

Research Article

Optimization and Development of Swellable Controlled Porosity Osmotic Pump Tablet for Theophylline

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Abstract

Purpose: To develop swellable controlled porosity osmotic pump tablet of theophylline and to define the formulation and process variables responsible for drug release by applying statistical optimization technique.

Methods: Formulations were prepared based on Taguchi Orthogonal Array design and Fraction Factorial design for core and coating, respectively. The tablets were prepared by direct compression and wet granulation methods; spray coated with ethyl cellulose solution containing varying amounts of PEG 400 and plasdone. Drug release from the osmotic drug delivery system was studied using USP Type I paddle type apparatus. The membrane morphology of the delivery system was determined by scanning electron microscopy (SEM).

Results: Optimization results indicated that the release rate of theophylline from the swellable controlled porosity osmotic pump tablet is directly proportional to the levels of osmotic agent, solubilizing agent and pore former in the tablet core and the membrane, respectively. SEM showed the formation of pores in the membrane through which drug release occurred. The best formulation showed 98.2 % drug release and complied with USP requirements.

Conclusion: The results confirmed that the factors responsible for drug release were osmotic agents (core) and pore former (membrane). Also, the preparation of swellable controlled porosity osmotic pump tablet was facilitated by coating the core tablet with pore forming agent, thus eliminating the need for the more expensive laser drilling.

Key words: Swellable, Controlled Porosity, Osmotic Pump Tablet, Taguchi Orthogonal design, Fraction factorial design, Osmotic agent, Pore former, Scanning electron microscopy.

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INTRODUCTION

In recent years, considerable attention has been focused on the development of novel drug delivery systems (NDDS)¹. Once-daily controlled release preparation is often desirable². However, drug release from oral controlled release dosage forms may be affected by pH, gastric motility, and presence of food. One practical approach with a potential to overcome these disadvantages is the osmotic drug delivery system where osmotic materials have been used extensively in the fabrication of drug delivery systems³. The historical developments of osmotic systems include seminal contributions such as the Rose-Nelson pump⁴, the Higuchi-Leeper pumps⁵, the Alzet osmotic pump⁶, the elementary osmotic pump (EOP)⁷ and the push-pull osmotic pump⁸. The osmotic drug delivery systems suitable for oral administration typically consist of a compressed tablet core that is coated with a semipermeable membrane that has an orifice drilled on it by means of a laser beam. The rate at which the core absorbs water depends on the osmotic pressure generated by the core components and the permeability of the membrane coating. As the core absorbs water, it expands in volume, which pushes the drug solution or suspension out of the tablet through one or more delivery ports⁹. To obviate the need for complicated laser drilling, tablets coated with a membrane of controlled porosity have been described. These membranes consist of a leachable material which dissolves upon contact with water, leaving behind the pores through which the drug solution is pumped out. However, due to the relatively low permeability of the dense coatings, osmotic delivery of drugs with moderate to low solubility is limited¹⁰.

Asthma is an inflammatory disease characterized by bronchial hyper-responsiveness that can proceed to life-threatening airway obstruction¹¹. Theophylline (THP), which was selected as a model poorly soluble drug, has been used in

asthma and chronic obstructive pulmonary disease for over 60 years and remains one of the most widely prescribed drugs in the treatment of airway diseases worldwide as it is inexpensive¹². THP (1,3-dimethylxanthine) is a member of the xanthine family, sometimes referred to as purine alkaloid, and seems to have the same precursor as the nucleic acid¹³. It has a molecular weight of 180.17 and pK_a of 3.5 and 8.6¹⁴; it relaxes smooth muscles and relieves bronchospasm¹⁵ by inhibiting the enzyme phosphodiesterase which degrades cyclic nucleotides intracellularly¹⁶. Theophylline may be a useful treatment for nocturnal asthma and a single dose of a slow-release theophylline preparation given at night may provide effective control of nocturnal asthma symptoms¹⁷.

