AAPS PharmSciTech, Vol. 13, No. 1, March 2012 (© 2011)
DOI: 10.1208/s12249-011-9738-3

Research Article

Solubility-Modulated Asymmetric Membrane Tablets of Triprolidine Hydrochloride: Statistical Optimization and Evaluation

Rahul Dev,[1] Anil Kumar,[1,2] and Kamla Pathak[1]

Received 30 July 2011; accepted 29 November 2011; published online 20 December 2011

Abstract. The aim of the present study was to develop asymmetric membrane (AM) tablets for controlled delivery of highly water-soluble antihistaminic drug triprolidine hydrochloride. The solubility of triprolidine hydrochloride was modulated through the incorporation of coated sodium chloride crystals encapsulated with asymmetric membrane coating polymer, cellulose acetate butyrate. Formulation of AM tablets was based on a 2^3 factorial design to study the effect of formulation variables, namely, polymer concentration, level of pore former, and amount of osmogen on the *in vitro* release. Core tablets prepared by wet granulation and coated with asymmetric membrane by a dip coating method were evaluated. Statistical analysis was done with the Design Expert Software 8.0.2 (USA), and the polynomial equation generated by Pareto charts was used for validation of the experimental design. The interaction chart and response surface plots deduced the simultaneous effect of independent variables on *in vitro* drug release. The *in vitro* drug release was inversely proportional and directly related to the level(s) of polymer and pore former in the membrane, respectively. The level of osmogen not only increased the osmotic pressure but also controlled the drug release due to a common ion effect. The drug release of the optimized formulation (F6) followed zero-order kinetics, which would be capable of reducing the administration, and was stable over 3 months. SEM photographs revealed asymmetry in membrane structure.

KEY WORDS: asymmetric membrane; coated sodium chloride; cellulose acetate butyrate; solubility modulation; 2^3 factorial design.

INTRODUCTION

Drug release through asymmetric membrane (AM) coating, prepared by phase inversion, is the personification of osmotic drug delivery. Asymmetric membrane prepared by varying types of hydrophobic coating polymers is a network of interconnecting pores. This net-like structure of polymer acts as a semi-permeable membrane barrier and the pores as drug delivery routes (1). Asymmetric membrane approach aims to provide drug release in a controlled manner based on the principle of osmosis and has been used by various research teams for the controlled drug release of both poorly water-soluble drugs (*e.g.*, nifedipine, lamivudine and famotidine) (2–4) and highly water-soluble drugs (*e.g.*, pseudoephedrine hydrochloride, diltiazem hydrochloride, and propranolol hydrochloride) (5–7). Research efforts on the development of asymmetric membrane capsules of a poorly water-soluble drug, flurbiprofen (8), and highly water-soluble drugs, phenylepherine hydrochloride (9) and promethazine hydrochloride (10), have been envisaged in our laboratory in the past 5 years. The drug delivery systems were successfully developed as osmotically controlled-release systems embodied in AM capsule, from which the release was independent of the gastrointestinal environment.

Though the AM capsules can be visualized as appropriate controlled release systems, they, however, suffer from certain limitations associated with capsular systems. Therefore, the present study has been undertaken with the aim of developing a robust asymmetric membrane system—asymmetric membrane tablets. Conventional tablets enjoy a number of advantages over capsules, such as (a) high-dose precision, (b) minimum content variability, (c) ease of preparing controlled-release dosage form, (d) lesser formulation cost, and (e) less time for preparation than filling of capsules (11). Owing to these tablets being able to be considered as robust and superior systems than capsules, thus, the current project was envisaged for the development of an AM tablet for the osmotically controlled release of a highly water-soluble drug. This system is proposed to enjoy the superior tablet dosage form over a capsular system and at the same time provides osmotically controlled release.

In the present study, triprolidine hydrochloride [(*E*)-2-(3-pyrrolidin-1-yl-1-(4-tolyl)prop-1-enyl)pyridine hydrochloride monohydrate] (12) (THCl), an H1 receptor antagonist (13), was chosen as the model drug. The drug's high aqueous solubility of 316 mg/mL (14) makes it a suitable candidate for the envisaged drug delivery system as a precise solubility modulation by common ion effect can ensure controlled temporal delivery of the drug. The usual dose of drug is 10–20 mg daily (15), with frequency of administration of three to four times per day and a half-life of 2–3 h (16), which are desirable features of a drug candidate, justifying its selection for formulation as a controlled-release system. Therefore, the aim of the project was to formulate and optimize osmotically controlled AM tablet of THCl that has the potential to reduce frequency of dosing (single dose/day) and improve patient compliance. For the purpose of formulation,

[1] Department of Pharmaceutics, Rajiv Academy for Pharmacy, National Highway #2, P.O. Chhattikara, Mathura, Uttar Pradesh 281001, India.
[2] To whom correspondence should be addressed. (e-mail: anilsoni.n@gmail.com)

cellulose acetate butyrate (CAB) was chosen as the asymmetric membrane coating polymer because CAB is water-insoluble, non-ionizable, and can be used for pH-independent coating (17,18).

MATERIALS AND METHODS

Materials

Triprolidine hydrochloride was obtained as a gift sample from Jai Radhe Sales, Gujarat, India. Cellulose acetate butyrate (2% by weight acetyl and 57% by weight butyl content) was obtained as a gift sample from Sigma-Aldrich Ltd., Germany. Sodium chloride (NaCl), acetone, ethyl alcohol, glycerol, lactose, magnesium stearate, and microcrystalline cellulose (MCC) were purchased from S.D. Fine Chemicals Ltd, Mumbai, India. Potassium bromide (KBr) was obtained from Spectrochem Pvt. Ltd, Mumbai, India. Starch was purchased from Central drug house (P) Ltd., New Delhi, India. Talc was obtained from Arora Pharmaceutical Ltd., New Delhi, India.

