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Preparation and Evaluation of Novel Extended Release Trihexyphenidyl Hydrochloride Tablets

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Abstract

Trihexyphenidyl Hydrochloride (THP) present in the international market as an immediate release tablets), and extended release capsules. The aim of this work was to develop an extended release tablets containing THP for the first time, and to evaluate these tablets according to the official and compendia requirements.

DSC thermograms and IR spectroscopy were studied for confirmation of the possible interaction of THP with the investigated excipients. The IR results revealed that there was no evidence of interaction between THP and any of the investigated excipients, The DSC thermograms of physical mixture illustrate distinguished drug peak deformation with Xanthan Gum which in turn reflected that a drug-excipient of Xanthan Gum interaction has occurred.

The results of release profile revealed that, none of Eudragit RLPO® trials were conforming the required release profile according to USP 38 (2015) (1). While on using Carbopol 971P® (containing 2 % or 1.5 % Carbopol 971P®) were conforming the required release profile acc). With regard to the mechanism of THP release, it was found that the best fit was achieved by zero order models for F8 and F9. Formulae F8 (containing 2 % Carbopol 971P®) have been chosen for further study of the influence of different conditions of stability and the effect of different packaging materials (30 °C & 40 °C / 75 % RH). Samples were investigated physically and chemically after 15, 60, 120, and 180 days. The results revealed that: the tablets packed in polyvinyl chloride enveloped in aluminum sachet is the most stable one .Also tablets packaged in polyvinyl chloride / polyvinyl dienchloride (PVC / PVDC / Aluminum blisters) have better stability and lower rate of degradation than those tablets packed in PVC / Aluminum blisters.

1. Introduction

Extended release dosage forms are formulated in such a manner as to make the contained drug available over an extended period of time following administration. An oral dosage form should allow a reduction in dosing frequency compared with conventional dosage form [2].

Trihexyphenidyl Hydrochloride (THP) is a tertiary amine anti muscarinic with actions similar to those of atropine. It also has a direct antispasmodic action on smooth muscle. THP is employed in the treatment of parkinsonism and alleviation of the extrapyramidal syndrome induced by drugs such as phenothiazines. It has been utilized in the treatment of dystonia. This drug is present in the international market as immediate release tablets (ARTANE® Tablets), and extended release capsules (ARTANE® Sequels). The general disadvantage of the capsule, is the fact that, capsule formulation is more expensive as compared to the tablet formulation since the capsule shell has to be bought additionally [3].

Hydrophilic matrix tablets are considered the most popular delivery system for oral controlled-release dosage forms [4, 5]. These hydrophilic matrices are mostly accepted because of their biopharmaceutical as well as pharmacokinetics advantages over other conventional dosage forms [6-8].This is due to, they offer precise and accurate modulation of drug release due to the hydration of the constituent polymer(s). The properties of the gelling agent are the material in the formulation that is responsible for the formation, after hydration, of a diffusion and erosion-resistant gel layer [9, 10]. In addition, matrices that can be continuously innovated as materials for formulation became commercially available.

Tablets are easier to be taken and swalled than capsules or granules, and are the most widely used dosage forms [11]. Moreover, sustained release technology of drugs has been developed recently to alleviate patient's burden and improve their quality of life by reducing the dosing frequency [12]. Molecular size as well as water solubility of a drug are important parameterss in the release of drug from swelling and erosion controlled polymeric matrices [13, 14]. Also, the amount of drug in the tablet affects the drug release profile [15-17]. Infiltration of medium into a matrix tablet occurs before erosion and as result; there are two proposed mechanisms.