In this study, an attempt was made to design a simplified new swellable controlled porosity osmotic system for the delivery of a poorly soluble drug that eliminates the need for complicated and expensive laser drilling. This device is known as swellable controlled porosity osmotic pump (SCPOP). The study involves the use of Taguchi Orthogonal Array design^{18,19} and fraction factorial design^{18,20} for core and membrane formulation, respectively, and was intended to determine the effect of different independent variables on dependent (response) variables. In these systems, the hydrostatic force were produced by osmotic agents and polymer swelling force concurrently to drive the drug out of the system through the pores created by the pore-forming agent in the membrane coating after exposure of the system to water. In order to optimize release rate from the osmotic devices, the data from *in vitro* release studies were subjected to analysis of variance (ANOVA), and polynomial equations were developed to determine the quantitative relationship between dependent and independent variables by using Design Expert software. (Stat-ease Inc, Minneapolis, USA)

EXPERIMENTAL

Materials

The theophylline (THP) and croscarmellose sodium (CCS) were obtained as gifts from Microlabs Pvt Ltd, Bangalore, India. Xanthan gum, plasdone S630, sodium lauryl sulphate (SLS), microcrystalline cellulose (MCC), ethyl cellulose, polyethylene glycol 400 (PEG 400), tartaric acid, sorbitol and triacetin were also obtained as gifts from Strides Arco Labs Pvt Ltd, Bangalore, India. All other chemicals used in the study were of analytical grade.

Methods

Formulation Development

Taguchi orthogonal array design^{18,19} was incatucated to develop formulations as outlined in Table 1. It is a large screening design that utilizes two-, three-, and mixed-level fractional factorial formats.

Tablet production

Core tablets of THP were prepared by both direct compression and wet granulation. In the direct compression method, all the ingredients were weighed accurately, as per Table 1, screened through a sieve of aperture size 250 μm and blended for 5 min using double cone blender (Rimek Kalveka HD-410 AC, Gujarat, India) at 100 rpm to get a uniform mix. Magnesium stearate and talc were added and blended for 2 min.

In the wet granulation method, the drug was mixed with all the excipients except the binding and solubilizing agents and passed through sieve of aperture size 250 μm . The blend was mixed for 5 min using a double cone blender (Rimek Kalveka HD-410 AC, Gujarat, India.) at 100 rpm. The mixture was granulated with a granulating fluid prepared by dissolving the binding and wetting/solubilising agents in water. The resulting wet mass was passed through a sieve of aperture size 710 μm and the

granules were dried at 50 °C for 15 min. The granules were then screened through a sieve of aperture size 355 μm , and blended with magnesium stearate and talc.

The granules obtained by both methods were compressed at a pressure of 6 tons in a laboratory press (Rimek RSB-4, Minipress, Gujarat, India) fitted with two sizes of concave punch sets - 10 and 12 mm diameter, respectively.

Measurement of tablet thickness

The thickness of ten tablet cores per batch was measured with electronic digital calipers (Aerospace, China) and mean thickness was calculated.

Assay of theophylline

The theophylline content of each tablet formulation was analyzed spectrophotometrically (Shimadzu UV-1601) at 271 nm based on the crushed material from 5 randomly selected tablets from each batch. The tablet material was dissolved in 0.1 M HCl and appropriately diluted with the same medium to yield a concentration that falls in the Beer's range of 2 – 16 $\mu\text{g/ml}$. The drug content was calculated using the formula in Eq 1.

$$X = Y - 0.019/0.0558 \dots\dots\dots (1)$$

where X = concentration ($\mu\text{g/ml}$) and Y = absorbance.

Coating of tablets

Coating formulations were designed based on fraction factorial design. This design reduces the number of experiments required, compared with Factorial Design (FD), especially when the numbers of factors are high. The higher and lower levels of independent variables selected are described in Table 2. Dependent variables selected for the study include % drug release at 24 h. Core formulation F1 was selected to optimize the coating formula.