Methods

Drug–Excipient(s) Compatibility Studies

Compatibility studies between the drug–excipient(s) and excipients–excipient were performed using binary mixture(s) of THCl with selected excipients (NaCl, CAB, KBr, MCC, talc, magnesium stearate, starch) in a ratio of 1:5. Two series of binary mixtures were prepared, one without moisture and the second with 5% moisture by weight. The binary mixtures were placed in sealed glass vials at 55°C for 2 weeks. The vials were examined at regular intervals for discoloration, caking, liquefaction, and odor. At the end of the test period, the mixtures were also evaluated for drug content analyzed spectrophotometrically (Shimadzu PharmaSpec1700, Kyoto, Japan) at 277 nm for phosphate buffer, pH 7.4.

Saturation Solubility Studies

The solubility of THCl in 0.1 N HCl and in phosphate buffer (pH 7.4) was determined using the shake flask method. An excess amount of drug was added to 2.5 mL test media separately in a closed container, kept in a water bath shaker (Hicon, New Delhi, India), and maintained at 37±0.5°C, for 72 h. At the end of the test period, the solution was filtered through a nylon disc filter (0.05 μm) and analyzed spectrophotometrically at 290 nm for 0.1 N HCl and 277 nm for phosphate buffer, pH 7.4.

Preparation and Characterization of Coated Sodium Chloride Crystals

Coated NaCl crystals were prepared using a lab-fabricated spray coater (FBD-1). The NaCl crystals were spray-coated with varying strengths (1–5%, *w*/*v*) of coating solutions of CAB (Table I) for 10 min under 40°C and 16–18 kg cm^{-2} pressure. Ten grams of NaCl (pre-screened through sieve no. 16) was coated with CAB solution(s) in the above-stated conditions of temperature and pressure. The coated crystals were stored in a dessicator for 3 days to ensure complete drying. The coated NaCl crystals were characterized for flow properties such as angle of repose, Carr's compressibility index, Hausner's ratio, bulk density, and tapped density. The coated crystals were also characterized for their influence on the release of THCl. For this, a preliminary drug release study was carried out wherein five prototype tablet formulations of THCl containing 13 mg THCl were prepared by the wet granulation method using talc (1%, *w*/*v*), magnesium stearate (5%, *w*/*v*), microcrystalline cellulose (5%, *w*/*v*), 100 mg of coated NaCl crystals, and lactose q.s. 200 mg. Thus, a total of five preliminary formulations that varied in the strength (1%, 2%, 3%, 4%, and 5%, *w*/*v*) of coating composition of NaCl crystals were prepared and assessed for their influence on drug release. The preliminary formulation that met the criteria of 50% cumulative drug release (CDR) at 12 h was identified and the corresponding coating strength of coated NaCl was selected.

Table I. Coating Composition of CAB Per 10 mL to Prepare Coated NaCl Crystals

Ingredients	Composition code				
	C1	C2	C3	C4	C5
CAB (%, *w*/*v*)	1	2	3	4	5
Ethanol (%, *v*/*v*)	3	2	2	1.5	1.2
Acetone (%, *v*/*v*)	5	5	4	3.5	2.8
Glycerol (%, *v*/*v*)	1	1	1	1	1

CAB cellulose acetate butyrate

Next, the solubility modulation effect was also assessed by varying the concentration of selected coated NaCl in the molar concentration range of 0.5–2.5 M and determining the equilibrium solubility of THCl, both in 0.1 N HCl and phosphate buffer, pH 7.4. Briefly, an excess amount of drug along with varying concentrations of coated NaCl was placed in 10 mL of test media. The flasks were shaken for 72 h in a water bath shaker. At the end of the test period, aliquot samples were filtered and analyzed spectrophotometrically. This study helped in the selection of the strength of AM coat on NaCl crystals that can ensure desired solubility modulation.

Formulation of Core Tablets

Core tablets were formulated by the wet granulation technique. Drug was uniformly mixed with coated NaCl crystals and other excipients. The dry blend was granulated with starch paste and dried at 50°C, sized through sieve no. 16, and mixed with talc and microcrystalline cellulose. The granules were lubricated with magnesium stearate and compressed into tablets using a single-punch (diameter, 6–7 mm) hand-operated machine.

Physical Characterization of Core Tablets of Triprolidine Hydrochloride

Core tablets were evaluated for thickness, hardness, percent friability, and assay for drug content. The thickness of all formulations was measured using a Vernier caliper (Mitutoyo, Japan). Hardness of the tablets was determined by Pfizer hardness tester (Hicon). Percent friability of the coated tablets (n=20) was determined using Roche friabilator (Hicon). Assay for drug content of all formulations was done by weighing crushed tablet powder equivalent to 10 mg of THCl and diluting with phosphate buffer (pH 7.4) analyzed spectrophotometrically at 277 nm. The drug content was determined against a calibration curve of the drug.

