in vitro release studies were conducted in media of different pH. The release media was SGF (pH 1.2), acetate buffer (pH 4.5), and simulated intestinal fluid (pH 6.8). Samples were analyzed by HPLC.

Effect of Agitational Intensity In order to study the effect of agitation intensity of the release media, release studies were performed in dissolution apparatus at various rotational speeds. USP-I (rotating basket) type dissolution apparatus with rotational speeds of 50, 100, and 150 rpm was used. Degassed SGF (without enzymes) was used as dissolution media (pre-equilibrated to $37^{\circ}\text{C} \pm 1^{\circ}\text{C}$). Samples were analyzed by HPLC method.

Effect of Osmotic Pressure To confirm the major mechanism of drug release, release studies of the optimized formulation were conducted in media of different osmotic pressure. To increase the osmotic pressure of the release media (pre-equilibrated to $37^{\circ}\text{C} \pm 1^{\circ}\text{C}$), mannitol (osmotically effective solute) was added in SGF (without enzymes). Release studies were

performed in 900 mL of media using USP-I dissolution apparatus (75 rpm). To avoid any interference in the analysis by mannitol, residual drug analysis methodology was used for construction of release profile. At predetermined time points, formulations were withdrawn from each vessel and cut open, and the contents were dissolved in sufficient volume of SGF. The samples were analyzed to determine the residual amount remaining in each formulation. Accuracy of this method was checked in SGF, where results after direct measurement of drug into the release media were similar to the results of residual drug analysis method.

Kinetics of Drug Release The cumulative amount of drugs released from the optimized system at different time intervals were fitted to zero-order kinetics using least squares method of analysis to find out whether the drug release from the systems provides a constant drug release pattern. The correlation coefficient between the time and the cumulative amount of drug released was also calculated to find the fitness of the data to zero-order kinetics. The fitness of the data to first-order kinetics was assessed by determining the correlation coefficient between the time and the amount of drug to be released from the formulations.

Drug Content and Physical Evaluation The assay of drug in various formulations varied between 98.6% and 101.5% (mean 100.05%). Core tablet weights varied between 235 mg and 245 mg (mean 240 mg); thickness of the core tablets was found to be in the range of 3.05 and 3.45 mm (mean 3.25 mm). The hardness of core tablets was found to be between 3.8 and 5.2 kg cm⁻² (mean 4.5 kg cm⁻²), while the friability of prepared core tablets ranged between 0.12% and 0.23% (mean 0.17%). Thus, all the physical parameters of the compressed matrices were practically within limits.

Effect of Ratio of Drug to Osmogent To optimize the amount of osmogent to be used in the formulation and to study the effect of drug-to-osmogent ratio, core formulations were prepared. The ratios of drug to osmogent studied were 1:0, 1:5, 1:10, and 1:20. All the core formulations were coated with coating composition, C-II containing 10% wt/wt (of cellulose acetate) of sorbitol. Release profile from these formulations. It is clear from that osmogent enhances the release of drug and thus had a direct effect on drug release. This finding is evidenced from formulation OXY/F01 that was devoid of any osmogent in the core and showed 61% drug release at 24 hours. However, the use of osmogent enhanced the release beyond 80% drug release at 24 hours depending on the amount of osmogent present in the core formulation, which might be due to the increased water uptake and hence increased driving force for drug release.

Effect of Pore Forming Level To study the effect of pore forming agent, core formulations were coated with varying coating compositions of pore forming agent containing 0%, 10%, and 20% wt/wt (of cellulose acetate) of sorbitol. Release profile from these formulations. It is clearly evident that the level of sorbitol had a direct effect on drug release. As the level of pore former increases, the membrane becomes more porous after coming into contact with the aqueous environment, resulting in faster drug release. The level of pore former also affects the burst strength of exhausted shells. The burst strength was inversely related to the initial level of pore former in the membrane. With the increase in the level of sorbitol, the membrane became more porous after exposure to water, leading to a decrease in its strength. The results in the present study are consistent with other reports.

Conclusion

It is advantageous to deliver some drugs with short half-life, and which are to be given

frequently for chronic ailments, in the form of controlled-release (CR) formulations. The orally administered drugs, in the form of conventional matrix or reservoir type formulations, pose problems of bioavailability fluctuations due to gastric pH variations. Moreover, the release of drug(s) from these systems is affected by the hydrodynamic conditions of the body. Osmotically controlled drug delivery systems utilize the principles of osmotic pressure for the controlled delivery of active agent.

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