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Development, optimization and pharmacokinetic evaluation of biphasic extended-release osmotic drug delivery system of trospium chloride for promising application in treatment of overactive bladder

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Abstract

Background: The research was aimed with an approach to formulate biphasic extended-release system of trospium chloride resulting in controlled release of drug up to 24 h with prospects of better control on urinary frequency, efficacy, tolerability, and improved patient compliance. The push–pull osmotic pump (PPOP) bi-layered tablet of trospium chloride (60 mg) was developed with the use of immediate-release polymers in the pull layer (30 mg drug) and polyethylene oxide in the push layer (remaining 30 mg drug). The tablet was formulated by compression after non-aqueous granulation, seal coating, and semipermeable coating. The tablet prepared was laser drilled to create an orifice for drug release.

Results: Comparative in vitro dissolution and in vivo pharmacokinetic analysis of available marketed formulations demonstrated the complete drug release within 16–18 h; hence the developed biphasic extended-release system has its great importance as it provides zero-order release up to 24 h.

Conclusions: The developed biphasic extended-release drug delivery system of trospium chloride provides the drug release for 24 h with effective plasma concentration in comparison with the available marketed formulation. Extended release of drug from the developed formulation provides scope for its promising application in the treatment of overactive bladder (OAB).

Keywords: Trospium chloride, Push–pull osmotic pump, Drug release, Pharmacokinetic, Overactive bladder

Background

The novel drug delivery technologies are gaining popularity as compared to conventional drug delivery due to their improved performance in terms of efficiency and patient compliance [1]. The conventional dosage forms have the limitation of sub-therapeutic and unpredictable plasma concentration. In a conventional oral drug delivery system, the drug release is immediate, whereas the extended-release of the drug provides effective concentration at the site of action for a long time and minimizes fluctuating drug levels [2]. Suboptimal physicochemical or physiological properties of drugs provide an opportunity to develop an optimized product with additional benefits. This is achieved by using the technique of controlled release and bioavailability enhancement [3]. Controlled release pharmaceutical dosage forms are superior to conventional dosage forms of the same drugs due to reduced dosing frequency, improved

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pharmacological activity, and a reduction in the fluctuation of drug concentration in plasma resulting in efficient and prolonged therapeutic effect [4]. Extended-release drug delivery is beneficial to deliver the drug molecules with a short plasma half-life. Most of the available oral controlled release drug delivery systems are matrix associated with diffusion as a drug release mechanism [5]. Multiple factors like pH of the medium, food-drug interaction, physiology of the body can influence the control on drug release and result in deprived in vitro–in vivo correlations (IVIVC). Advanced drug delivery systems improve the pharmacokinetic efficiency of the drug molecule. Recently, multiple drug delivery advancements have been proposed for controlled or modified release drug delivery systems. Novel techniques proficiently control the amount of drug delivery, sustaining the duration of therapeutic activity, and drug targeting to the tissue [6]. Formulation of an existing drug into a novel drug delivery system provides better patient compliance with efficiency and safety [7].

Osmotic drug delivery is a very promising approach based on the principle of osmotic pressure which controls the delivery of drugs [8]. The release proportion of activity from these systems is independent of the physiological factors of the gastrointestinal tract to a great extent. Osmotic systems have a better IVIVC, as the factors that are responsible for the variation of IVIVC affect the systems to a much lesser extent [9]. Push–pull osmotic pump, controlled porosity osmotic pump, and elementary osmotic pump are the key system for efficient and controlled drug delivery [10].

Trospium chloride is the leading drug in the treatment of overactive bladder in multiple clinical conditions. Trospium chloride has a half-life of 20 h and volume of distribution about 395 ± 140 L. The bioavailability of the drug is about 96%. Presently trospium chloride is available in immediate-release (20 mg) and extended-release (60 mg) unit dose formulations [11]. Extended-release formulations have the major drawback of decline plasma concentration after 16–18 h. This limitation of formerly available formulations creates an opportunity for the development of extended-release systems in the form of push–pull osmotic pump (PPOP) tablet with better pharmacokinetic performance. The important characteristic of the push–pull osmotic pump is a bilayer in the tablet. In the upper layer, the tablet drug is placed along with an osmogen. In the lower layer, polymeric osmogen is present. After the semipermeable coating, in the upper layer of the tablet, the delivery orifice is created. In preparation of controlled porosity osmotic pump, the tablet is simply coated and when it comes in contact with water or an aqueous medium, the delivery of the drug takes place by leaching water-soluble components from the pores of the tablet [12]. Laser drilling is not required in controlled porosity osmotic tablets as it does not require delivery orifice for drug delivery. An elementary osmotic pump is fabricated by coating the drug core with a semipermeable membrane and with the laser drilling the delivery orifice is created for the delivery drug from the osmotic pump. The investigation was aimed to formulate a push–pull osmotic pump (PPOP) bilayer tablet of trospium chloride with initial fast release and followed by sustained release with each layer of 30 mg dose [13]. The biphasic release was intending to maintain the plasma concentration within the therapeutic range up to 24 h.

Methods

Materials

Trospium chloride was procured from Macleods Pharma Ltd, India, Mannitol USP from Roquette, India, Povidone NF from ISP Ltd., India, Hydroxy Ethyl Cellulose NF from Ashland pvt ltd., Mumbai, India, Isopropyl alcohol NF from S.D.Fine Chem Ltd., Mumbai, India, and Magnesium Stearate NF from Mallinckrodt Inc, USA, whereas Polyethylene Oxide NF was procured from Dow Chemicals, United states, and Iron Oxide Yellow NF from Rockwood Pigments NA, Inc.

Experimental animals

The beagle dogs used for the research study were from the animal house of Wockhardt research center. The written informed consent was obtained to use the animals for the research study. The beagle dogs were housed in the Animal testing facility of Wockhardt Research Centre under standard recommended environment. The temperature and relative humidity were maintained at 22 °C ± 3 °C and 30 to 70% RH, respectively, in the animal room. Illumination was controlled to give 12 h of light and 12 h of dark cycles in the animal room. All the animal experiments were performed after approval of the protocol by the Institutional Animal Ethics Committee of Wockhardt research center, Aurangabad with registration no. 13/99 CPCSEA dated 01/04/2015. After the study, the beagle dogs were kept under observation for the period of five plasma half-life cycles (100 h) of trospium chloride for complete excretion of the drug. No physical and behavioral changes were observed with beagle dogs during and after the washout period (100 h) so there was no euthanasia required.

Compatibility study using differential scanning calorimetry

Trospium chloride was stored with individual ingredients for 4 weeks and then subjected to differential scanning calorimetry (DSC) analysis. The thermograms of the trospium chloride along with the physical mixture of drug and excipients were obtained using a DSC (Mettler

Toledo, Switzerland) in the nitrogen atmosphere. The scanning temperature range was 50–300 °C with a heating rate of 10 °C / min while the empty pan was taken as a reference. The obtained thermograms were analyzed to confirm the compatibility of the drug and the excipients [14].

Preparation of trospium (TSP) chloride push–pull osmotic pump tablets

Preparation of push–pull bi-layer tablet

The pull layer was prepared with TSP (30 mg), Mannitol USP, and different intra-granular ingredients. TSP, Hydroxy Ethyl Cellulose (Natrosol 250 L) NF, and Mannitol USP were co-sifted through sieve 20 # ASTM. Binder solution was prepared using Povidone NF (Kollidon K30) and Isopropyl alcohol with stirring. Granulation was carried out in a rapid mixer granulator using a binder solution. After passing through sieve 20 # ASTM, the granules were subjected to drying at 60 °C for 30 min in Fluidized Bed Dryer (FBD) (Retsch, Germany). Sifting was done through sieve #30 mesh. Magnesium stearate was screened through sieve #60 ASTM and mixed with the dried granules. The push layer was prepared with TSP (30 mg) Polyethylene Oxide NF (Polyox N80), Iron Oxide Yellow intra-granular ingredients separately with the same procedure of granulation subjected to the pull layer (Table 1). After the preparation of both the layers, the lubricated blend was compressed with a double rotary compress tablet machine with concave punches of 10.3 mm diameter [15].

Table 1 Composition of trospium chloride push–pull osmotic pump (PPOP) ER tablet

S. no	Ingredients/grade	mg/tablet
(A) Layer I (Pull layer)		
Intra-granular		
1	Trospium chloride*	30
2	Mannitol USP*	62
Binder#		
3	Povidone NF	4
4	Hydroxy Ethyl Cellulose	3
5	Isopropyl alcohol NF#	q.s
Extra-granular		
6	Magnesium Stearate NF (Veg grade)	1
	Layer I weight (mg)	100
(B) Layer II (Push layer)		
Intra-granular		
1	Trospium chloride	30
2	Polyethylene Oxide NF	250
3	Iron Oxide Yellow NF	1
Binder#		
4	Povidone NF	11
5	Isopropyl alcohol NF#	q.s
Extra-granular		
6	Magnesium Stearate NF (Veg grade)	3
	Layer II weight (mg)	295
	Core tablet weight (mg)	395

*Quantity based on 100% assay

#indicates, in finished product Water, Acetone and Isopropyl alcohol will be available in traces

Coating and laser drilling of tablets

In the coating process, isopropyl alcohol is transferred to stainless steel container. Hydroxypropyl Cellulose and Polyethylene glycol (PEG) 400 were added to Isopropyl alcohol with continuous stirring. The transparent mixture obtained after 45 min of stirring was used for seal coating. To achieve the desired weight gain tablet was subjected to seal coating in a coating machine (Gansons Limited, Mumbai). To perform the extended-release (ER) coating, mixture of acetone and purified water was transferred in a stainless steel container. To the above mixture polyethylene glycol, 3350 NF was added with continuous stirring. To this cellulose acetate (NF) was added slowly with stirring and the resultant solution was used for ER coating. The composition for both seal coating and ER coating is elaborated in Table 2. Laser drilling with an orifice diameter of 0.6 mm ± 0.05 mm was done on the pull side using a laser drilling machine (Control Micro System, USA) to release the drug from the immediate-release layer [16].