Table II. Composition of Asymmetric Membrane Coated Tablets of Triprolidine Hydrochloride

Ingredients	Formulation code							
	F1	F2	F3	F4	F5	F6	F7	F8
Triprolidine hydrochloride (mg)	13	13	13	13	13	13	13	13
CAB-coated NaCl (mg)	117	117	117	117	146.5	146.5	146.5	146.5
CAB (%, *w/v*)	25	30	25	30	30	25	30	25
Ethanol (%, *v/v*)	30	30	30	30	30	30	30	30
Acetone (%, *v/v*)	50	50	50	50	50	50	50	50
Glycerol (%, *v/v*)	5	5	10	10	10	10	5	5

Tablet Coating with Asymmetric Membrane

The core tablets were coated in a solution of coating polymer (Table II) made using the method outlined. Asymmetric membrane (thin, dense region supported on a thicker, porous region) was made using the dip coating method in which two separate solutions—*i.e.*, solution I, constituting cellulose acetate butyrate (25% or 30%, *w/v*) in acetone (50%, *v/v*, in water), and solution II, made of an aqueous solution of glycerol (5% or 10%, *v/v*) in ethanol (30%, *v/v*, in water)—were mixed together with continuous stirring to make the final coating solution. The core tablets were dip-coated using a lab-fabricated two-pin apparatus where a forceps device with very fine needle(s) perpendicular to the forceps limb was used as holder. The tablet was held diametrically and dipped in the final coating solution for 5 min and air-dried under 25°C for 12 h

Experimental Design for Asymmetric Membrane-Coated Tablets of Triprolidine Hydrochloride

A 2^3 factorial design (Table III) was used for the formulation and optimization of AM-coated tablets. Cellulose acetate butyrate (X_1), glycerol (X_2), and coated NaCl (X_3) were taken as independent variables. Each variable was taken at high and low levels. Response parameter (%CDR) at 12 h was considered as the dependent variable. Core tablets were formulated using the wet granulation technique. Drug was uniformly mixed with coated NaCl crystals and other excipients in the amounts specified in Table II. The dry blend was granulated with a starch paste and dried at 50°C in a digital oven (Hicon), screened through sieve no. 16, and mixed with talc and MCC. The granules were lubricated with magnesium stearate and compressed into tablets using a single-punch (diameter, 6–7 mm) hand-operated tablet machine (Hicon).

In Vitro Drug Release Studies of Asymmetric Membrane-Coated Tablets

In vitro drug release test was carried out for 12 h. The study was performed in 0.1 N HCl (simulated gastric fluid, pH 1.2) for the first 2 h and followed by release in phosphate buffer (simulated intestinal fluid, pH 7.4) for 10 h using USP apparatus II (Hicon) at 37±0.5°C. One milliliter of the sample was withdrawn at 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and the 12th hour and suitably diluted by a fresh dissolution medium and analyzed at 290 and 277 nm for acidic and alkaline media, respectively, spectrophotometrically. The percent cumulative drug release was determined at various time intervals and plotted. The release kinetics of THCl from various formulations was analyzed by modeling the data for the zero-order release rate ($Q_t=k_0t$) (19), first-order release ($\ln Q_t=\ln Q_0-k_1t$) (20), Higuchi model ($Q_t=K_Ht^{1/2}$) (21), and Hixson–Crowell cube root law ($Q_0-Q_t=k_{HC}t$) (22), where Q_t is the amount of drug release at time t, Q_0 is the initial amount of the drug in the formulation, and k_0, k_1, k_H, and k_{HC} are the release rate constants for the zero-order, first-order, Higuchi model, and Hixson–Crowell rate equations, respectively. The *in vitro* drug release plots were statistically analyzed by Design Expert software 8.0.2 for the selection of optimized formulation.

Statistical Analysis by Design Expert Software 8.0.2

Response Coefficient Siginificance Study

The effect of coefficients (factors at low and high levels) on drug release were studied graphically by a Pareto chart

Table III. 2^3 Factorial Designs for Formulation of AMTs of Triprolidine Hydrochloride

Formulation code	Drug (mg)	Factors			Response parameter
		CAB (%, *w/v*)	Glycerol (%, *v/v*)	Coated NaCl (4%, *w/v*, in mg)	
F1	13	25	5	117	
F2	13	30	5	117	
F3	13	25	10	117	
F4	13	30	10	117	%CDR
F5	13	30	10	146.5	
F6	13	25	10	146.5	
F7	13	30	5	146.5	
F8	13	25	5	146.5	

CAB cellulose acetate butyrate, %*CDR* percent cumulative drug release

Table IV. Extra Design Checkpoint Formulation for Validation of Experimental Design

Independent variables	Coded value	Actual value	Dependent variable (% CDR in 12 h)	
Cellulose acetate butyrate	0	27.5% (*w*/*v*)	Predicted value	Observed value
Glycerol	0	7.5% (*v*/*v*)	47.08%	47.16%
Coated NaCl	0	131.75 mg		

using Design Expert 8.0.2 software. Factors such as concentration of CAB (X_1), level of glycerol (X_2), and the amount of osmogen (coated NaCl, X_3) were taken for study. The value of effect of coefficients was interpreted with the help of a bar graph of coefficients obtained between the Bonferroni line and the *t* limit line. This statistical analysis generated a polynomial equation for the response parameter ($\%CDR_{12\ h}$) that was also used for the validation of design.

Interaction Study Between the Independent Factors

The effect of interaction between the factors on $\%CDR_{12\ h}$ was studied graphically using the interaction profiles generated by the Design Expert software. The interactions were visualized by a lack of parellism in the lines. The interaction study was performed to check the effect of one factor on both low and high levels of other factors.

Selection of Optimized Formulation

Optimized AM tablet formulation amongst the non-significant pairs of formulation (F1–F8) was selected for the response parameter $\%CDR_{12\ h}$ and the value of coefficient of determination (r^2). Statistical significance was tested at $P<0.05$.

Validation of Experimental Design

The experimental design was validated by preparing an extra design checkpoint formulation (F9). For validation, the F9 formulation was prepared by taking the mean value of two levels for all three factors. The coded value (all factors at zero level) and the actual value (all factors at their midpoint) are given in Table IV. The predicted value of $\%CDR_{12\ h}$ was determined by the Design Expert software 8.0.2 and the experimental value obtained by the *in vitro* drug release test. The values were compared for validation of the design.