Investagation of possible incompatibility between the active component and the different excipients with the evaluation of

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thermal stability is an important part of pre-formulation study performed for a solid dosage form. [18]. the compatibility of the active substances with the formulation ingredients or excipients is necessary for to detect any possible physical or chemical interactions, since these interactions can either alter the stability and/or the bioavailability of a product [19].The excipient can alter the solid state stability of a drug in various ways; this may occur either directly as a chemical reaction between the drug and the excipients or mostly through sorption of moisture and/or catalysis [20]. Interactions in dosage forms can causes change in the chemical nature, solubility, absorption and consequently the therapeutic response of drugs. So, on the formulation of new drugs or the reformulation of existing products, the study of the interaction between drug and excipients in the solid state is an important step. DSC can be a useful method of predicting and/or investigating compatibility during pre-formulation studies [21, 22].

The purpose of stability test is to ensure the effect of quality of a proprietary medicinal product differs as functions of environmental factors. Stability testing was done to establish the storage conditions and shelf life for the manufactured products [23, 24] Thus, the manufacturer must consider possible problems created by physical and chemical changes of the drug and the drug products.

2. Experimental

2.1. Materials

THP was get from Sir Laboratories, India. Carbomeor (carbopol971P® Magnesium stearate, Mallinckrodt Microcrystalline cellulose (Avicel PH 102 FMC Biopolymer and Xanthan gum were get from U.S.A. Colloidal Silicon Dioxide (Aerosil 200®) Evonik Polymethacrylates (Eudragit RLPO)and Acetonitril HPLC grade and triethylamine from (Scharleau Italy).

2.2. Methodology

2.2.1. Differential Scanning calorimetry study (DSC) of the prepared samples

Samples (3-6 mg) were accurately weighed and thermetically sealed in flat-bottomed aluminum pans .Samples of each drug and excipients alone as well as their corresponding physical mixtures (1:1 w/w) prepared by simple blending and perfect mixing on a clean waxy paper .DSC curves of the samples were performed using Shimadzu® model DSC-50. The DSC thermograms were carried out over temperature range from 30-400 °C with a thermal analyzer equipped with computer software program at a scanning rate of 10 °C/ min and nitrogen gas purge of 40 ml / min .the instrument was calibrated with indium as the standard .

2.2.2. Infrared study (IR) for the prepared samples

Samples (1-2 mg) of drug and excipients alone as well as the physical mixtures of THP with the investigated excipients (1:1 w/w) were prepared by simple and perfect mixing on a clean waxy paper and then mixed with potassium bromide (IR grade), compressed into discs in the compressor unit under vacuum, and scanned from 4000 cm-1 to 800 cm-1 with an empty pellet holder as a reference using IR-spectrophotometer, IR - 470(Shimadzu®, Japan).

2.2.3. Preparation of THP Tablets

Trihexyphenidyl hydrochloride tablets were prepared using direct compression technique. Trihexyphenidyl hydrochloride was blended with microcrystalline cellulose PH 102 (Avicel pH 102®) and sustained release matrix polymer, using a pestle and mortar for at least five minutes for each step. This was followed by adding colloidal silicone dioxide (Aerosil 200®) then tumbling mixing in a clean glass bottle of 250 ml capacity for 15 minutes. The efficiency of mixing was ascertained by determination of the drug content. Magnesium stearate was then added to the blend and mixed for another 5 minutes. This mixture was then compressed into tablets using Erweka tablet press machine (Rotary tablet press), Germany, GMBH. The machine was adjusted to produce tablets of 150.0 mg in weight and each one contains 5.0 mg of THP. **(Table 1)** shows the composition of all formula of THP tablets prepared.

2.2.4. Evaluation of THP tablets

The formulated THP Tablets were evaluated for the following parameters:

2.2.4.1. THP tablet weight uniformity

Tablets were prepared and evaluated according to the USP pharmacopeia standards and specifications of tablet mass variation [1].

2.2.4.2. Uniformity of THP content

Samples of 10 tablets from each batch were tested for the uniformity of drug content in which tablets were grinded and powdered individually and the drug in each was extracted three times by 100 ml of mobile phase acetonitrile: water: and triethylamine (920: 80:0.2) adjusted to pH 4.0 by orthophosphoric acid and filtered and assayed by HPLC (Agilent 1100 series, Japan) [1].