Table 1: Taguchi orthogonal array design for core tablet formulations*

Ingredient (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Plasdone	30	30	5	30	5	5	5	30
CCS	5	5	50	50	5	5	50	50
Xanthum gum	10	25	25	25	25	10	10	10
Potassium chloride	300	300	300	150	150	150	300	150
Tartaric acid	100	50	50	100	100	50	100	50
SLS	2.5	12.5	2.5	2.5	12.5	2.5	12.5	12.5
Total (mg)	572.5	547.5	557.5	482.5	422.5	347.5	602.5	427.5

*Compositions are given in terms of mg per tablet. Each formulation contained 100 mg, 10 mg, 10 mg, and 5 mg of theophylline, MCC, magnesium stearate and talc, respectively. (CCS = crosscarmellose sodium; SLS = sodium lauryl sulphate, MCC = microcrystalline cellulose)

Table 2: Fraction factorial design for 12 coating formulations*

Ingredients	PEG 400 (ml)	Triacetin (ml)	Sorbitol (g)	Plasdone (g)
Formulations	C1	0.707	-	1.2
	C2	-	0.173	1.2
	C3	0.353	-	-
	C4	0.707	-	0.6
	C5	0.707	-	-
	C6	-	0.519	-
	C7	-	0.173	0.6
	C8	0.353	-	-
	C9	-	0.519	1.2
	C10	0.353	-	0.6
	C11	-	0.519	-
	C12	-	0.173	-

*Each formulation contained 2 g and 100 ml of ethyl cellulose and ethanol, respectively.

A coating solution (2% w/v) of ethyl cellulose in ethyl alcohol (containing varying amounts of plasticizer and pore forming agent) was used to apply a semi permeable film on the tablets. The coating was carried out by spraying in a coating pan (Rimek Kalveka HD-410 AC, Gujarat, India) equipped with a hot air blower. The stainless steel pan was set a rotating speed of 25 rpm and a spray rate of 5 ml/min. The coated tablets were dried at 50 °C for 4 h.

***In vitro* release studies**

In vitro drug release of the formulations was carried out in a USP dissolution apparatus (paddle type) set at a rotating speed of 100

rpm and temperature of 37±1 °C. The dissolution medium (900 ml) was Simulated Gastric Fluid (SGF IP 2007, pH 1.2) for the first 2 h and Simulated Intestinal Fluid (SIF IP 2007, pH 6.8) thereafter. Samples (4 ml) were withdrawn at specified time intervals over a 24 h period and the medium was replenished with fresh dissolution fluid. The samples were suitably diluted, analyzed spectrophotometrically at 271 nm and drug release computed.

Measurement of film thickness

Following the completion of dissolution, the film was isolated from the tablets and dried at 40 °C for 1 hr. Thickness was measured at

three different points on the film using electronic digital calipers (Aerospace, China.) and the mean values were taken.

Optimisation studies

The response values (24 h drug release) of coating formulations based on Fraction Factorial Design were subjected to analysis by response surface reduced quadratic model. The optimized coating formula was used to coat the 8 batches of tablets formulated according to Taguchi orthogonal array design. Core optimization was carried out based on Factorial model for 1, 4, 8, and 24 h drug release.

Scanning electron microscopy

The surface morphology of the optimized tablet film coating before and after dissolution was examined by scanning electron microscope. The samples were fixed on a brass stub using double-sided tape and then gold-coated in vacuum by a sputter coater. Scans were taken at an excitation voltage of 20 KV in a JSM-840A scanning electron microscope fitted with JFC-1100E ion sputtering device (Jeol, Japan).

RESULTS

Tablet thickness and drug content

The thickness of tablet formulations F1 – F8 (10 mm diameter) and the optimized core tablet formulation (12 mm diameter) was in the range 3.87 – 5.92 mm for the former and 5.2 mm for the latter. Thickness depended on punch size and tablet weight; coefficient of variation (based on 20 tablets/batch) for each batch was less than $\pm 5\%$, which indicates good thickness uniformity. Drug content was uniform within each batch and ranged from 97 – 110 % of the theoretical value.

Coating optimization

The optimized coating formula in Table 3 obtained after optimization showed a weight

gain of 2% w/w, compared with the uncoated tablet. Film thickness of 0.065 mm and maximum *in vitro* release of 94.12 % were observed.

Table 3: Composition of optimized formulations of coating and core

Ingredient	Quantity
Coating	
Ethylcellulose	2 g
Ethanol	100 ml
PEG 400	0.674 ml
Plasdone	1.10 g
Core (tablet)	
Theophylline	100
Plasdone	29.91
CCS	12.98
Xanthan gum	24.17
KCl	299.99
Tartaric acid	99.91
SLS	12.49
Microcrystalline cellulose	10
Mg stearate	10
Talc	5

DISCUSSION

First, the coating formulation was optimized using Response Surface Reduced quadratic model based on core formulation F1.