Scanning Electron Microscopic Study of Asymmetric Membrane Coating

Asymmetric membrane of CAB was examined for its porous morphology using a scanning electron microscope (Zeiss EVO® 50, UK). Visualization was done before and after dissolution of the optimized AM tablet. In this study, the samples were fixed on a brass stub using a double-sided tape and then gold-coated in vacuum by a sputter coater. The pictures were taken at an excitation voltage of 15 kV and magnifications of 500× and 2,500×.

Effect of System Variables on Drug Release from the Optimized Formulation

Variable Agitational Intensity

The *in vitro* release study to determine the effect of agitation intensity on drug delivery from AM tablet was carried out using USP apparatus II, maintained at 37±0.5°C. The study was carried out at three different speeds, namely, 50, 100, and 150 rpm, for 12 h. The samples were analyzed for the amount of drug release from the formulation at predetermined intervals of 290 and 277 nm for acidic and alkaline media, respectively.

Variable pH of Dissolution Media

The effect of varying pH of the dissolution media on the drug release from AM tablet was studied in two different media, 0.1 N HCl and phosphate buffer (pH 7.4). The release profiles were statistically compared using *t* test.

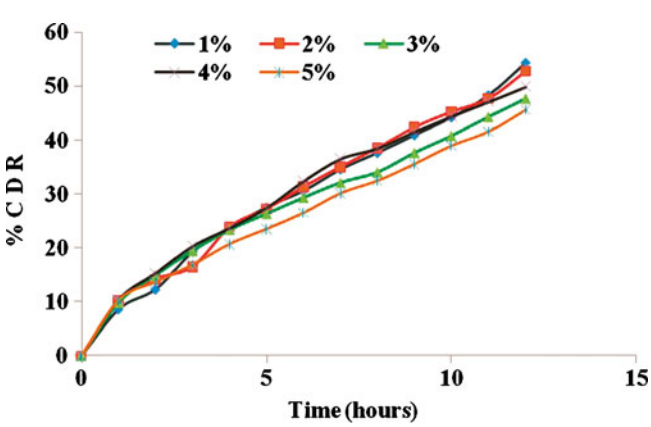

Fig. 1. Comparative drug release profile through 1–5% (*w*/*v*) AM-coated NaCl crystals

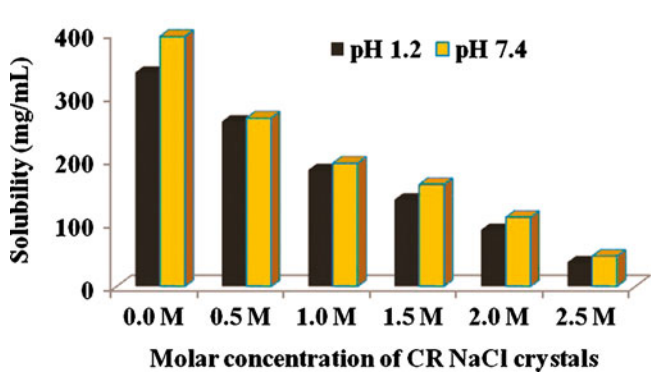

Fig. 2. Modulated solubility profile of triprolidine hydrochloride in two media of different pH using different molar concentrations (0.0–2.5 M) of 4% (*w*/*v*) CAB-coated NaCl crystals

Table V. Physical Characterization of Core Tablets Formulation

Formulation code	Weight variation (mg)	Hardness (kg cm$^{2)}$	Thickness (mm)	% Friability	% Drug content
F1	202.16±1.13	4.53±0.30	3.03±0.057	0.57	96.93±1.08
F2	201.01±1.26	4.80±0.12	3.34±0.12	0.78	96.55±1.24
F3	202.63±2.31	4.58±0.20	3.0±0.14	1.10	98.36±1.01
F4	200.83±1.52	4.96±0.73	3.06±0.25	0.76	99.04±0.94
F5	200.16±0.83	4.73±0.08	2.96±0.20	0.83	97.72 ±1.65
F6	203.72±0.64	3.96±1.1	3.11±0.34	0.95	100.12±0.98
F7	201.17±0.60	4.91±1.2	3.54±0.26	0.90	99.83±0.89
F8	202.34±0.19	4.39±1.6	3.61±0.46	1.12	97.23±0.93

Variable Osmotic Pressure of Drug Release Media

To determine the effect of osmotic pressure on drug release, the medium was made osmotically active by adding coated NaCl crystals as an osmogen to get the dissolution media with three different osmotic pressures of 21.18, 42.21, and 63.61 mmHg. The *in vitro* drug release from F6 was studied in the media without osmotic agent or 0 mmHg osmotic pressure and at variable osmotic pressure(s) and interpreted.

Stability Studies

The stability studies of the optimized formulation (F6) was performed according to International Conference on Harmonization guidelines Q_1 A. The formulation was kept in sealed and unsealed containers at 40±2.0°C/75±5% RH for 3 months. Tablets were evaluated for their appearance and drug content and *in vitro* rug release after 1, 2, and 3 months.

RESULTS

Drug–Excipient(s) Compatibility

On visual observation of the binary mixtures, no signs of caking, odor, liquefaction, and discoloration were observed after 2 weeks of storage under the experimentally stressed conditions. The assay of the binary mixtures reported drug content in the range of 98.76–99.54%, indicating compatibility between the drug and excipients.

Saturation Solubility

The solubility of THCl in 0.1 N HCl was found to be 337.74 mg/mL, which is slightly more than the literature value of 319 mg/mL (12). The solubility of THCl in phosphate buffer (pH 7.4) was found to be at a higher value of 394.79 mg/mL.