2.2.4.3. Tablet thickness

The average thickness of the prepared tablets was determined by means of tablet tester (Dr. Schleuniger Model 6D Germany, GMBH) .For each batch, thickness of 20 tablets was measured and the standard deviation were calculated [1].

2.2.4.4. Hardness of tablets

The hardness of the prepared tablets was investigated via tablet tester (Dr. Schleuniger Model 6D) .For each batch, hardness of 20 tablets was determined and the average values were calculated [1].

Table1: Composition of Trihex .Hcl tablet formulations

Formula	mg Drug	mg Mg Stearate	Aerosil	Avicel PH 102	Eudragit RLPO	Carbomer	Povidone K30	Total Weight
F1	5	1.5	1.5	134.5	7.5	x	X	150
F2	5	1.5	1.5	127	15	x	X	150
F3	5	1.5	1.5	119.5	22.5	x	X	150
F4	5	1.5	1.5	112	30	x	X	150
F5	5	1.5	1.5	130.7	x	11.25	X	150
F6	5	1.5	1.5	134.5	x	7.5	X	150
F7	5	1.5	1.5	138.25	x	3.75	X	150
F8	5	1.5	1.5	139	x	3	X	150
F9	5	1.5	1.5	139.75	x	2.25	X	150
F10	5	1.5	1.5	127	x	15	X	150

#Each formula containing 5mg ofdrug,1.5 mg of Mg sterate and 1.5 mg of Avicel

The final total weight of each tested tablet is 150 mg

2.2.4.5. Tablet friability

Friability of the prepared tablets was determined by calculating the percentage loss in the weight of 6.5 g of tablets before and after the revolution in the friabilator (Erweka friabilator apparatus, Germany, GMBH) at 25 round per minute (r.p.m.), for 4 minutes in accordance to the USP, The percent loss was calculated from the following equation: [1]

Friability% = [(weight before test- weight after test)/weight before test] X 100.

The friability of the prepared tablets experiment was repeated 3 times and the average value was determined.

2.2.5. In vitro release of THP Tablets

Tablets containing 5 mg of THP were placed in 500 ml of degassed purified water and temperature adjusted at 37 ± 0.5 °C using USP dissolution apparatus type I with rotating basket at 100 rpm .At the specified time intervals a (5 ml) sample was withdrawn and replaced with the same volume of medium maintained at the same temperature .The amounts of THP released were determined using HPLC method .The experimnts were carried out   in triplicate and the means values were calculated [1].

2.2.6. Stability testing of THP Tablets

The data obtained served as the basis to reach a secondary objective which is the stability testing through effect of aging, where samples of the selected formulae of THP extended release tablets containing 2 % Carbopol 971P® (F8) were stored in different packaging materials of, polyvinylchloride /aluminum strips, polyvinylchloride / polyvinyl dienchloride/ aluminum strips and polyvinylchloride /aluminum strips enveloped in well-sealed aluminum sachet. All types of samples in different packaging materials were stored in closed desiccators containing saturated solution of sodium chloride .These desiccators were placed in hot air ovens maintained at 30 °C and 40 °C $\pm$ 1.0 °C and 75 % relative humidity. The selected formula in different packaging materials was tested for its THP content and physical stability testing after 15, 30, 60,120 and 180 days.

2.2.7. HPLC procedure for determining THP in the stability studies

2.2.7.1. Construction of standard calibration curve of THP

Trihexyphenidyl Hydrochloride standard solution (13μg/ml) was prepared in the used solvent mixture (Acetonitril 80: Water 20: Triethylamine 0.5). From this solution, dilutions were made using solvent mixture to have different concentrations of THP, as 1.0, 3.0, 5.0, 7.0, 9.0, and 13 μg/ml. Solutions were filtered through 0.45 μm disc filter, degassed and the amount of samples 20.0 μl were injected into HPLC column. The standard calibration curve was constructed by plotting the area under the peak versus THP concentrations.