Influence of coating formulation variables on drug release

The response values for percentage drug release at 24 h in the design run formulations were subjected to multiple analysis of variance. The model expressions were found to be significant with an F value of 7.63, Probability value (P-value) 0.0108 as the probability value is less than 0.1 (upper limit). To understand the mathematical relationship between independent and dependent variables studied, a polynomial equation (Eq 2) was generated using the Design Expert.

$$\% \text{ drug release (24 h)} = 117.15 + 0.2973 * A + 24.8262 * D \dots\dots\dots (2)$$

The independent factors PEG 400 (A) and plasdone (D) had positive influence on drug release, while triacetin (B) and sorbitol (C) showed antagonistic effect on the response and, therefore, were excluded from the model.

Influence of plasticizer on drug release

In order to study the influence of plasticizer level on drug release profile, different types and levels of plasticizers were used. A polynomial model shows that increment in the plasticizer (PEG 400) led to an increase in drug release. Since PEG 400 is a hydrophilic plasticizer, it could be leached out easily and increase the flux rate of fluid. The more PEG 400 incorporated into ethyl cellulose membrane, the lower the membrane permeability and drug release obtained due to the increased plasticity of the membrane. Another plasticizer, triacetin, is also a hydrophilic plasticizer but had negative influence on drug release; this could be due to its lower hydrophilicity compared to PEG 400.

Effect of level of pore former

To study the effect of level of pore forming agent, core compositions were coated with coating compositions containing different types and levels of pore formers (Table 2). As the levels of pore formers (plasdone and sorbitol) increased from lower to higher level, the release also increased. The increase in theophylline release could be due to formation of more pores after coming in contact with aqueous environment. Drug release is higher with plasdone than with sorbitol owing to the greater aqueous solubility of the former.

Influence of core formulation variables

The response values of 1, 4, 8 and 24 h theophylline release were subjected to multiple analyses of variance using factorial model. For 1 h response, the model expressions were found to be significant with

F (P - value) value of 0.7783 (0.0464). The polynomial equation for the factorial model is given by Eq 3.

$$\% \text{ drug release (1h)} = 13.7475 + 0.9175 * A + 1.505 * E + 0.055 * F \dots\dots\dots (3)$$

For 4 h response, the model was found to be significant with F (P- value) of 4.1088 (0.02073). The model is represented by Eq 4.

$$\% \text{ drug release (4h)} = 47.9725 + 0.3875 * B + 2.7175 * C + 1.6475 * E + 1.4525 * F + 0.9325 * G \dots\dots\dots (4)$$

The model for the response 8 h drug release was found to be consequential as the F (P - value) is 0.3509 (0.0185), and the model can be written as in Eq 5.

$$\% \text{ drug release (8 h)} = 64.385 + 7.1525 * A + 0.13 * B + 1.0125 * D + 2.5525 * E + 1.135 * F \dots\dots\dots (5)$$

At 24 h response, the model was found to be significant with F (P value) of 6.65 (0.049) as shown in Eq 6.

$$\% \text{ drug release (24h)} = 80.8562 + 0.3687 * A + 5.1362 * D + 3.4987 * E \dots\dots\dots (6)$$

Where A = plasdone, B = crosscarmellose sodium, C = xanthan gum, D = potassium chloride (KCl), E = tartaric acid, F = sodium lauryl sulphate, and G = in process parameters.

In all the four responses, factors with positive coefficients influence response synergistically, while factors with negative coefficients show antagonistic effect on the response.

Influence of osmotic agents

To study the compositive influence of osmotic agents (KCl and tartaric acid), drug delivery systems were developed with different concentrations of KCl and tartaric acid. From the polynomial equations obtained for all responses, it was confirmed that increase in the concentration of osmotic agent increases drug release as the positive coefficient value found for factors D and E is high and their

influence was seen in all the responses. When the coated tablet is exposed to an aqueous environment, water diffuses through the film coating (due to the active gradient of water), hydrating the core. The solvation of the osmotic agents creates osmotic pressure difference between the core contents and external environment results in greater theophylline release.