Characterization of Coated NaCl Crystals

The coated NaCl crystals were not different from uncoated NaCl and were evaluated for the flow property and solubility modulation effect on drug. The coated NaCl crystals demonstrated passable flow properties with an angle of repose <40° and Hausner's ratio and Carr's compressibility index values less than 1.6 and 21, respectively. Further characterization of coated NaCl crystals was done by preliminary *in vitro* drug release of THCl. As observed in Fig. 1, the drug release was almost linear and inversely proportional to the concentration of the CAB polymer. The extent of drug release from the tablet formulation containing 4% (*w*/*v*) coated NaCl crystals was 49.91% at the 12th hour; hence, the $t_{50\%}$ was calculated as 12.02 h. This meant that 4% coated NaCl crystals would create the desired molar environment in core tablet formulations and can be incorporated in tablet formulations to provide drug release in a controlled manner over a period of 24 h.

Solubility Modulation

Solubility modulation study revealed that solubility of the THCl was successfully reduced (Fig. 2) in the presence of varying molar concentrations of 4% (*w*/*v*) coated NaCl crystals both in acidic and alkaline media. At 2.0 M concentration of 4% (*w*/*v*) coated NaCl crystals, the solubility of THCl was modulated to 89.11 mg/mL in 0.1 N HCl and 109.07 mg/mL in phosphate buffer (pH 7.4), in contrast to the original solubility of 337.72 and 394.711 mg/mL in acidic and alkaline media without NaCl. Further reductions in solubilities were observed at 2.5 M concentration of 4% (*w*/*v*) coated NaCl crystals so that the

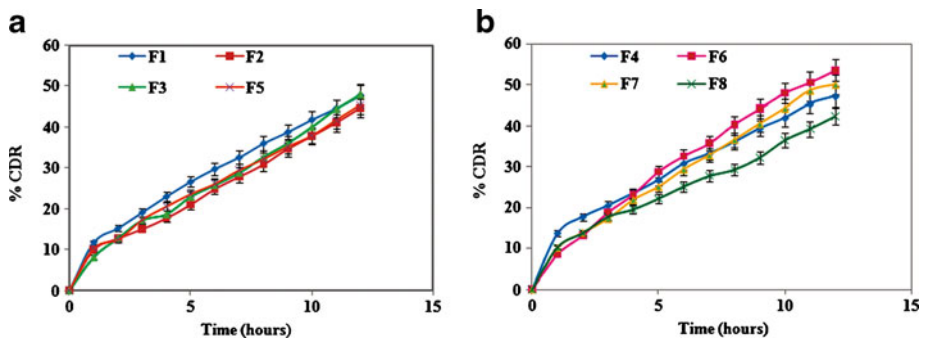

Fig. 3. *In vitro* drug release profile of group I (**a**) and group II (**b**) formulations, in 0.1NHCl in initial two hours followed by release in phosphate buffer,pH7.4

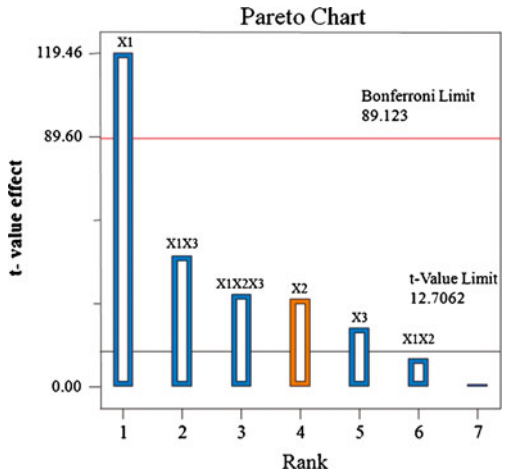

Fig. 4. Response coefficient significance study using Pareto chart

solubility reduced (almost half the value recorded with 2.0 M concentration) to 45.16 mg/mL in 0.1 N HCl and 47.54 mg/mL in phosphate buffer, pH 7.4. An almost 50% reduction in solubility at 2.5 M coated NaCl with respect to 2.0 M concentration guided the low and high levels of coated NaCl to be used in factorial design for the formulation of the AM tablet.

Evaluation of Asymmetric Membrane-Coated Tablets

The prepared core tablets were tested for their physical properties and assay for drug content. The results showed that the weight of tablet formulations (F1–F8) ranged between 200.16 and 203.72 mg. For the other physical parameters, hardness ranged between 4.39 and 4.96 kg/cm^2, thickness between 2.96 and 3.11 mm, and friability was between 0.57% and 1.12%. An assay of all formulations documented a drug content of more than 98.33±5% (Table V). The observed values showed that the compressed tablets were uniform and had sufficient strength to withstand processing. The core tablets were subjected to asymmetric coating by CAB as per the experimental design. The AM-coated tablets were divided into two groups based on the level of osmogen. Thus, group I comprised formulations (F1–F4) containing a low level of osmogen and group II constituted the formulations (F5–F8) with a high level of osmogen (Table III).

In Vitro Drug Release

The *in vitro* drug release profiles of group I (with a lower level of osmogen) and group II (with a higher level of osmogen) formulations are presented in Fig. 3a, b, respectively. All the formulations showed an initial burst release in the first hour followed by a gradual, almost linear release for the rest of the study period. Group I, containing formulations F1–F4, showed maximum drug release of 48.04% for F3, while a minimum drug release of 44.62% was documented for F2 at the 12th hour. Group II formulations F5–F8 coated with NaCl at its high level showed a maximum drug release of 53.52% for F6, while a minimum release of 44.57% was documented for F5. On comparing the best formulations of both groups, F6 emerged as the better formulation as it exhibited a higher release than F3 in 12 h.