2.2.7.2. Determination of THP content of in the stored tablets

Formulae F8, containing 2 % Carbopol 971P, was selected to study the stability of the drug. Accordingly 20 tablets were finely grinded and powdered, and accurately weight amount equivalent to 5.0 mg THP, was transferred to 100 ml volumetric flask containing 30 ml of solvent mixture, sonicated for 10 minutes, and completed to the volume .The solutions were filtered and 5.0 ml of filtrate was transferred to 100 ml volumetric flask and the volume was completed with the solvent mixture. The obtained solution was filtered through 0.45 μm disk filter, and 20.0 μl of the solution then injected into HPLC column.

2.2.7.3. Conditions for drug assay

Column: Inertsil C18 column (150 ×4.60 mm, 4 μm)
Mobile Phase: (Acetonitril 80: Water 20: Triethylamine 0.5)
Detector: UV lamp at λ 210 nm
Flow rate: 1.5 ml/ minute
Injection volume: 20 μl
The column and the mobile phase were used at ambient conditions

3. Results and discussion

3.1. Differential scanning calorimetry (DSC)

Sometimes when two substances are mixed, the purity of each may be reduced and generally slightly lower melting point are observed .If the solid –solid interaction is extremely weak or non-existent the reduction in the melting point is usually inconsequential .On the other hand, high shift in the melting point signifies that a strong solid –solid interaction has occurred (26). The drug shows a sharp endothermic peak at 256.47 °C corresponding to the melting of the drug with a heat of fusion enthalpy ΔH of -54.56 J/G.

Figures (1-4) Show the thermograms of the physical mixtures of THP at (1:1 w/w) with Xanthin gum, Avicel pH 102 Eudragit RLPO® and Carbopol 971P®. Trace A of figures represents the DSC thermogram of THP alone. Trace B represents the DSC thermograms of each excipient alone and trace C of the same figures represents each of the investigated physical mixtures of THP with the used excipient.

In **(Figure 1)** DSC curve of this mixture reflects the characteristic endothermic peak of the drug at 249.61 °C, negligible shift happens to the melting point of the drug. But enthalpy change for THP in physical mixture with xanthan gum shifted from 54.56 for pure drug to 96.92 in physical mixture with xanthan gum. This reveals that, the presence of interaction between the drug and xanthan gum. On the other hand, Trace C of **(Figure 2)** Shows the thermogram of the physical mixture of THP with Avicel PH 102 .The DSC curve of this mixture reflects the endothermic peak of the drug at 253.2 °C in which negligible shift happens to the melting point of the drug, which indicates also the absence of interaction between the drug and Avicel pH 102. Also figures 3,4 reveal there is no interaction between the drug and Eudragit RLPO® (Since endothermic peak of the drug at 250.9 °C) as well as Carbopol 971P® (since endothermic peak of the drug at 255.5 °C)where negligible shift happens to the melting point of the drug.)

3.2. Infrared spectroscopy (IR)

For further elucidation and confirmation of the possible interaction of THP with the investigated excipients, the IR absorption spectra were obtained for THP alone, each excipient alone, and their corresponding physical mixtures (1:1 w/w). The IR spectra of pure drug shows characteristic functional peaks at 3303 cm-1 (for OH stretching), 3023 cm-1 (for Aromatic C-H stretch), 936cm-1 (for C-N) and 700 cm-1 (for C-H bending) (25).   The infrared spectra of all mixtures show characteristic functional peaks not changed. This reveals that the absence of chemical interaction between the drug and any of the excipients **(Figure 5)**.