Optimization of the formulation by factorial design

Optimization of the formulation was done with Design Expert (Stat-Ease, Version 11). 2^4 factorial design was applied with consideration of the highest influencing factors. Response surface methodology (RSM) was used to study the influence of process parameters. Polyethylene oxide, cellulose acetate, polyethylene glycol, and orifice diameter were selected as independent factors in design, whereas percent drug release at 2 h (Acid stage), 5 h (Buffer stage), 11 h (Buffer stage), and 20 h (Buffer stage) were selected as the dependent factors to be analyzed (Table 3) [17].

Preformulation characteristics of tablet blend

The prepared blend of tablets was evaluated for preformulation parameters like angle of repose, density, Hausner's ratio, and Carr's index. The purpose of evaluation parameters was to study flow properties and

Table 2 Coating composition for trospium chloride push–pull osmotic pump (PPOP) ER tablet

Seal coating composition				ER coating composition		
Sr. no	**Ingredients**	**% w/w**	**mg/tablet**	**Ingredients**	**% w/w**	**mg/tablet**
1	Core tablet	–	395	Seal coated tablet	–	407
2	Hydroxypropyl Cellulose NF	83.33	10	Cellulose Acetate	94.05	42.7
3	Polyethylene glycol 400 NF	16.67	2	Polyethylene glycol 3350 NF	5.95	2.7
4	Isopropyl alcohol NF	–	q.s	Acetone NF (99% part)	–	q.s
	Solid content of coating solution (%w/w)	5		Purified water USP (10% part)	–	q.s
	Target Weight Gain (%w/w)	3		Solid content (%w/w)	3	
	Seal coated tablet weight (mg)	**407**		Target Weight Gain (%w/w)	11	
	–	–		Seal coated + ER coated tablet weight (mg)	**452.4**	

Bold indicates the total weight after seal coating and Extended Release (ER) coating

compressibility of the powder blend to formulate tablets [18].

Evaluation of trospium chloride PPOP tablets

PPOP tablets of trospium chloride were evaluated for different official and non-official evaluation parameters, viz. weight variation, friability, drug content, and hardness. Weight variation was determined by a random selection of 20 tablets, and the procedure was followed as per United States Pharmacopoeia (USP). The Friability test was carried out using 10 tablets in a friabilator with 25 rpm for 4 min. The percent friability was determined using the following formula:

$$\text{Percent friability} = W_0 - W/W \times 100$$

Table 3 Experimental design layout and observed responses for trospium chloride ER tablets

Batches	Factor A	Factor B	Factor C	Factor D	Response			
	Polyethylene oxide	Cellulose Acetate	Polyethylene glycol 6000	Orifice diameter	% drug release at 2 h (Acid stage)	% drug release at 5 h (Buffer stage)	% drug release at 11 h (Buffer stage)	% drug release at 20 h (Buffer stage)
	mg	% ratio	% ratio	mm	%	%	%	%
TSP1	250	94	6	0.6	20	42	66	97
TSP2	250	94	6	0.6	18	43	65	96
TSP3	300	97	3	0.5	4	19	46	96
TSP4	200	91	3	0.5	10	25	65	100
TSP5	200	97	9	0.5	14	32	76	98
TSP6	200	91	9	0.7	42	65	82	100
TSP7	300	91	3	0.5	12	22	50	95
TSP8	300	91	9	0.5	14	52	70	94
TSP9	200	91	3	0.7	14	28	68	99
TSP10	300	97	9	0.5	12	32	58	95
TSP11	200	97	3	0.5	7	23	58	99
TSP12	300	97	3	0.7	5	17	43	92
TSP13	250	94	6	0.6	22	39	67	97
TSP14	300	97	9	0.7	15	36	61	93
TSP15	250	94	6	0.6	25	45	71	98
TSP16	300	91	3	0.7	10	27	50	92
TSP17	200	91	9	0.5	45	71	85	99
TSP18	300	91	9	0.7	19	43	65	96
TSP19	200	97	9	0.7	12	28	72	100
TSP20	200	97	3	0.7	8	21	60	100

% Drug release values are expressed as mean where, $n = 3$

Table 4 In vivo animal study details

Group	Number of samples		Time points (h)	Study days	Blood volume collected	Anticoagulant
	Male	Female				
Trospium chloride ER tablets 60 mg OROS tablets (test product)	03	00	0 h before administration and 1, 3, 5, 8, 10, 12, 14, 16, 18, 21, 24 h after administration	1 day	0.7 mL	K_3 EDTA
Sanctura® XR capsules 60 mg (innovator CAPSULES) (reference product)	02	01	0 h before administration and 1, 3, 5, 8, 10, 12, 14, 16, 18, 21, 24 h after administration	1 day	0.7 mL	K_3 EDTA

where W_0 is the initial weight of 10 tablets and W is the weight of 10 tablets after 100 rotations. The hardness was measured using a hardness tester in kg/cm^2 [19].

Comparative in vitro dissolution analysis of PPOP tablet of trospium chloride and marketed formulation with release kinetics

In vitro dissolution study was carried out in both acid and buffer stage at 37 ± 0.5 °C at 50 rpm with 900 mL of 0.1 N HCl and pH 7.4 phosphate buffer as a dissolution media in acid stage and buffer stage, respectively, using USP type-II dissolution apparatus (Electrolab, Mumbai). Initially, the dissolution was performed for 2 h and 15 mL of aliquots was withdrawn from each vessel. The solution was filtered through a Nylon filter with a pore size of 0.45 µm, after discarding the first 5 mL the filtrate was collected analyzed for drug content. The aliquots were subjected to UV analysis at 215 nm (UV spectrophotometer, Shimadzu Corporation, Kyoto, Japan) for drug concentration determination. The dissolution at the buffer stage was performed with pH 7.4 phosphate buffer and parameters were set. With the maintenance of the sink condition, the in vitro drug release was analyzed for 24 h with a specific time interval. The dissolution study of the optimized batch of trospium chloride PPOP tablet was compared with the marketed formulation (Sanctura XR® Capsule 60 mg). The release kinetics was obtained from dissolution analysis by DD solver trial version [20].

Dissolution analysis by hydration study

To study the solvent permeation through semi-permeable coating membrane and hydration of core part of tablets, the hydration study was performed with optimized tablet formulation (TSP-18). At different dissolution time intervals, the tablet was cut into two half portions using the sharp blade. The photographs were captured and labeled to interpret the hydration of the core membrane and release of drug through the orifice at different time intervals [21].

Coating membrane morphology of initial and after dissolution samples

To interpret the drug release mechanism, the scanning electron microscope (SEM) (Philips, XL 30 ESEM TMP + EDAX, Netherland) studies of coating membranes of the tablets were carried out before and after the dissolution. Initially, the coating membrane of the optimized tablet formulation was taken out by thin cutting with the help of sharp bled. After the cleaning drying with the help of a cloth, the membrane was subjected to SEM. Similarly after 24 h of dissolution again the coating membrane was taken out. After washing 3–4 times the coating membrane was dried at 45 °C for 12 h in tray dryer and subjected to SEM. Finally the coating morphology was comparatively analyzed from SEM images [22].

Table 5 Parameters for analytical method development for in vivo estimation of trospium chloride

	Chromatographic specifications		Mass spectrometric specifications	
1	Stationary Phase	Zorbax SB C18, 75 × 2.1 mm, 3.5 µm with guard column	MRM transition (amu)	392.2 > 182
2	Mobile Phase	Mixture of Buffer: Organic mixture (20:80; v/v)	Declustering potential (V)	120
3	Organic mixture	Acetonitrile: Methanol (95:5; v/v)	Entrance potential (V)	8
4	Flow rate	0.3 mL/min	Collision energy (V)	41
5	Auto-injector temperature	5 ± 1 °C	Collision cell exit potential (V)	8
6	Column temperature	30 ± 1 °C	Dwell time (ms)	300
7	Injection volume	5 µL		-
8	Run time	3.5 min	-	-
9	Detector	Triple quadrupole mass spectrometer	-	-