Statistical Analysis

Response Coefficient Siginificance

The effect of independent variables on the response parameter %CDR$_{12\ h}$ was analyzed by a Pareto chart (Fig. 4), generated by the Design Expert software, 8.0.2. A graphical study of the chart established the *t* value of effect which was studied by two limit lines, namely, Bonferroni line (*t* value limit= 89.123) and *t* limit line (*t* value limit=12.7062). The value of effects above the Bonferroni line was considered to be significant, while those between Bonferroni line and the *t* limit line were likely to be significant; the effects below the *t* line are considered non-significant. Thus, significant coefficients were selected for the generation of polynomial equation and the non-significant coefficients were removed. The reduced polynomial equation thus obtained is given below:

$$\%\mathrm{CDR}_{12h} = 12.94 - 1.94X_1 + 0.5\mathrm{X}1X_2 - 0.34X_3 - 0.76X_1X_3 + 0.54X_1X_2X_3 \quad (1)$$

The coefficients with a positive sign indicated a positive contribution in enhanced drug release, while those with a negative sign have a negative impact on drug release. This polynomial equation was used for the validation of experimental design. In order to validate the experimental design, an extra design checkpoint formulation was made and evaluated for *in vitro* drug release. The predicted value of %CDR$_{12\ h}$ was deduced as 47.08% and the experimental value of % CDR$_{12\ h}$ found to be 47.16% (Table IV). The values were very close to each other; hence, the experimental design is said to be validated.

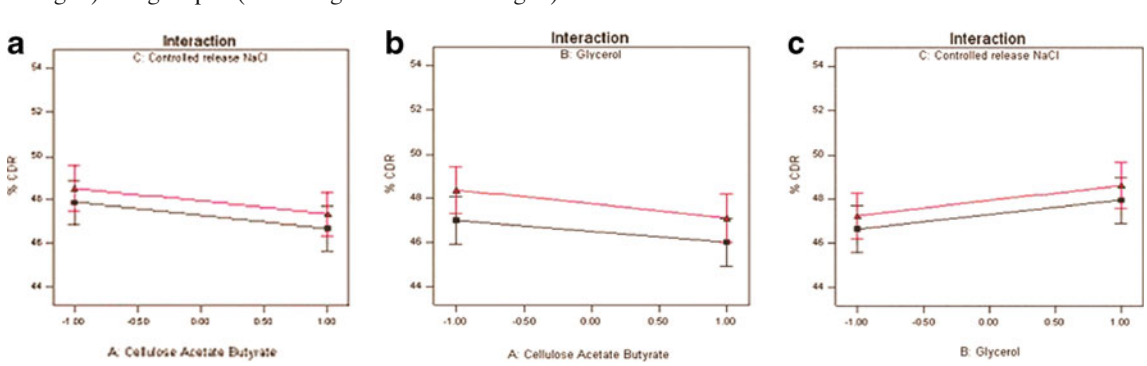

Fig. 5. Interaction studies between variables of optimized formulation

Table VI. Different Kinetic Models Applied on Optimized Formulation (F6)

Variable	Kinetic model	Coefficient of determination (r^2)
Dependent	Zero order	0.9989
	First order	0.9634
	Higuchi	0.9778
	Peppas	0.9726

Interaction Study Between Independent Factors

Possible interactions between various combinations of the independent variables—X_1X_3, X_1X_2, and X_2X_3—that can effect the response parameter were studied and are shown in Fig. 5. Graphically, interaction was visualized by the lack of parallelism in the lines for each interaction in terms of the response parameters. The result of the study indicated a lack of parallelism for X_1X_3 (Fig. 5a) and X_2X_3 (Fig. 5c). A slightly additive effect between X_1 and X_2 (less lack of parallelism in Fig. 5b) is attributable to the high level of glycerol (X_2) and low level of CAB (X_1) that supported drug release from the AM tablet. Thus, it can be stated that the design has maximum efficiency in estimating the effects of variables on drug release.

Selection of Optimized Formulation

On comparing the response parameter $\%CDR_{12h}$ and value of coefficient of determination (r^2) among the non-significant pairs of formulation (F1–F8), the highest value was found for F6 (%CDR=53.52%, r^2=0.9989). Hence, F6 was selected as the optimized formulation. Model fitting of the *in vitro* drug release data of F6 revealed zero-order as the best fit model with r^2=0.9989. The rest of the models were relatively poorly fitted, with coefficient of determination values below 0.9989 (Table VI).

Scanning Electron Microscopic Study of Asymmetric Membrane Coating

Scanning electron micrographs of the CAB coating membrane before and after dissolution of F6 revealed asymmetry in structure, showing an outer thin dense region (Fig. 6a). Exhausted membrane (obtained after complete dissolution) displayed many pores on the outer region of membrane (Fig. 6b).

Effect of Agitational Intensity, pH of Dissolution Media, and Osmotic Pressure on Drug Release

In vitro release profiles were generated for F6 (optimized formulation) to study the effect of agitational intensity, pH of dissolution media, and osmotic pressure on drug release. The release profiles at three different stirring speeds (Fig. 7a) were compared using one-way ANOVA (23). The calculated F value (2.15) was found to be less than the tabulated F value (3.26), suggesting that the release of THCl from the AM tablet was independent of agitational intensity. Thus, it can be stated that drug release from F6 was due to the controlled entry of dissolution medium across the CAB barrier (24) and not due to turbulence in dissolution medium. In order to analyze the effect of pH on the release media, a study was performed in extreme physiological pH values across the gastrointestinal tract. The release profiles (Fig. 7b) were compared using a t test. The calculated F value (0.0017) was found to be less than the tabulated F value (3.54). Thus, the release of THCl from the AM tablet was independent of media pH. Next, the effect of varying osmotic pressures of the release media was assessed on the drug release from F6. Figure 7c displays that drug release is inversely proportional to the osmotic pressure. It is evident that the drug release decreased as the osmotic pressure of the release media increased. The release profiles, when compared using one-way ANOVA, led to a calculated F value of 2.82, which was more than the tabulated F value of 2.78. This confirmed that the mechanism of drug release from the developed AM tablet was solely dependent on the osmotic pressure gradient across the asymmetric membrane coat that enveloped the core tablet.