3.3. Evaluation of THP tablets

The physical properties of THP tablets are depict in **(Table 2)**. The performance of the physical properties was assessed via the influence the following factors; the weight of THP uniformity, THP content, thickness, hardness, and friability of the tablets. It was found that, THP tablets prepared by direct compression technique were uniform in weight and thickness and all comply and fullfil the USP requirements. **(Table 2)** reveals that, the percent of drug contents in THP tablets are found to be within the range of 96.9 to 99.5 % .The value of friability of the tested tablets is ranging from 0.09 to 0.2 % which are acceptable according to USP 38 (2015). Also **(Table 2)** shows the prepared THP tablets give rise to hardness levels in the range of 5.0 to 5.9 Kp. [1].

3.4. In vitro release of THP tablets

In vitro release profiles of THP tablets prepared using different polymers are shown in figures 6-7. The release of THP varies according to both the type and ratio of matrix-forming polymers.

In case of formulations F1-F4 containing Eudragit RLPO® as the extending release polymer **(Figure 6)**. It is evident that the release rate of THP is higher than the required release rate of USP 38 [1].,this may be attributed to the fast erosion of tablets and this can be proved by the results of dissolution in **(Table 3)** which gave 81.6 % for F1 at the first hour of dissolution, 71 % for F2, 66 % for F3 and 63.4 for F4 while the required release for the third hour of dissolution is from 20 % to 50 % according to USP 38 (2015) [1].So the higher the percentage of Eudragit RLPO® in tablet as extending release polymer the lower the release of THP from the tablet.

(Figure 7) reveals that the release rate of THP tablets is highly dependent on the concentration of Carbopol 971P®. As the concentration of Carbopol 971P® Increases the release rate decreases in the order of: F9 (1.5%) >8(2%) >F7 (2.5%) >F6 (5 % > F5 (7.5 %). Considering the percent of drug release from the formulae of highest ratio F10 (10 % w/w) of carbomer (Carbopol 971 P®), it is evident that, the higher concentration of (Carbopol 971 P®) give rise to a tremendous decrease in release rate (less than 50 % at 12 hours), while the pharmacopeial requirements stated the percent of drug release at 12 hours more than 70 %

The drug release from Carbopol 971P® matrices may be explained as follow, in the dry state, the drug is entrapped in the glassy core of carbopol matrix. Upon hydration of the surface, a gelatinous layer is obtained which consists of discrete microgels made up of many polymer particles in which the drug is dispersed. However, when the hydrogel is fully hydrated, it does not dissolve, but osmotic pressure acts to break up the structure, through sloughing off discrete pieces of the hydrogel. The hydrogels remain intact, and then the drug diffuse through the gel layer at a continuous rate. It is assumed that, as the concentration of the drug becomes high within the gel matrix and its thermodynamic potential increases, the gel layer around the tablet core do as a rate-controlling membrane, and finally resulting in a linear release of the drug [26-28].