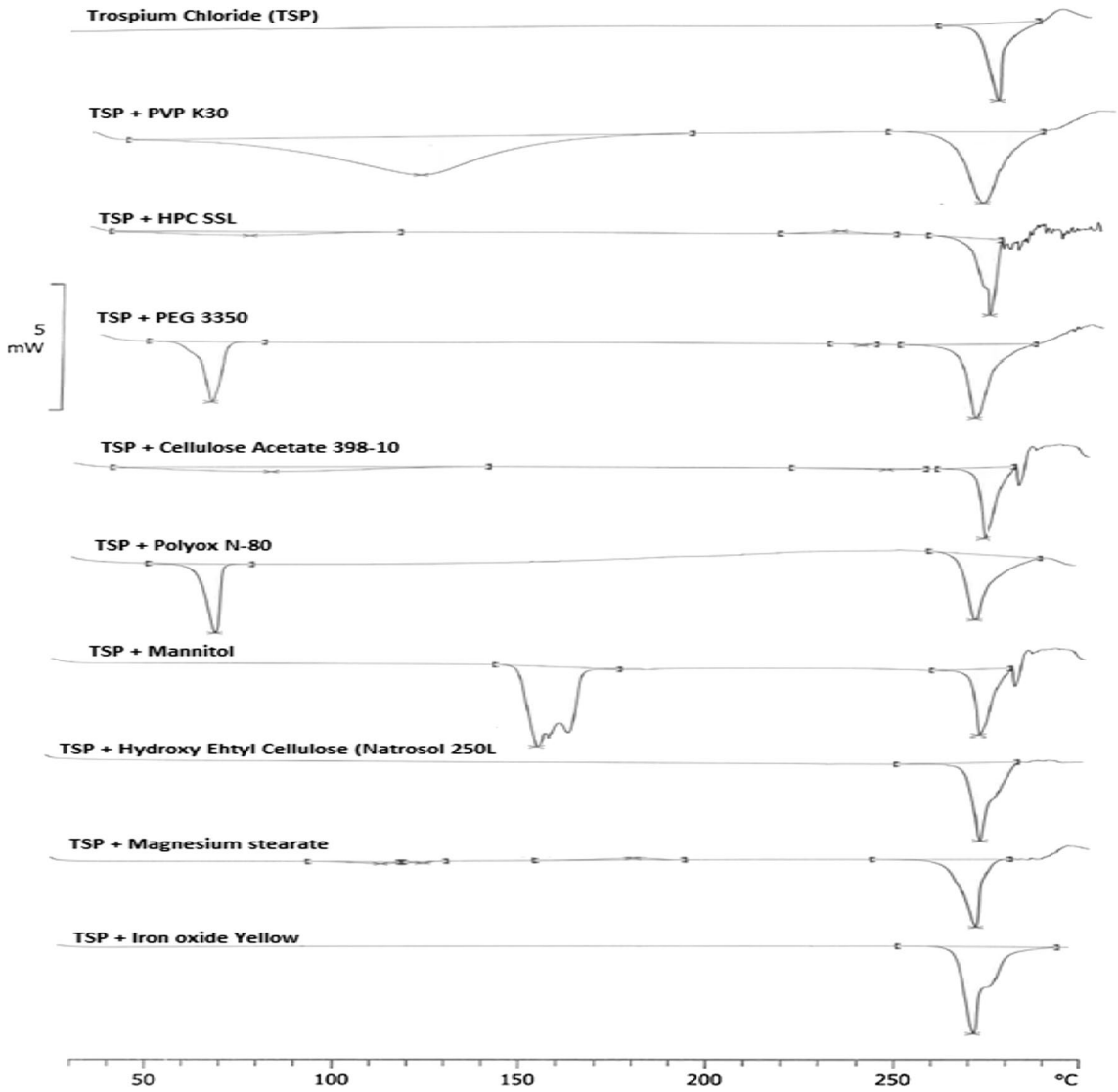


Fig. 1 DSC thermograms of the pure drug and physical mixtures of drug and excipients

Table 6 DSC data of the peak values of the pure drug and the mixture of drug and excipients

S. no	Ingredients	API: excipient ratio	Peak value (°C)
1	Trospium chloride (API)	–	272.89
2	API + Povidone NF (Kollidon K30)	1:0.5	265.78
3	API + Hydroxypropyl Cellulose NF (Nisso HPC SSL)	1:0.1	270.17
4	API + Polyethylene glycol 3350 NF (Polyglykol 3350 P)	1:0.1	266.61
5	API + Cellulose Acetate NF (CA-398–10)	1:2	272.09
6	API + Polyethylene Oxide NF (Polyox N80)	1:10	272.18
7	API + Mannitol USP (Pearlitol SD 200)	1:2	272.09
8	API + Hydroxy ethyl cellulose NF (Natrosol 250 L)	1:0.25	272.81
9	API + Magnesium Stearate NF (Veg grade)	1:0.25	267.51
10	API + Iron Oxide Yellow NF (Sicovit Yellow)	1:0.1	272.06

Table 7 Preformulation characteristics of tablet blend of all experimental batches

Batch	Angle of repose (°)	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Compressibility Carr's index	Hausner's ratio
TSP1	28.61 ± 0.12	0.492 ± 0.02	0.579 ± 0.02	15.25 ± 0.01	1.18 ± 0.09
TSP2	28.24 ± 0.11	0.495 ± 0.01	0.582 ± 0.01	15.21 ± 0.03	1.19 ± 0.07
TSP3	28.76 ± 0.09	0.488 ± 0.02	0.575 ± 0.02	15.18 ± 0.05	1.17 ± 0.04
TSP4	28.85 ± 0.08	0.491 ± 0.02	0.581 ± 0.02	15.28 ± 0.1	1.16 ± 0.04
TSP5	28.58 ± 0.13	0.493 ± 0.01	0.576 ± 0.01	15.23 ± 0.02	1.18 ± 0.03
TSP6	28.45 ± 0.14	0.489 ± 0.03	0.585 ± 0.02	15.18 ± 0.09	1.19 ± 0.05
TSP7	28.39 ± 0.11	0.491 ± 0.02	0.574 ± 0.02	15.21 ± 0.03	1.17 ± 0.06
TSP8	28.67 ± 0.15	0.486 ± 0.01	0.579 ± 0.01	15.26 ± 0.04	1.18 ± 0.01
TSP9	28.51 ± 0.12	0.494 ± 0.02	0.580 ± 0.02	15.22 ± 0.02	1.19 ± 0.04
TSP10	28.73 ± 0.11	0.491 ± 0.01	0.578 ± 0.02	15.28 ± 0.03	1.18 ± 0.10
TSP11	28.43 ± 0.15	0.486 ± 0.01	0.586 ± 0.02	15.21 ± 0.1	1.17 ± 0.09
TSP12	28.58 ± 0.15	0.488 ± 0.02	0.575 ± 0.01	15.26 ± 0.04	1.16 ± 0.03
TSP13	28.34 ± 0.09	0.490 ± 0.02	0.571 ± 0.01	15.22 ± 0.05	1.18 ± 0.05
TSP14	28.57 ± 0.11	0.493 ± 0.02	0.576 ± 0.01	15.18 ± 0.07	1.18 ± 0.09
TSP15	28.69 ± 0.10	0.499 ± 0.03	0.578 ± 0.01	15.21 ± 0.1	1.2 ± 0.10
TSP16	28.24 ± 0.07	0.487 ± 0.02	0.584 ± 0.02	15.23 ± 0.06	1.18 ± 0.11
TSP17	28.56 ± 0.17	0.491 ± 0.02	0.572 ± 0.02	15.16 ± 0.08	1.19 ± 0.03
TSP18	28.49 ± 0.14	0.493 ± 0.01	0.577 ± 0.01	15.22 ± 0.01	1.17 ± 0.04
TSP19	28.53 ± 0.12	0.490 ± 0.02	0.579 ± 0.01	15.25 ± 0.06	1.20 ± 0.03
TSP20	28.58 ± 0.11	0.489 ± 0.02	0.578 ± 0.02	15.18 ± 0.09	1.18 ± 0.04

Values are expressed as mean ± S.E.M; $n = 3$

Coating thickness measurement and study of its impact on drug releases

In laser drilled tablets, cellulose acetate coating was removed with a cutter and thin sections were done using a cutter. The membrane was cleaned with water, dried with tissue paper to remove any adherent particles. The thickness of coated surface images was captured using a microscope (Nikon, Eclipse Ni-U enabled NIS-Elements BR software) at 10 × magnification [23].

Impact of semipermeable coating weight gain on drug release

To determine the effect of % weight gain on dissolution, the formulation TSP-18 was coated with a coating composition, to obtain the tablets with varying weight gain (10, 11 and 12% w/w). The in vitro release profiles of the drug from these formulations were analyzed to interpret the effect [24].

Impact of drill orifice diameter on drug release

Drill diameter impact on dissolution was studied as an independent factor in DOE trials. This study was carried out by drilling orifices of various diameters of 0.5 mm, 0.6 mm, and 0.7 mm on the semi-permeable membrane of the optimized formulation. Then the tablets were subjected to dissolution and analyzed at different time intervals [25].

Impact of dissolution media pH on drug release

To study the effect of pH on drug release, the formulation was subjected for dissolution in mediums with varying pH like water (7.0), 0.1 N HCl (pH 1.2), acetate buffer (pH 4.5), phosphate buffer (pH 6.8), and phosphate buffer (pH 7.4). USP-II (paddle apparatus) was used at 50 rpm for 24 h. 10 ml sample was withdrawn at predetermined intervals using an autosampler and further analysis was carried out [26].

Impact of agitation speed on drug release

To assure that the release of drug from coated tablets follows only osmotic pressure, it is important to prove that the intensity of agitation does not affect the drug release. To analyze the effect of agitation intensity, the USP type II dissolution apparatus (paddle) was used with varying speeds of rotations like 25, 50, and 100 rpm. The withdrawn samples at different time intervals were passed through a filter with a pore size of 10 µm and analyzed for percent cumulative drug release [27].

