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

Ramakanth Gundu1*, Sanjay Pekamwar1, Santosh Shelke2, Deepak Kulkarni1,2 and Santosh Shep3

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
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].

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].

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     | Tropium 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     | Tropium 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

Optimization of the formulation by factorial design

Optimization of the formulation was done with Design Expert (Stat-Ease, Version 11). 2⁴ factorial design was applied with consideration of the highest influencing factors. Response surface methodology (RSM) was used to study the influence of process parameters. Polyehtylene 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 reposes, density, Hausner’s ratio, and Carr’s index. The purpose of evaluation parameters was to study flow properties and
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:

\[
\text{Percent friability} = \frac{W_0 - W}{W} \times 100
\]

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 | | Seal coated + ER coated tablet weight (mg) | 452.4 | |

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

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) |
| 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
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/cm² [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 $37 \pm 0.5$ °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 4 In vivo animal study details

| Group | Number of samples | Time points (h) | Study days | Blood volume collected | Anticoagulant |
|-------|------------------|----------------|------------|------------------------|---------------|
| 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 |

### 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 x 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          |
TSP20 28.58
TSP19 28.53
TSP18 28.49
TSP17 28.56
TSP15 28.69
TSP14 28.57
TSP13 28.34
TSP12 28.58
TSP10 28.73
TSP9 28.51
TSP8 28.67
TSP7 28.45
TSP6 28.45
TSP5 28.58
TSP4 28.85
TSP3 28.76
TSP2 28.24
TSP1 28.61

vals [25].

jected to dissolution and analyzed at different time inter -

of the optimized formulation. Then the tablets were sub -

0.6 mm, and 0.7 mm on the semi-permeable membrane 

out by drilling orifices of various diameters of 0.5 mm, 

Impact of drill orifice diameter on drug release
Drill diameter impact on dissolution was studied as an 

erate particles. The 

ickness of coated surface images was captured using a 

microscope (Nikon, Eclipse Ni-U enabled NIS-Elements 

thicknes 

Impact of dissolution media pH on drug release
To study the effect of pH on drug release, the formula -

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 

tissue paper to remove any adherent particles. The 

Impact of semipermeable coating weight gain on drug 

impact on drug releases
In laser drilled tablets, cellulose acetate coating was 

Coating thickness measurement and study of its impact 

through a filter with a pore size of 10 µm and analyzed 

Impact of agitation speed on drug release
To assure that the release of drug from coated tablets fol-

Impact of agitation speed on drug release
To analyze the effect of agitation intensity, the USP type 

Impact of % weight gain on dissolution, the formulation TSP-18 was coated with a coating com -

position, to obtain the tablets with varying weight gain 

(10, 11 and 12% w/w). The in vitro release profiles of the 

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 

dependent 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 sub-

jected to dissolution and analyzed at different time inter-

vals [25].

Impact of dissolution media pH on drug release
To study the effect of pH on drug release, the formula-

tion was subjected for dissolution in mediums with vary-

ing 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].

Table 7 Preformulation characteristics of tablet blend of all experimental batches

| Batch | Angle of repose (°) | Bulk density (g/cm³) | Tapped density (g/cm³) | 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          | 0.580±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

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/cm²) | 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

(refference 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
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.

### 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 | 1.040 | 0.580 | 0.802 | 0.821  |
|              | KKP  | 14.068| 14.075| 2.774 | 6.490 | 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  |
| (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  |
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; \( \alpha \) = 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)    | \( + 34.19 - 2.44A - 8.19B + 11.44C + 2.44AB - 0.9375AC - 5.44BC + 2.94ABCD \) | 0.9807     | 0.9685              | 0.9332              |
| Percent drug release at 11 h (Buffer stage)   | \( + 63.50 - 7.25A - 4.25B + 8.50C + 0.00D + 0.5AC + 0.25AD - 0.2 5CD + 1.25ACD \) | 0.9815     | 0.9666              | 0.9335              |
| Percent drug release at 20 h (Buffer stage)   | \( + 96.81 - 2.69A - 0.0625B + 0.187C - 0.187D - 0.062AB - 0.687A - 0.062BD + 0.687CD - 0.5625ABD \) | 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
| Time [h] | Two half portions after cross section |
|---------|-------------------------------------|
| Initial DP(1) | Immediate release, drug layer, cellulose acetate coated membrane, extended release drug layer |
| Swollen coated membrane |
| Uniformly hydrated, peripheral core surface closed to coating membrane |