Tablets containing 1.5 % and 2 % w/w carbomer (Carbopol 971P®) exhibited dissolution rate conforming the pharmacopeial limits of the stated intervals which are (release of 20 % to 50 % at 3 hours, release of 40 % to 70 % at 6 hours and release of not less than 70 % at 12 hours).
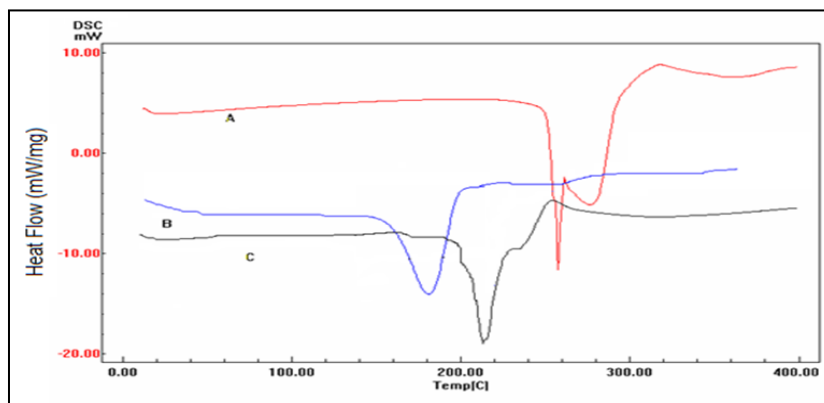
Figure 1: Differential Scanning Calorimetry thermograms of trihexyphenidyl HCl /xanthan gum physical mixture, trace A: trihexyphenidyl HCl, trace B: xanthan gum, trace C: trihexyphenidyl HCL: xanthan gum physical mixture (1:1 w/w).
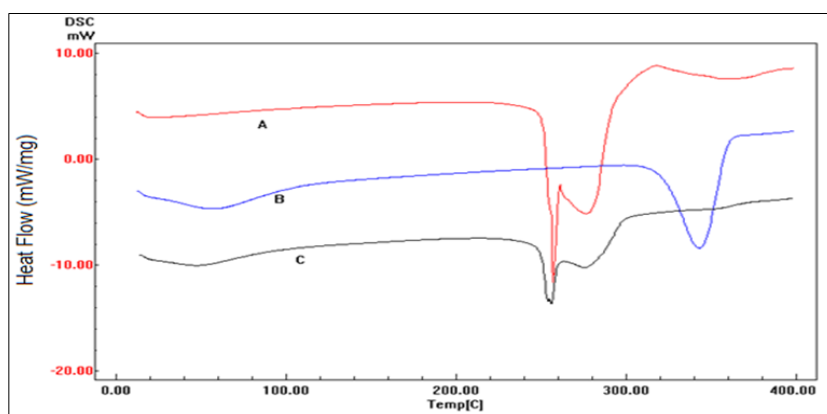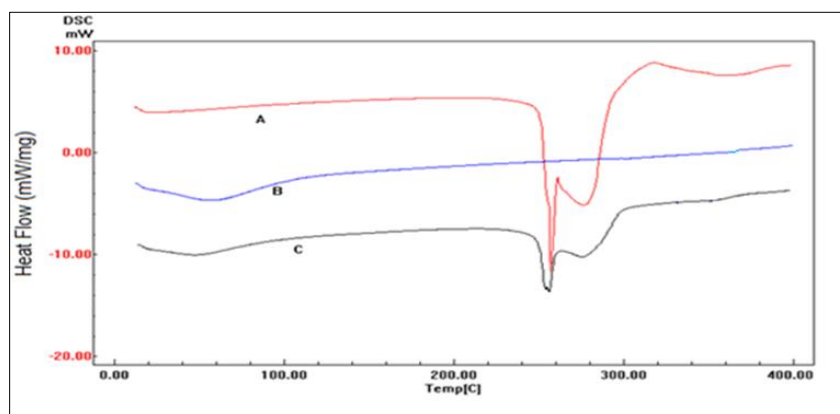
Figure 2: Differential Scanning Calorimetry thermograms of trihexyphenidyl HCl / Avicel PH 102® physical mixture, trace A: trihexyphenidyl HCl, trace B: Avicel PH 102®, trace C: trihexyphenidyl HCL: Avicel PH 102® physical mixture (1:1 w/w).