In vivo pharmacokinetic analysis of trospium chloride ER formulation

Two groups of each three beagle dogs (male/female) were selected for in vivo pharmacokinetic analysis. Trospium chloride ER tablet 60 mg, OROS tablet (Test product) (60 mg single dose), and Sanctura® XR capsules 60 mg

Table 8 Evaluation parameters of core and push–pull osmotic pump (PPOP) tablets of trospium chloride

Batch	Evaluation parameters of core tablets					Parameters of developed osmotic pump tablets			
	Weight (mg)	Diameter (mm)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight (mg)	Diameter (mm)	Thickness (mm)	Drug content (%)
TSP1	396 ± 5	10.32	6.42 ± 0.01	14.40 ± 2	0.05	452 ± 5	10.80 ± 0.01	6.75 ± 0.01	98.65 ± 2
TSP2	392 ± 4	10.32	6.45 ± 0.02	14.32 ± 1	0.05	455 ± 6	10.83 ± 0.02	6.78 ± 0.02	101.36 ± 1
TSP3	446 ± 6	10.33	6.82 ± 0.01	17.54 ± 2	0.2	500 ± 3	10.86 ± 0.02	6.71 ± 0.02	100.54 ± 0.5
TSP4	345 ± 3	10.31	6.11 ± 0.02	15.69 ± 2	0.1	402 ± 8	10.78 ± 0.01	6.84 ± 0.01	97.85 ± 2
TSP5	350 ± 7	10.32	6.18 ± 0.03	16.98 ± 1	0.13	409 ± 9	10.81 ± 0.01	6.71 ± 0.01	102.12 ± 0.05
TSP6	348 ± 3	10.33	6.15 ± 0.02	18.32 ± 1	0.11	402 ± 3	10.75 ± 0.02	6.78 ± 0.02	98.42 ± 1
TSP7	445 ± 4	10.31	6.81 ± 0.01	16.58 ± 1	0.05	501 ± 7	10.82 ± 0.02	6.70 ± 0.02	97.27 ± 1
TSP8	449 ± 9	10.32	6.86 ± 0.01	15.74 ± 2	0.1	499 ± 4	10.86 ± 0.01	6.76 ± 0.01	100.95 ± 0.05
TSP9	345 ± 5	10.32	6.12 ± 0.02	14.52 ± 2	0.12	405 ± 9	10.80 ± 0.01	6.67 ± 0.01	99.47 ± 0.05
TSP10	445 ± 4	10.33	6.88 ± 0.02	18.65 ± 1	0.12	505 ± 10	10.81 ± 0.02	6.75 ± 0.01	97.36 ± 2
TSP11	351 ± 3	10.31	6.10 ± 0.01	16.21 ± 1	0.14	404 ± 3	10.78 ± 0.02	6.68 ± 0.01	102.11 ± 1
TSP12	445 ± 7	10.32	6.90 ± 0.01	15.45 ± 2	0.12	503 ± 5	10.82 ± 0.01	6.81 ± 0.02	100.34 ± 1
TSP13	397 ± 5	10.32	6.42 ± 0.02	13.20 ± 2	0.16	448 ± 4	10.81 ± 0.01	6.80 ± 0.03	98.67 ± 2
TSP14	447 ± 8	10.32	6.87 ± 0.02	16.00 ± 2	0.14	508 ± 5	10.79 ± 0.02	6.74 ± 0.02	98.28 ± 3
TSP15	394 ± 4	10.33	6.41 ± 0.01	18.10 ± 1	0.14	454 ± 8	10.80 ± 0.01	6.70 ± 0.03	97.73 ± 2
TSP16	443 ± 3	10.33	6.89 ± 0.01	14.36 ± 2	0.13	507 ± 7	10.84 ± 0.02	6.75 ± 0.02	101.36 ± 2
TSP17	346 ± 6	10.31	6.13 ± 0.02	14.49 ± 3	0.11	402 ± 4	10.82 ± 0.02	6.69 ± 0.01	96.35 ± 1
TSP18	444 ± 4	10.31	6.91 ± 0.02	15.00 ± 1	0.09	509 ± 5	10.77 ± 0.01	6.82 ± 0.02	100.84 ± 2
TSP19	346 ± 5	10.32	6.18 ± 0.01	17.75 ± 1	0.05	401 ± 9	10.83 ± 0.01	6.85 ± 0.02	98.91 ± 1
TSP20	348 ± 3	10.32	6.11 ± 0.01	16.00 ± 2	0.12	405 ± 9	10.81 ± 0.02	6.74 ± 0.03	99.35 ± 2

Values are expressed as mean ± S.E.M; $n = 3$

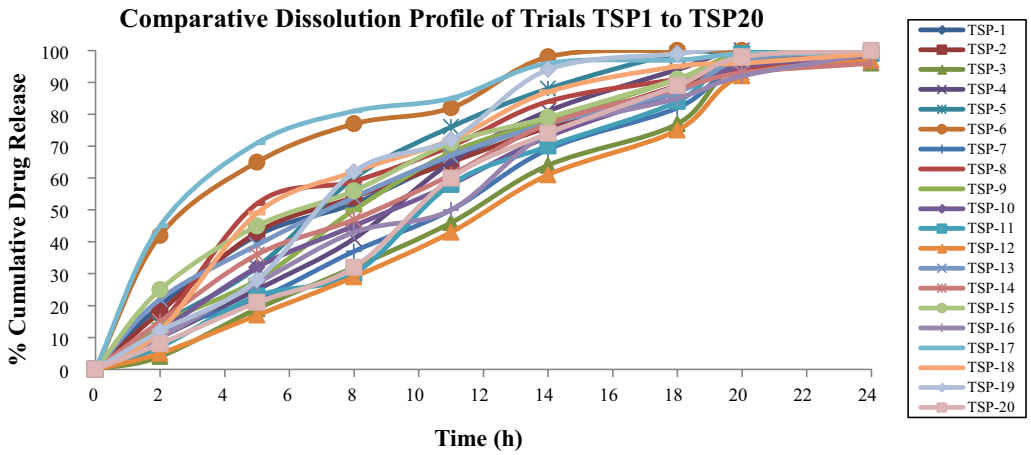


Fig. 2 In vitro dissolution and release kinetics of DOE batches trospium chloride PPOP tablet

(reference product) were administered to each beagle dog orally and plasma sample was collected through the cephalic vein of beagle dog (Table 4). Plasma was separated using Heraeus Biofuge centrifugation. The plasma samples were further processed for drug measurement using LC/MS/MS method [28].

An analytical method for in vivo estimation of trospium chloride

Simple and efficient liquid chromatography/tandem mass spectrometry (LC–MS/MS) analytical technique was developed and used to estimate the concentration of trospium chloride in dog plasma after administration of trospium chloride extended-release tablets (60 mg) and

Table 9 (a) Release kinetics of DOE batches TSP-1 to TSP-10, (b) release kinetics of DOE batches TSP-11 to TSP-20

Trials	Unit	TSP-1	TSP-2	TSP-3	TSP-4	TSP-5	TSP-6	TSP-7	TSP-8	TSP-9	TSP-10
(a)											
Zero order	K0	5.298	5.277	4.468	5.303	5.730	6.260	4.693	5.489	5.314	5.000
	R2	0.921	0.918	0.986	0.987	0.933	0.551	0.996	0.849	0.974	0.984
First order	K	0.107	0.107	0.070	0.097	0.122	0.208	0.077	0.122	0.101	0.090
	R2	0.984	0.986	0.902	0.924	0.957	0.981	0.931	0.983	0.958	0.966
Korsmeyer Peppas	N	0.642	0.640	1.173	0.931	0.720	0.360	1.001	0.580	0.802	0.821
	KKP	14.068	14.075	2.774	6.409	12.340	35.520	4.669	17.262	9.142	8.163
	R2	0.998	0.996	0.994	0.989	0.976	0.990	0.996	0.971	0.992	0.999
Higuchi	KH	20.348	20.272	16.496	19.881	21.860	24.778	17.533	21.229	20.128	18.913
	R2	0.979	0.978	0.819	0.885	0.937	0.958	0.874	0.965	0.929	0.930
Hixon–Crowell	KHc	0.029	0.029	0.020	0.027	0.033	0.054	0.022	0.033	0.028	0.025
	R2	0.991	0.992	0.934	0.959	0.984	0.961	0.960	0.982	0.984	0.987
Trials	**Unit**	**TSP-11**	**TSP-12**	**TSP-13**	**TSP-14**	**TSP-15**	**TSP-16**	**TSP-17**	**TSP-18**	**TSP-19**	**TSP-20**
(b)											
Zero order	K0	4.832	4.272	5.284	5.096	5.474	4.810	6.259	5.648	5.794	4.969
	R2	0.986	0.984	0.916	0.960	0.878	0.988	0.401	0.872	0.936	0.987
First order	K	0.080	0.065	0.107	0.096	0.118	0.083	0.237	0.127	0.122	0.084
	R2	0.905	0.901	0.986	0.978	0.986	0.950	0.984	0.980	0.934	0.905
Korsmeyer Peppas	n	1.074	1.216	0.632	0.735	0.577	0.898	0.304	0.613	0.762	1.055
	KKP	3.938	2.356	14.399	10.522	17.307	6.371	41.223	16.245	11.103	4.268
	R2	0.988	0.996	0.999	0.996	0.999	0.992	0.988	0.971	0.965	0.988
Higuchi	KH	17.943	15.738	20.311	19.414	21.151	18.088	24.960	21.776	22.014	18.468
	R2	0.842	0.810	0.982	0.954	0.993	0.900	0.916	0.958	0.913	0.846
Hixon–Crowell	KHc	0.023	0.019	0.029	0.027	0.032	0.023	0.061	0.034	0.033	0.024
	R2	0.938	0.932	0.992	0.994	0.987	0.974	0.954	0.989	0.966	0.940

Sanctura XR® Capsules (60 mg). All the specifications of the analytical method are illustrated in Table 5. For the analysis dog plasma sample (50 µL) was added to 400 µL of acetonitrile in a 1.5 ml centrifuge tube and vortex for 1 min. The internal standard (50 µL) was added, vortex, and centrifuged at 10,000 rpm for 5 min, and the supernatant was placed for auto-sampling for LC–MS [29].

Stability study of optimized batch

For stability study samples were stored at two different storage conditions. The samples stored at 40 °C ± 2 °C and 75% ± 5% RH were analyzed at the interval of 1 month, 2 months, 3 months, and 6 months, whereas samples preserved at 25 °C ± 2 °C and 60% ± 5% RH were analyzed at the interval of 3 months, 6 months and 12 months. The results were compared concerning the physical changes in the tablet along with assay, and dissolution at acid and buffer stage [30].