(A)

| Time [h] | Two half portions after cross section |
|---------|-------------------------------------|
| 2 hr dissolution (A) | Drug released from immediate release part, swollen coated membrane, uniformly hydrated, peripheral core surface closed to coating membrane |
| Swollen coated membrane |

(B)

| Time [h] | Two half portions after cross section |
|---------|-------------------------------------|
| 3 hr dissolution (B) | Swollen coated membrane, uniformly hydrated, drug and push layer core surface which further swells |

| Time [h] | Two half portions after cross section |
|---------|-------------------------------------|
| 6 hr dissolution (A) | Swollen coated membrane, highly hydrated, drug and push layer core surface which further swells |
| Uniformly hydrated, peripheral core surface which further swells, push layer core surface which further swells to push drug layer surface |

(B)

| Time [h] | Two half portions after cross section |
|---------|-------------------------------------|
| 15 hr dissolution (A) | Swollen coated membrane, uniformly hydrated, drug layer core surface released, push layer core surface further swells to push drug layer surface |

(B)

| Time [h] | Two half portions after cross section |
|---------|-------------------------------------|
| 15 hr dissolution (B) | Expanding coated membrane, uniformly hydrated, drug layer core surface released, which further swells, push layer core surface further swells to push drug layer surface |

(B)

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

---

**Table 3:**

| Parameter | Acid Stage | Buffer Stage |
|-----------|------------|--------------|
| $R^2$     |            |              |
|           |            |              |
|           |            |              |

**Table 10:**

| Model Terms | F-value |
|-------------|---------|
| Percent drug release at 2 h (Acid stage) | 62.76 |
| Percent drug release at 5 h (Buffer stage) | 79.95 |
| Percent drug release at 11 h (Buffer stage) | 66.20 |
| Percent drug release at 20 h (Buffer stage) | 25.50 |

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

| Tablet No. | Position | Surface side |
|------------|----------|--------------|
|           | Left | Middle | Right | Upper side | Lower Side |
| 1          | 269.42 | 270.03 | 268.22 | Upper side | Lower Side |
|            | $\mu$m | $\mu$m  | $\mu$m  | $\mu$m    | $\mu$m   |
| 2          | 271.62 | 272.99 | 269.25 | Upper side | Lower Side |
|            | $\mu$m | $\mu$m  | $\mu$m  | $\mu$m    | $\mu$m   |

*Fig. 7 Coating thickness of semipermeable membrane (TSP-18)*
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-18)
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-18) 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 12 Pharmacokinetic parameters summary of trospium chloride osmotic tablets vs Sanctura XR® capsules

| Parameter       | Trospium chloride ER tablets 60 mg (Osmotic) | Trospium chloride (ng/mL) measured in dogs | Sanctura XR® capsules 60 mg (Extended Release) | Trospium chloride (ng/mL) measured in dogs |
|-----------------|---------------------------------------------|--------------------------------------------|-----------------------------------------------|--------------------------------------------|
| Analyte         | Trospium chloride measured in dogs          | Trospium chloride 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
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 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 calorimetry; 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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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.

Author details
1 School of Pharmacy, Swami Ramanand Teerth Marathwada University, Vishnupuri, Nanded, Maharashtra 431606, India. 2 Sirinath College of Pharmacy, Bajaj Nagar, Wali Midc, Aurangabad, Maharashtra 431136, India. 3 Shenfudu Fakirba Sonavane Institute of Pharmacy, Khamgaon, Aurangabad, Maharashtra 431151, India.

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