Influence of swelling agents

In the present study, swelling agents were used as drug entraining polymer, consisting of one or more swellable hydrophilic polymers (crosscarmellose sodium (factor B) and xanthan gum (factor C)) selected such that the polymeric swelling agent exhibits controlled swelling, the wall does not rupture or burst, and the desired rate of drug delivery can be obtained. However, swelling agents have less influence on all the responses (1, 8, and 24h) except 4th h which was endorsed by polynomial models.

Influence of wetting agent

Since theophylline is a poorly soluble drug, a micellar solubilizer, sodium lauryl sulphate (SLS), was used to enhance drug solubility for faster release. In addition, SLS (factor F) has been used as an osmotic agent to create osmotic pressure; this dual nature caused increase in drug release.

In vitro release study

Formulations F1+C3, F1+C11 and F1+C12 showed 81.62 %, 75.85 % and 79.14 % drug release, respectively, as compared to other formulations, could be due to minimum level of plasticizer and maximum level of pore forming agent, but the release profile did not comply with USP limits for extended release capsules with 24 hour dosing interval ²¹ (see Table 4). In order to achieve USP release levels, responses (24 h release) from all the coating runs were included in the optimization design (i.e., Response surface reduced quadratic model) and the best solution for

coating formulation was obtained. Optimized coating formula with F1 core formulation exhibited 94.12 % drug release which is near to the predicted value of 99.84 %, although it did not comply with USP limits except for 1st and 2nd h. The optimized coating was used to optimize tablet core runs of Taghuchi Orthogonal Array design. Formulations F1, F3, F8 showed 94.12%, 85.13% and 70.76% release respectively in relation to other formulations. The reason could be the elevated levels of osmotic agent (plasdone) which modifies crystalline nature of the drug, thus facilitating drug release, and the increased levels of solubilizing and swelling (crosscarmellose sodium) agents as they increase solubility and delivery rate, respectively; this is true for formulations F1 and F8. However, in the case of formulation F3, the sudden increase in drug release after 8 h was due to 'burst' effect. Responses of all design runs were added in the optimization model. The results of optimization indicate the significant effect of osmotic agents (KCl and tartaric acid), plasdone and solubilizing agent on drug release. The ultimate optimized formulation showed 94.02 % with USP compliance in terms of release (see Table 4).

Table 4: Comparison of release profile of USP theophylline extended release capsules (labeled for 24 h dosing) with optimized SCPOP formulation

Time (h)	Release profile of theophylline extended release capsules labeled for 24h dosing (USP tolerance limit) (%)	Release profile of optimized SCPOP formulation (%)
1	5 - 15	15.98
2	12 - 30	30.56
4	25 - 50	52.04
5	30 - 60	59.9
8	55 - 75	75.88

Scanning electron microscopy

Ethyl cellulose membranes obtained before and after dissolution, were studied by SEM. After the completion of dissolution, exhausted membrane contained plasticizer (PEG 400, 38.10 %) and pore former (plasdone, 55.32 %) showed a microporous region surrounded by a macroporous region (Fig 1).

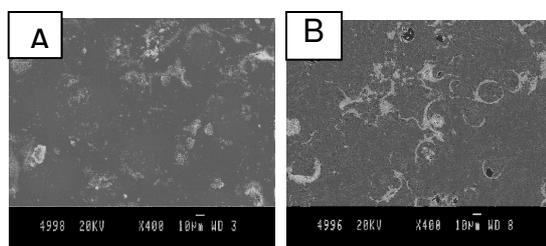


Fig 1: Scanning electron microphotographs of coating membranes of optimized formulation before dissolution (A) and after dissolution (B)

CONCLUSION

Taguchi orthogonal design (for tablet core) and fraction factorial design (for coating) were adequately applied to study the effect of different formulation variables on the release profile to select optimized formulations. Membranes were found to develop pores/channels after coming in contact with aqueous environment; the number of pores being dependent on the initial level of the pore former in the membrane. Finally, it can be concluded that preparation of osmotic pump tablet can be simplified by coating the core tablet with a pore-forming agent which is likely to be more cost-effective than laser drilling.

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