Results

DSC analysis for physical compatibility

The physical mixture compatibility is an important parameter to be considered for drug formulation. The DSC thermograms obtained of physical mixtures of drug and inactive ingredients provide evidence of the compatibility of excipients with trospium chloride as there are no significant changes in the thermogram of drug and physical mixtures. The DSC studies confirm the compatibility of the excipients with the drug used in the formulation. The DSC thermogram for the pure drug and mixtures of drug and different excipients are given in Fig. 1. The data obtained from the DSC studies are reported in Table 6. The results indicate that there is no significant change in the peaks of drug-excipient mixtures in comparison with the pure drug, indicating that there is no incompatibility of excipients with the drug.

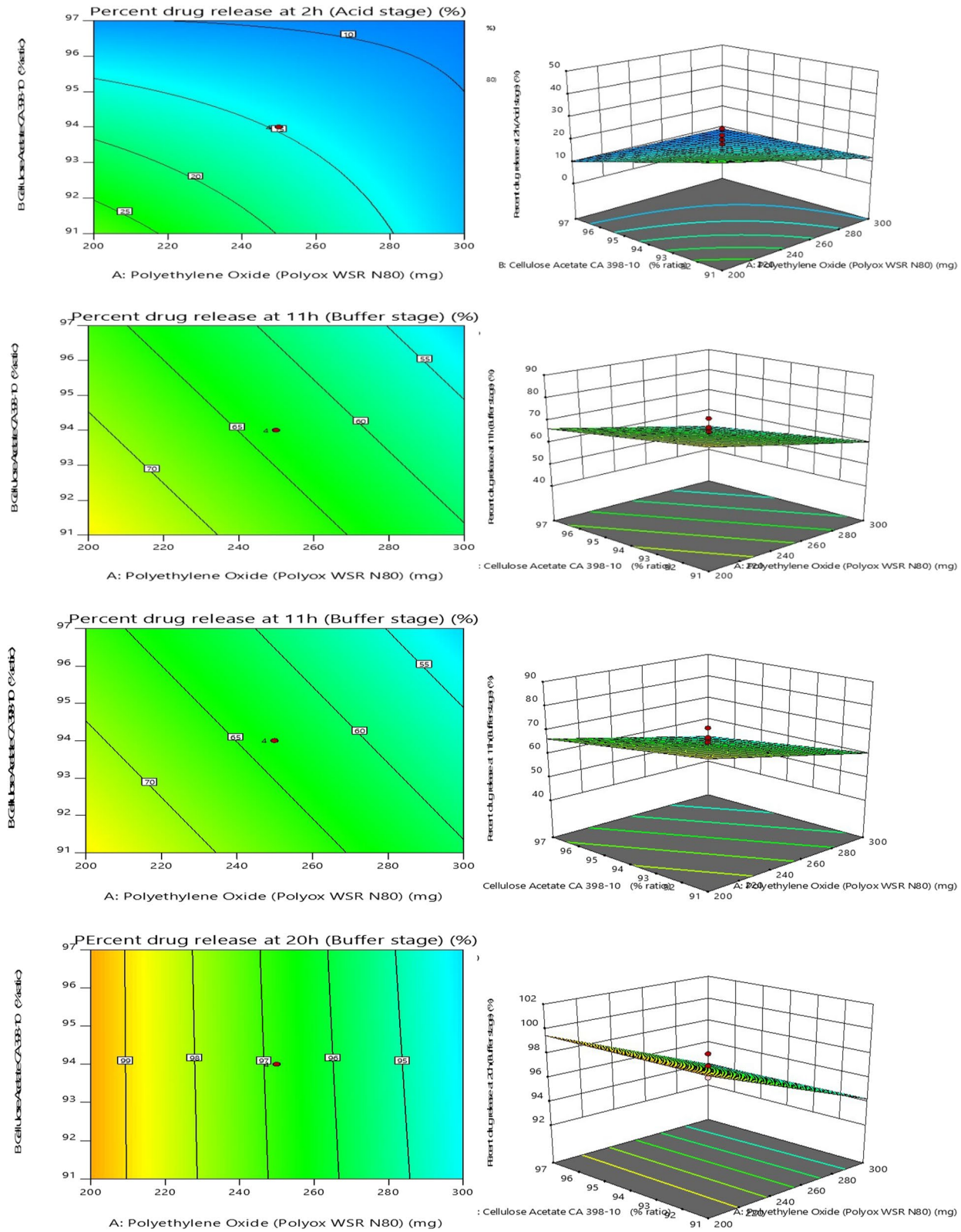


Fig. 3 Percent drug release at 2 h (Acid stage), 5 h, 11 h, 20 h (Buffer stage) showing Contour plot and Response surface graph

Table 10 ANOVA analysis for trospium chloride ER tablets DOE batches

Response	Source	Sum of squares	*df*	Mean square	*F* value	*p* value	Remarks
Percent drug release at 2 h (acid stage)	Model	2027.00	7	289.57	62.76	< 0.0001	significant
	Residual	50.75	11	4.61			
	Cor Total	2212.95	19				
Percent drug release at 5 h (Buffer stage)	Model	3980.94	7	568.71	79.95	< 0.0001	significant
	Residual	78.25	11	7.11			
	Cor Total	4267.20	19				
Percent drug release at 11 h (Buffer stage)	Model	2317.00	8	289.63	66.20	< 0.0001	significant
	Residual	43.75	10	4.37			
	Cor Total	2405.75	19				
Percent drug release at 20 h (Buffer stage)	Model	137.06	9	15.23	25.50	< 0.0001	significant
	Residual	5.37	9	0.5972			
	Cor Total	142.55	19				

df degrees of freedom, *Cor Total* Corrected total sum of squares; *α*: 0.05

Table 11 The regression equation obtained for percent drug release

Response	Regression equation for coded factors	R^2	Adjusted R^2	Predicted R^2
Percent drug release at 2 h (acid stage)	= + 14.75 − 4.25A − 5.13B + 6.00C + 3.63AB − 3.25AC − 2.37BC + 4.12ABC	0.9756	0.9600	0.9309
Percent drug release at 5 h (Buffer stage)	= + 34.19 − 2.44A − 8.19B + 11.44C + 2.44AB − 0.9375AC − 5.44BC + 2.94ABC	0.9807	0.9685	0.9332
Percent drug release at 11 h (Buffer stage)	= + 63.50 − 7.25A − 4.25B + 8.50C + 0.00D + 0.5AC + 0.25AD − 0.25CD + 1.25ACD	0.9815	0.9666	0.9335
Percent drug release at 20 h (Buffer stage)	= + 96.81 − 2.69A − 0.0625B + 0.187C − 0.187D − 0.062AB − 0.687AD − 0.0625BD + 0.687CD − 0.5625ABD	0.9623	0.9245	0.8065

(A) Polyethylene oxide (mg), (B) cellulose acetate (% ratio), (C) polyethylene glycol 3350 (% ratio) and (D) orifice diameter (mm)

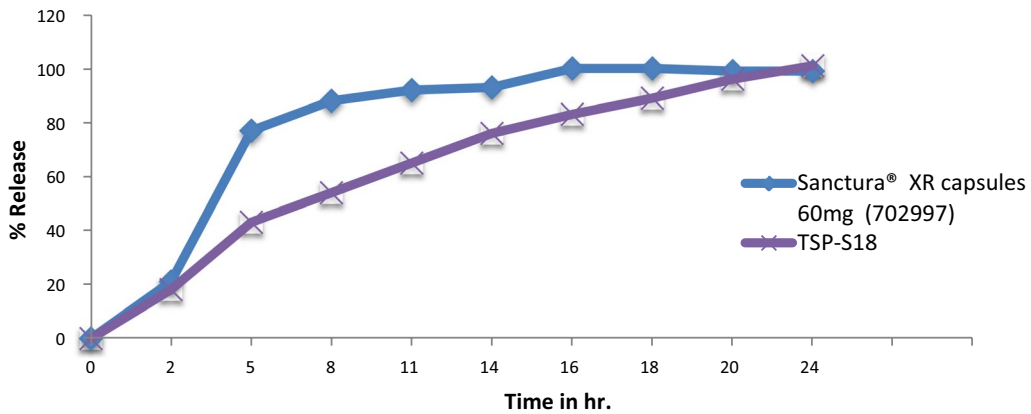


Fig. 4 Comparative dissolution results of marketed and optimized osmotic tablet formulation (TSP-18)

Preformulation characteristics of tablet blend

The preformulation evaluation for packing and flow properties of all 20 batches of trospium chloride showed that the blends multiple batches have good flow properties and compressibility index and suitable for tablet compression (Table 7).