Stability Studies

The stability studies of optimized formulation F6 revealed (Table VII) that the formulation was stable for 3 months when stored in sealed and unsealed containers at 40±2.0°C/75±5% RH. No physical or chemical changes were recorded in the experimental conditions. The tablets remained unchanged in

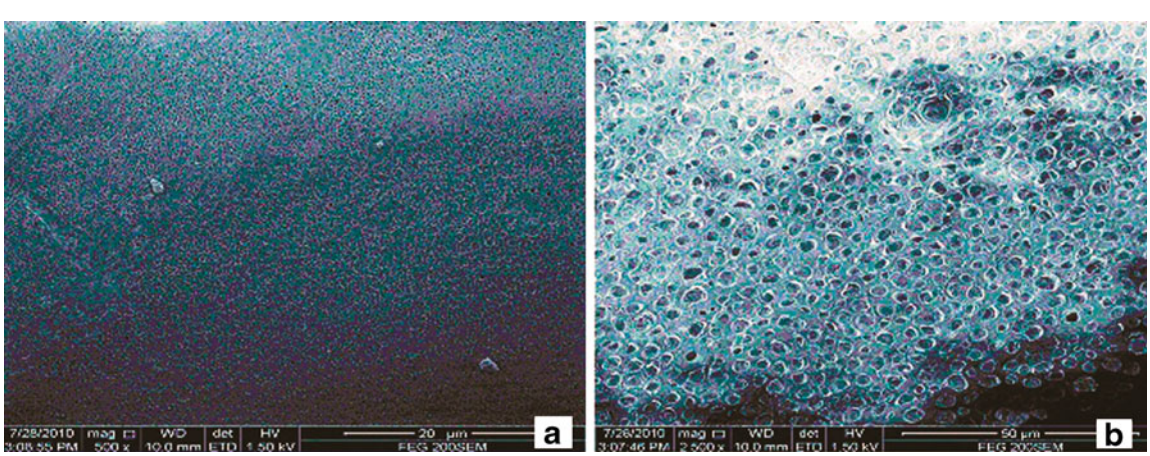

Fig. 6. SEM images of asymmetric membrane. **a** Before dissolution, outer region with 5% (*v*/*v*) glycerol. **b** After dissolution, outer region with 5% (*v*/*v*) glycerol

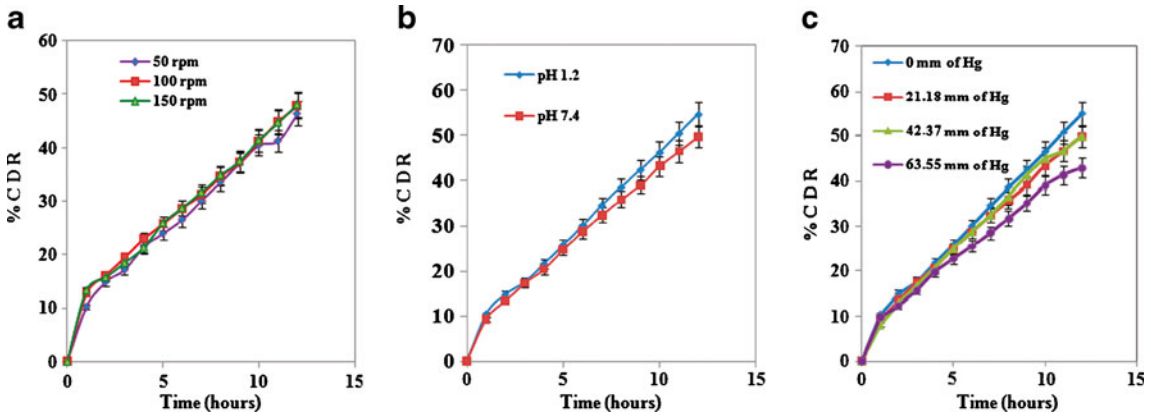

Fig. 7. *In vitro* drug release study of F6 to analyze the effect of agitational intensity (**a**), pH of the dissolution media (**b**), and variable osmotic pressure (**c**) on the release of THCl

color and appearance and the drug content remained within the standard limit until the end of 3 months. The tablets were also subjected to *in vitro* drug release, and the extent of drug release after 12 h was comparable for fresh and aged samples.

DISCUSSION

In order to develop osmotically controlled AM-coated tablets of THCl, systematic studies were performed. The excipients selected for the study did not exhibit incompatibility with the drug; hence, the AM tablets were formulated using the selected excipients and eight formulations were proposed based on a 2^3 factorial experimental design. Before proceeding for the AM tablet formulation of THCl, solubility modulation was attempted based on a common ion effect. The common ion selected was chloride ion and NaCl was selected as the salt of the ion. NaCl is readily soluble in water; hence, its solubility suppression effect on THCl would result in single-point solubility suppression. As the current work was aimed at preparing controlled-release formulation of the drug, it is imperative to design a controlled-release solubility suppressing agent that can exhibit suppression in solubility in a controlled manner over a designated period of time. Therefore, NaCl crystals were coated with a CAB solution of varying strengths (1–5%, *w/v*); the high solubility of THCl was successfully modulated (reduced) on the basis of a common ion effect (25). The inclusion of the water-soluble inorganic osmogen (NaCl) in the AM tablet of THCl shifted the equilibrium toward the unionized salt, thereby causing a reduction in the solubility of the hydrochloride salt. Interestingly, the suppression in solubility was dependent on the concentration of Cl^- ions that was in turn dependent on the strength of coating solution. Consequently, maximum reduction in solubility was observed at 5% (*w/v*) coating strength. NaCl coated with 4% CAB was selected as it displayed 49.91% of cumulative drug release at the 12th hour that is close to the target of achieving 50% drug release in 12 h. On the other hand, NaCl coated with 5% CAB suppressed the solubility to a greater extent and exhibited 45% CDR in 12 h, which was away from the target %CDR. Thus, NaCl coated with 4% CAB was expected to create the desired molar environment in core tablet formulation and is capable of providing osmotically controlled release of THCl over a period of 24 h.