Preparation and evaluation of trospium chloride PPOP tablet

The prepared extended-release formulation of TSP was developed for once in a day dosing. The prepared formulations were evaluated for friability, weight variation, and hardness. The results for the evaluation parameters

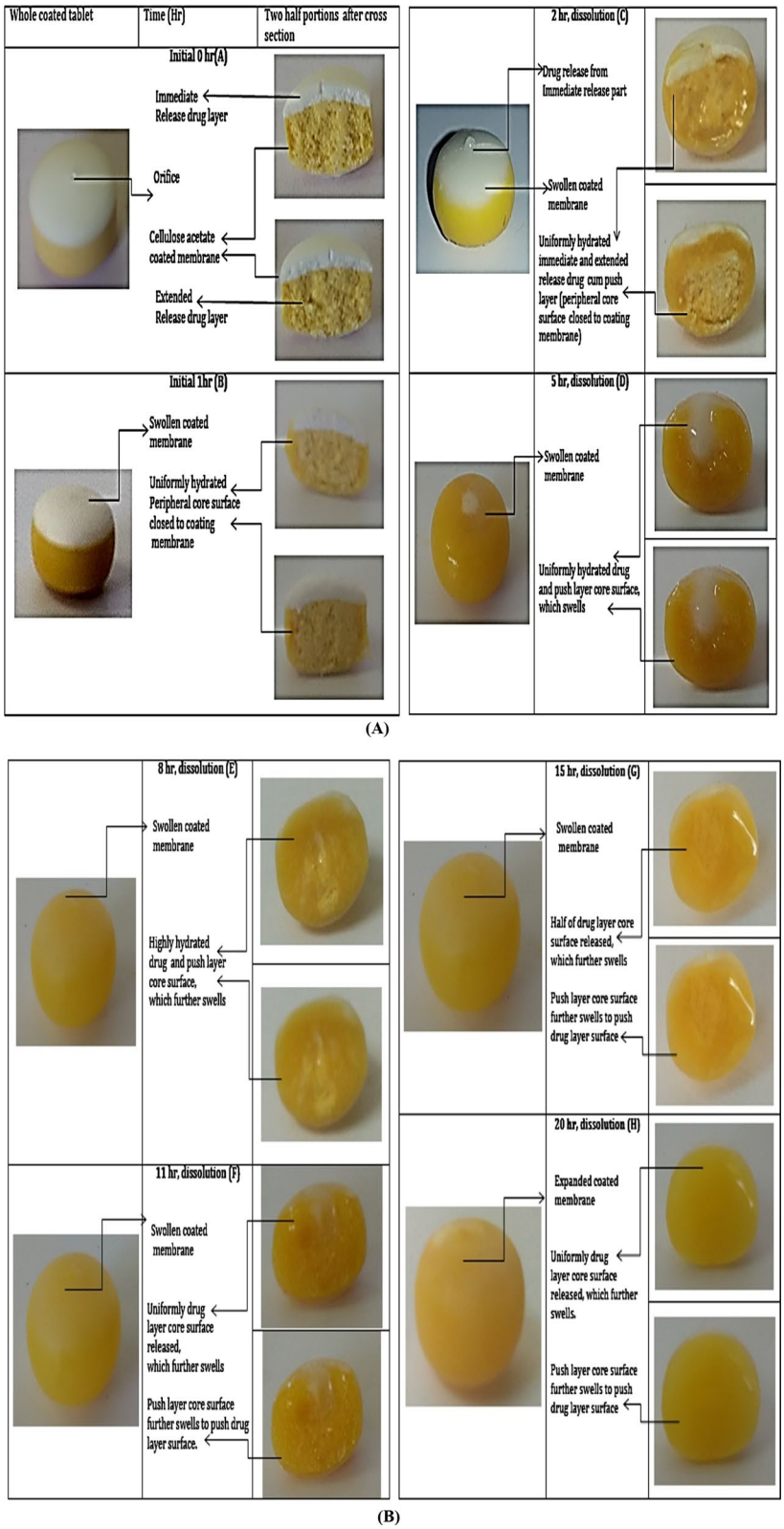


Fig. 5 TSP-18 coated tablets after exposure to the dissolution buffer (hydration study) at 0–20 h

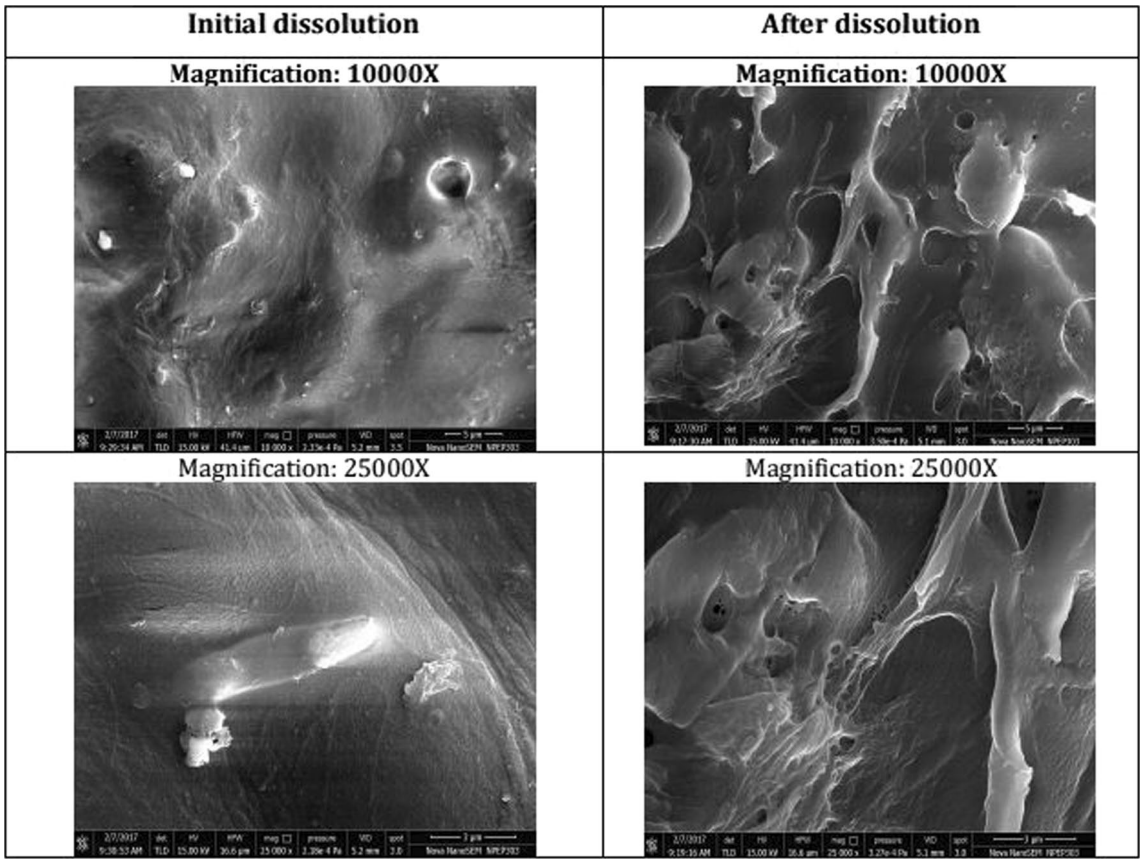


Fig. 6 Coating membrane morphology of initial and after dissolution samples by SEM

are recorded in Table 8 and were found to be within the desired limit.

The evaluation parameters for the compressed tablets showed that the formulation is comfortable with the respective granulation process, blend, and core tablet parameters at small-scale batches. All the parameters evaluated are demonstrating the expected zero-order release from the osmotic system. The uniformity of content, limited weight variation, optimum hardness, and friability show précised execution formulation process.

In vitro dissolution analysis of PPOP tablet of trospium chloride

All 20 DOE batches OF PPOP tablets of trospium chloride were subjected for dissolution analysis in the acid stage and buffer stage. The response for the *in vitro* dissolution analysis at a different stage is tabulated in Table 3 and graphically presented in Fig. 2. The drug release kinetics was studied using different kinetic models along with regression analysis (R^2), and results are demonstrated in Table 9a, b.

Experimental design and optimization

The formulation was optimized by DOE using a 2^4 factorial design and analysis was done by response surface methodology. The drug release was a dependent response which was predicted at 2 h (acid stage), 5 h, 11 h, and 20th hour (buffer stage) in response to various levels of the independent variable. All factorial design results can be depicted from the contour plot and response surface graphs shown in Fig. 3.

ANOVA analysis

The ANOVA study carried out was multiple ANOVA as there were four independent variables including orifice diameter, and their effect on drug release (dependent variable) was determined. The Design-Expert®11.0.5.0 (Stat-Ease, USA) software was used to perform an ANOVA study. The ANOVA analysis of trospium chloride is given in Table 10. The Model F-value of 62.76, 79.95, 66.20, and 25.50 implies the model is significant for the Percent drug release at 2 h (Acid stage), 5 h (Buffer stage), at 11 h (Buffer stage), and 20 h (Buffer stage), respectively. The model terms can be considered

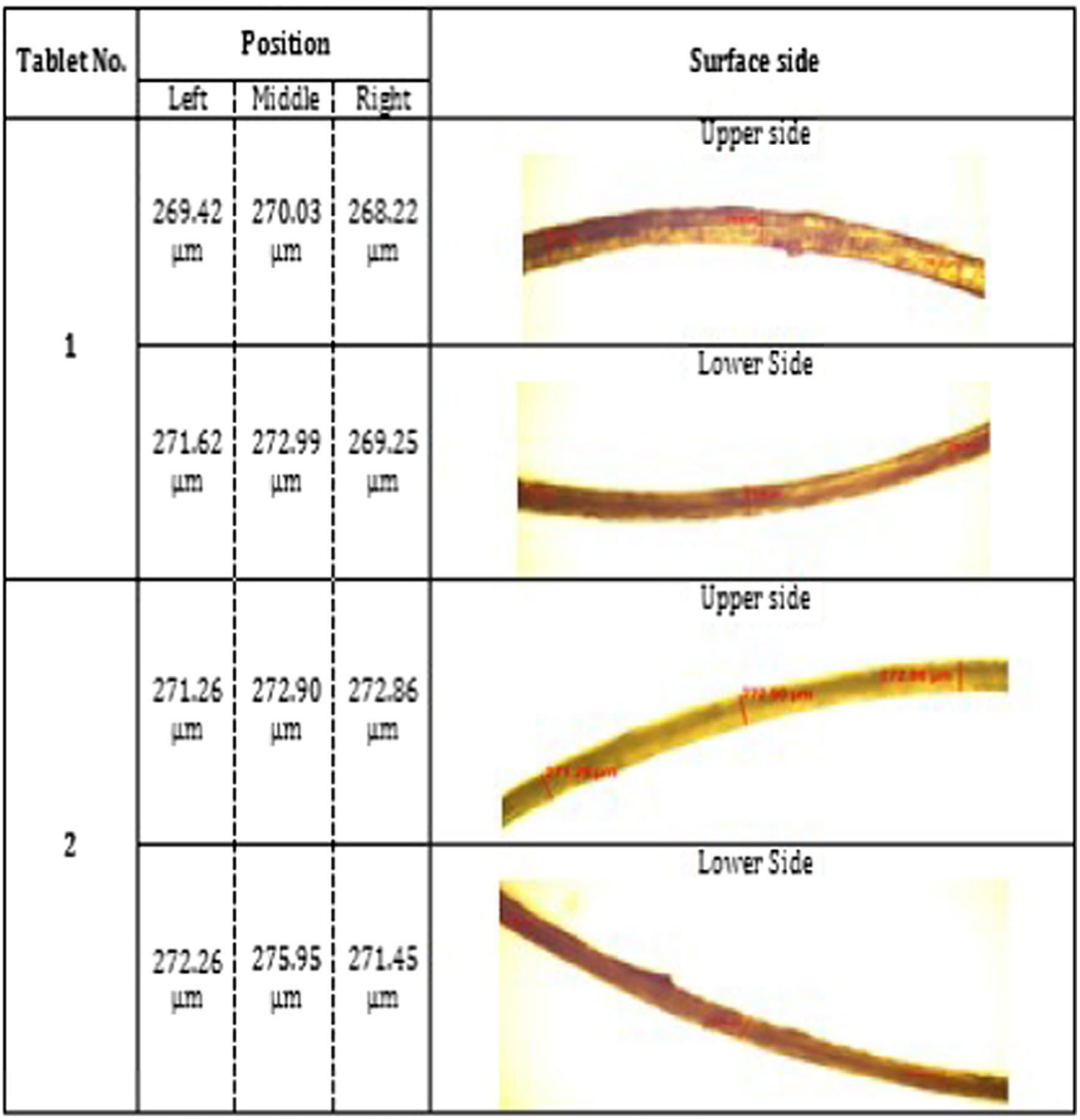


Fig. 7 Coating thickness of semipermeable membrane (TSP-18)

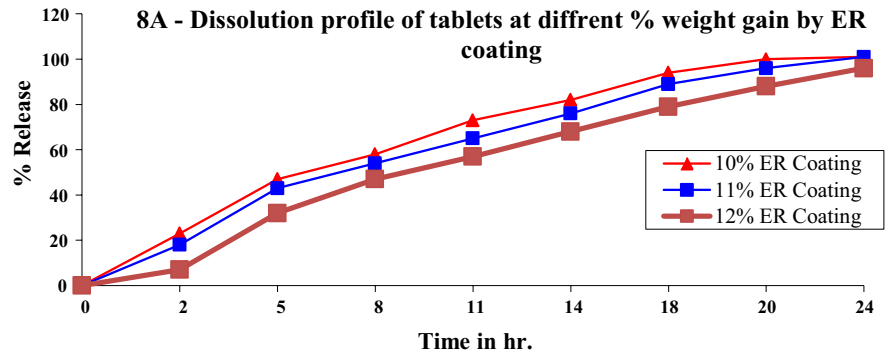
significant since the P-values are less than 0.05. The P-values greater than 0.1000 indicate the insignificance of model terms. The regression parameters studied for percent drug release at 2 h, 5 h, 11 h, and 20 h are tabulated in Table 11. The predicted R^2 for all the responses was in reasonable agreement with the adjusted R^2.

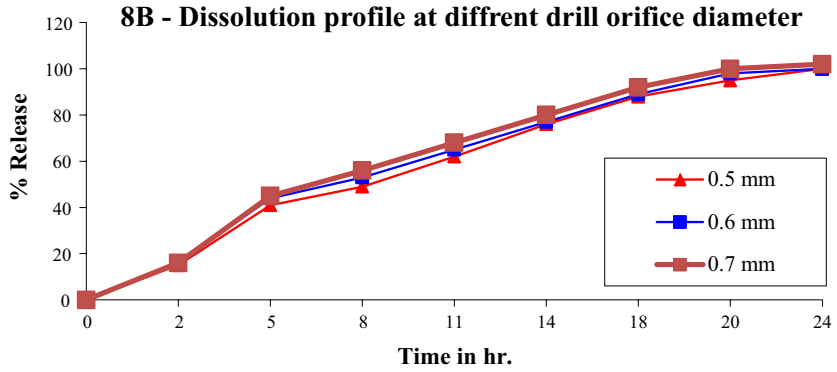
Comparative drug release of trospium chloride PPOP tablet and marketed formulation

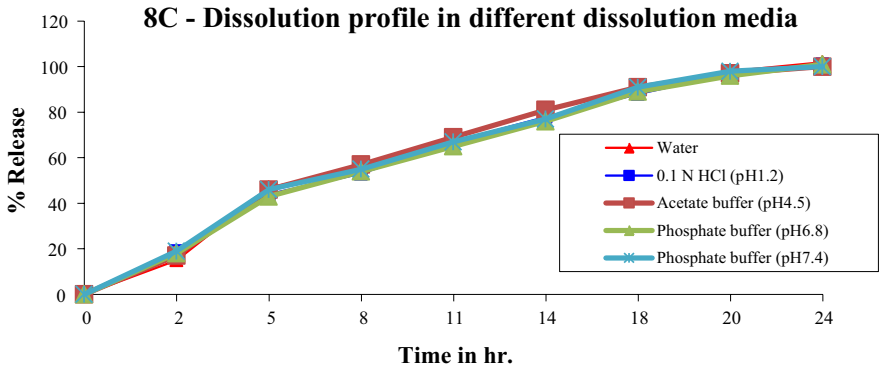
Comparative in vitro drug release of formulated ER tablet was studied against marketed formulation, and it was found that the prepared formulation shows continuous drug release up to 24 h due to bilayer technology which is more efficient than the marketed formulation which releases the complete dose of the drug within 16 h (Fig. 4).

Dissolution analysis by hydration study

Hydration study of optimized osmotic bilayered ER tablet of trospium chloride showed uniform hydration of pull and push layer at different time points which can be depicted from Fig. 5.







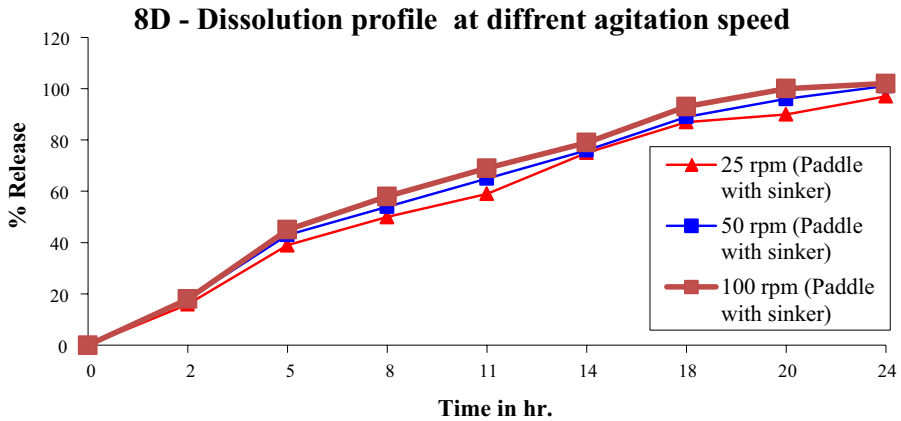


Fig. 8 **a** Impact of different % weight gain by ER coating on drug release (TSP-18), **b** impact of drill orifice diameter on drug release (TSP-18), **c** Impact of dissolution media pH on drug release (TSP-18), **d** impact of agitation speed on drug release (TSP-S18)

Table 12 Pharmacokinetic parameters summary of trospium chloride osmotic tablets vs Sanctura XR® capsules

Product	Trospium chloride ER tablets 60 mg (Osmotic)	Sanctura XR® capsules 60 mg (Extended Release)
Analyte	Trospium chloride (ng/mL) measured in dogs	Trospium chloride (ng/mL) measured in dogs
Parameter	Single dose (0–24 h)	Single dose (0–24 h)
Cmax (µg/mL)	5.077 (0.754)	5.965 (0.888)
Tmax (h)	3.000 (0.000)	3.000 (0.000)
AUC (µg h/mL)	32.632 (4.096)	32.911 (3.076)
T1/2 (h)	19.523 (7.282)	3.504 (0.247)

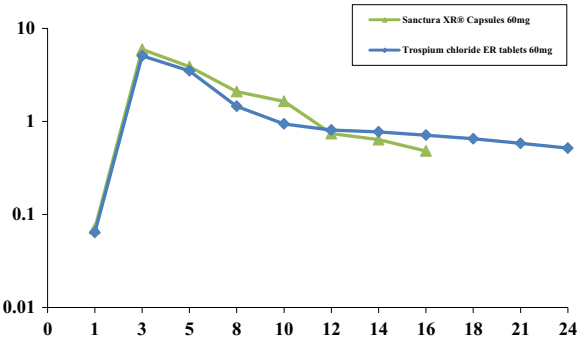


Fig. 9 Comparative mean plasma concentration of trospium chloride osmotic tablets and Sanctura XR® capsule 60 mg

Coating membrane morphology of initial and after dissolution samples

To study the influence of ER coating, the coated tablets of optimized formulation (TSP-18) were subjected to scanning electron microscopy (SEM) with 1000× and 10,000× magnification power. SEM images captured before and after dissolution showed the extension in a drug release as a result of the osmotic phenomenon (Fig. 6).

Coating thickness measurement and study of its impact on drug releases

ER coating thickness is a critical part of osmotic formulation and thus variation between different tablets shall minimum to get consistent drug release through an orifice. A perusal to Fig. 7 coating thickness was found precise and consistent throughout the semi-permeable membrane of the optimized formulation.