Next, to select the levels of 4% coated NaCl to be included in the experimental design, the effect of varying molar concentrations on the solubility of drug was analyzed. At 2.0 M concentration of 4% (*w/v*) coated NaCl crystals, approximately a four times reduction in solubility with respect to original solubility was observed both in acid and alkaline media. At 2.5 M concentration, the solubility reduced to almost half the value recorded with 2.0 M concentration of coated NaCl. An almost 50% reduction in solubility at 2.5 M coated NaCl with respect to 2.0 M concentration guided the selection of low and high levels of coated NaCl to be used in factorial design for the formulation of AM tablet.

Eight batches of AM tablets were formulated based on a 2^3 factorial designs. First, the core tablets were made and evaluated for weight variation, hardness, thickness, friability, and drug content. Thereafter, the core tablets were dip-coated with CAB solution, as indicated in the design. Two different strengths of coating solutions were utilized so as to vary the thickness of the asymmetric membrane that can affect the drug release. *In vitro* release of factorially designed batches (F1–F8) was studied, and as a general release pattern, an initial faster phase was recorded in the first hour followed by a gradual linear release. The faster release can be the uncontrolled drug release phase attributed to

Table VII. Compiled Data for Stability Study of Asymmetric Membrane-Coated Tablets of Triprolidine Hydrochloride

Parameters	Time intervals (months)			
	0	1	2	3
Appearance	White, smooth	White, smooth	White, smooth	White, smooth
Drug content (%)	100.48±0.98	99.67±0.79	99.56±0.87	99.20±0.64
%CDR (after 12 h)	53.43±1.12	53.32±0.98	53.25±1.03	53.18±1.23

the lag time in the development of the osmotic pressure within the core tablet as the osmogen was not in a free state but was in a coated state. The coating around the inorganic osmogen delayed the process of its solution and, hence, delayed the osmotic effect. Once the osmotic effect got developed within the first hour, a controlled release phenomenon could be observed.

Analysis of the release profiles of group I formulations showed that F3 gave maximum drug release of 48.04% while F2 showed minimum drug release of 44.62% at the 12th hour. This might be due to the low level of CAB and high level of glycerol present in F3. It is suggested that a low level of CAB might reduce the diffusion path length for the drug to traverse before being released into the dissolution medium and that high level of glycerol might increase the number of pores on the membrane. Thus, a decrease in the thick wall of AM coat and an increase in the number of pores are assumed to exhibit a synergistic effect on the drug release from F3. A similar effect had been repeated from earlier studies that emerged from our laboratory for ketoprofen, flurbiprofen, and cefadroxil. (26–28). In group II, formulation F6 showed maximum drug release (53.52%) while F5 displayed minimum drug release of 44.57% at the 12th hour. This is due to the low level of CAB used for AM coating in F6 than F5 which reduced the diffusion path for drug released into the dissolution medium. Comparing groups I and II, it was found that F6 had a higher drug release (53.52%) than F3 (48.04%) due to the high osmotic gradient in F6 that favored the entry of the dissolution medium into the tablet. This not only increased the drug release but also controlled the release of drug for a prolonged time period (29).

The response coefficient significance study and the interaction study between independent variables explained the factors that had a significant effect on the *in vitro* drug release. Glycerol showed a positive effect on %CDR while CAB retarded the drug release. Coated NaCl produced sufficient osmotic pressure within the core and reduced the solubility of drug within the core formulation, thereby controlling the drug release in a desired manner. A graphical study of the interaction between the variables explained an interactive effect of variables on the drug. Predominantly, the lack of parallelism between CAB (X_1) and glycerol (X_2) indicated that the interaction between these two factors had maximum effect on the %CDR. However, the effect of interaction between glycerol (X_2) and coated NaCl (X_3), and CAB (X_1) and coated NaCl (X_3) on %CDR cannot be ignored. Both showed their effect on drug release. A high amount of coated NaCl would create more osmotic pressure and reduce drug solubility within the core, while glycerol at a higher level (10%, *v*/*v*) is assumed to enhance drug release due to its pore formation ability in the membrane. A slight interaction was also observed between CAB and glycerol in which glycerol displayed a stronger effect on rate control than CAB. These studies demonstrated that the design utilized was preferable for the development of optimized asymmetric membrane tablet preparation.

Physiological factors such as the effect of media pH and agitation rate did not show any effect on drug release as while the osmotic pressure of media increased the drug release was decreased (5). This confirmed that the drug release was solely dependent on osmotic pressure gradient across the asymmetric membrane and the surrounding environment. Scanning electron microscopy of the asymmetric membrane formed by CAB had outer thin, dense region supported on thick porous region. This asymmetric structure was a result of phase inversion, the transformation of polymer in its liquid phase to a state in which polymer is in its continuous phase. The results of accelerated stability on the tablets revealed a stable formulation.

CONCLUSION

Osmotically controlled triprolidine hydrochloride AM tablets that can provide controlled drug release for 12 h or longer and that have the potential of reducing the frequency of administration associated with the repeated administration of conventional triprolidine hydrochloride tablets were successfully developed. The formulation based on osmotic delivery can be claimed as a more robust formulation than capsules and was stable for 3 months.

ACKNOWLEDGMENTS

The authors are greatly thankful to the Indian Institute of Technology, New Delhi, India, for extending facilities for SEM for the characterization of asymmetric membrane and AICTE, India, for providing financial assistance to Mr. Rahul Dev.

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