Impact of semipermeable coating weight gain on drug release

The in vitro dissolution profile of trospium chloride from formulations of 10%, 11%, and 12% ER coating is shown in Fig. 8a; it reveals that drug release decreases with an increase in % weight gain of the coating membrane. The burst release of drugs from the tablet was not observed during the drug release studies in any of the formulation.

Drill orifice diameter impact on drug release

To determine the effect of orifice diameter on the release of the drug, the optimized formulation TSP-18 was analyzed for different orifice diameters of 0.5, 0.6, and 0.7 mm using a laser drilling machine. The release profiles obtained from the dissolution studies are shown in Fig. 8b which concludes that the release of the drug from the osmotic pump tablet was not significantly get affected by the orifice diameter to some extent.

Impact of dissolution media pH on drug release

To interpret the effect of pH on drug release, the dissolution of optimized formulation (TSP-S18) was studied in different media of varying pH. The in vitro release profile of the drug from these studies is shown in Fig. 8c which indicates that the drug release was found to be complete and almost the same in all the dissolution media, assuring that the release of the drug is independent of pH.

Impact of agitation speed on drug release

The data of the drug release profile of the tablets at different rpm conditions was recorded in Fig. 8d. The cumulative percentage of drug release in 24 h was found to be 97, 101, and 102% at 25, 50, and 100, rpm, respectively, which means there was no drastic change in the drug release. This showed that the drug release from the PPOP tablet is not depend on the intensity of agitation.

An analytical method for in vivo estimation of trospium chloride

Chromatography-tandem mass spectrometric (LC–MS/MS) method was used for the estimation of trospium chloride in dog plasma, and it was found suitable for analysis. With the help of the developed analytical method, comparative pharmacokinetic estimations from the plasma sample of beagle dogs became possible.

In vivo pharmacokinetic analysis

The pharmacokinetic study of the prepared formulation was carried out in beagle dogs to demonstrate the comparative efficiency of formulated drug delivery system. The pharmacokinetic parameters of trospium chloride ER tablets 60 mg (Osmotic) and Sanctura XR® Capsules 60 mg (Extended Release, once daily) were carried out and the results are elaborated in Table 12. It is apparent from Fig. 9 that once-daily TSP ER formulation can consistently maintain drug release for nearly about 24 h. On the contrary, the therapeutic levels are declined after 16 h

Table 13 Stability data trospium chloride ER tablets 60 mg

Batch no. TSP-18			Packing: 10's tablets in blister pack							
Sr. no	Tests	Specification	Initial	40 °C ± 2 °C and 75% ± 5% RH			25 °C ± 2 °C and 60% ± 5% RH			
				1 M	2 M	3 M	6 M	3 M	6 M	12 M
1	Description	Transparent/Translucent White and yellow colored bi-layered round biconvex tablet with preformed passageway at the center of the white layer side of tablet	No change	No change	No change	No change	No change	No change	No change	No change
2	Assay (%)	NLT 90% and NMT 110%	101.1	101	100.2	100.0	98.2	101	99.8	99.2
3	Dissolution (% drug release)									
	2 h	NMT 30%	20	18	22	25	19	20	19	17
	5 h	Between 35 and 50%	42	43	39	45	43	39	43	39
	11 h	Between 55 and 75%	66	65	67	71	63	68	65	62
	20 h	NLT 85%	97	96	97	98	99	101	100	99

for the extended-release marketed formulation Sanctura XR® capsules (60 mg).

Stability study of optimized PPOP tablets

The stability of the optimized batch was conducted for physical properties, assay, and dissolution at different storage conditions. Data obtained for the stability study is illustrated in Table 13. Data recorded revealed that the tablet formulation was stable in varying storage conditions with efficient drug release [46].

Discussion

The DSC thermograms obtained of physical mixtures of drug and inactive ingredients provide evidence of the compatibility of excipients with trospium chloride [31]. The results of preformulation studies demonstrate the good flow characteristics properties of the tablet blend. The angle of repose for all the experimental batches was between 28.24 and 28.85 which demonstrates optimum flowability of all the tablet blends. The results of density determinations Hausner's ratio and Car's index also demonstrate the efficient flow properties of tablet blends [32]. The developed push–pull osmotic pump tablets formulation (OROS® Technology based), formulated to provide controlled release of trospium chloride over 24 h with a bi-phasic release. In the formulation, the 30 mg drug in the pull layer (as fast release portion) and 30 mg drug in the push layer (as slow-release portion); the core is surrounded by a seal and subsequent semipermeable polymer coating. The osmotic delivery system consists of a drug, hydrophilic polymers like polyethylene oxide (PEO), and an osmotic agent and it contributes to the controlled drug delivery of TSP, whereas the core tablet is surrounded by a semi-permeable coating which works as an extended-release coat, which acts as a rate-controlling membrane. The resulting membrane allows the permeation of both water and dissolved solute. The drug release from the tablet is primarily governed by the phenomenon of osmosis. The variation in tablet evaluation parameters was optimum which indicates the optimized following of process parameters [33]. In vitro dissolution analysis revealed the continuous drug release up to 24 h. DD solver trial version was used to determine drug release kinetics. The zero-order kinetics was followed for batch TSP-7 with R^2 0.996 which indicates that the drug released from the formulation by a zero-order mechanism independent of drug concentration. The Batch also shows R^2 0.996 for the Korsmeyer Peppas model. First-order kinetics was shown by TSP-8 batch with R^2 of 0.983, Korsmeyer Peppas release kinetics was followed by TSP-1, TSP-2, TSP-3, TSP-4, TSP-6, TSP-7, TSP-9, TSP-10, TSP-11, TSP-12, TSP-13, TSP-14, TSP-15, TSP-16, TSP-17, and TSP-20 batches with R^2 between 0.988 to 0.999. None

of the batches followed the Higuchi model for release kinetics. Hixon–Crowell release kinetics was shown by TSP-5, TSP-18, and TSP-20 with R^2 between 0.966 and 0.989 [34]. In a factorial design, the TSP-18 was found to be an optimized batch from Design Expert analysis. At 2 h, 5 h and 11 h polyethylene glycol (Factor C) had a great influence on drug release as compared to cellulose acetate (Factor D) and polyethylene oxide (Factor A). Also at all these three-time points, the increase in the level of cellulose acetate and polyethylene oxide decreases drug release [35]. The ANOVA analysis revealed that at 20th hour polyethylene oxide was found to be the most influencing factor. An increase in the level of polyethylene oxide decreases drug release while cellulose acetate and polyethylene glycol are having no such effect [36].

The Model F-values found were 62.76, 79.95, 66.20 and 25.50 which revealed that the model is significant for the Percent drug release at 2 h (Acid stage), 5 h (Buffer stage), 11 h (Buffer stage) and 20 h (Buffer stage), respectively, P-values obtained for the dependent variable were less than 0.0500 which shows that the model terms are significant.

The comparative in vitro drug release study with marketed formulation showed the comparative efficiency of prepared PPOP tablets. The marketed formulations release the complete dose within 16–18 h while the prepared osmotic formulation releases the drug up to 24 h [37]. The hydration study during the dissolution shows the biphasic release of the drug from two different layers. This biphasic release pattern is an important parameter responsible to extend the drug release. The SEM analysis of tablet dissolution showed that the significant porosity during the dissolution is the result of the leaching of water-soluble additives during dissolution [38]. The multiple parameters like weight gain (coating), agitation speed, orifice diameter, coating membrane thickness pH of media showed negligible effect on drug release [39–44]. As per the expectations of in vitro drug release results, *in vivo* also TSP osmotic tablet (60 mg) shows zero-order release with efficient plasma concentration of drug over 24-h period as compared to once a day (*o.d*) extended-release commercially available TSP capsule 60 mg (Sanctura XR® capsules, 60 mg) in the beagle dog. The prepared osmotic formulation maintains the effective concentration range up to 24 h while the available marketed formulation maintains it only up to 16–18 h. The bilayer formulation plays important role in this improved pharmacokinetics. Plasma concentration within the therapeutic window cannot be achieved for 24 h without the initial loading dose (30 mg) which is sufficient to saturate the first-pass effect. Fast onset of action is achieved with an initial loading dose of 30 mg with effective therapeutic concentration. Results recorded conclude that the developed osmotic pump tablet efficiently maintains the drug concentration within the plasma in the required therapeutic range over 24 h [45].

Conclusions

The proposed PPOP tablet of trospium chloride 60 mg provides extended-release over 24 h. Bilayer in tablet with each layer of 30 mg of trospium chloride provides loading and maintenance dose. From the in vitro drug release and in vivo pharmacokinetic evaluation, it can be concluded that the prepared PPOP tablet of trospium chloride provides the drug release with effective plasma concentration for 24 h while the marketed formulation shows drug release only up to 16 h so, this proposed formulation is the efficient drug delivery system with once a day dosing for the patients suffering from overactive bladder.

Abbreviations

TSP: Trospium chloride; PPOP: Push–pull osmotic pump; ER: Extended-release; DOE: Design of experiment; ANOVA: Analysis of variance; DSC: Differential scanning colorimetry; FTIR: Fourier transform infrared.

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Authors' contributions

Author RG performed complete research work. Author SP guided for the research work. Author SS, DK and SS contributed in result interpretation, writing and editing of manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data or analysis during the current study will be made available on request by corresponding author.

Declarations

Ethics approval and consent to participate

All animal experiments were performed with protocol approved by Institutional Animal Ethics Committee of Wockhardt research center, Aurangabad with registration no. 13/99 CPCSEA dated 01/04/2015. The beagle dogs used for research study were from animal house of Wockhardt research center. The written informed consent was obtained to use the animals for research study.

Consent for publication
Not applicable.

Competing interests
The authors don't have any competing interest.

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