Figure 3: Differential Scanning Calorimetry thermograms of trihexyphenidyl HCl / Eudragit RLPO® physical mixture, trace A: trihexyphenidyl HCl, trace B: Eudragit RLPO®, trace C: trihexyphenidyl HCL: Eudragit RLPO® physical mixture (1:1 w/w).
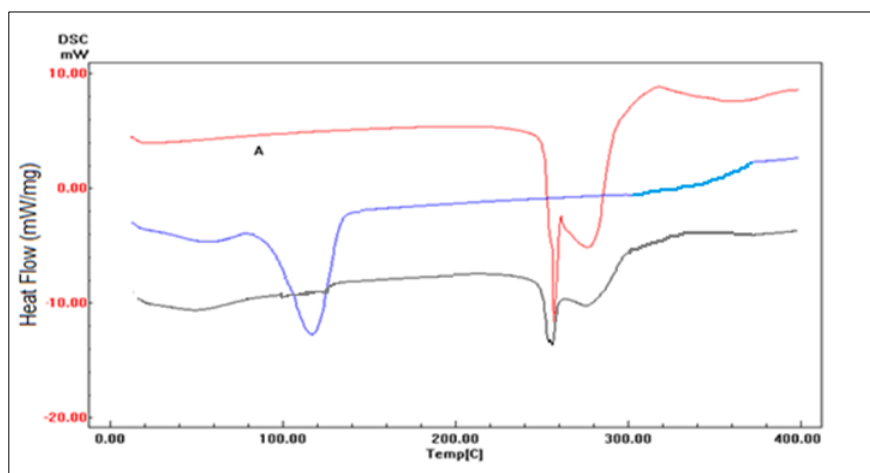
Figure 4: Differential Scanning Calorimetry thermograms of trihexyphenidyl HCl/ Carbopol 971P®
physical mixture, trace A: trihexyphenidyl HCl, trace B: Carbopol 971P®, trace C:
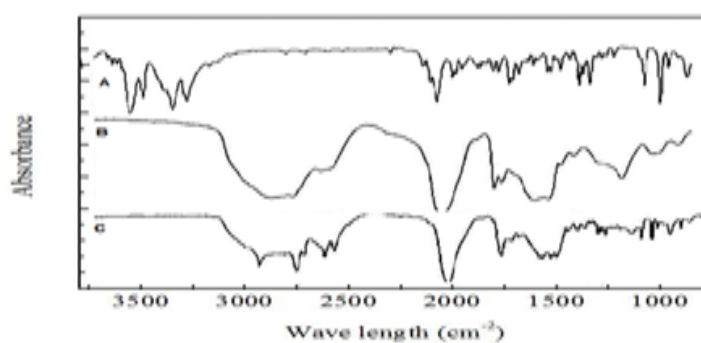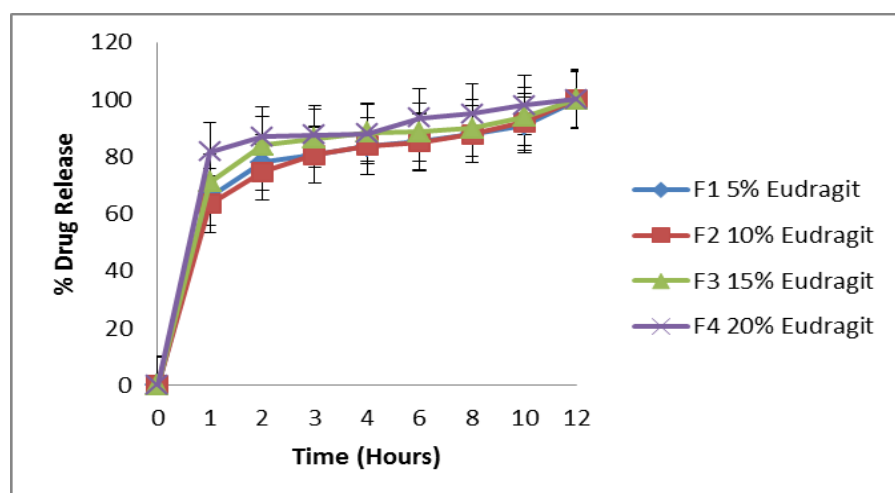trihexyphenidyl HCL: Carbopol 971P® physical mixture (1:1 w/w).

Figure 5: IR absorption spectra of trihexyphenidyl HCl / Carbopol 971P® physical mixture, trace A:
trihexyphenidyl HCl, trace B: Carbopol 971P®, trace C: trihexyphenidyl HCL: Carbopol
971P® physical mixture (1:1 w/w).

Figure 6: The release profiles of Trihexyphenidyl Hydrochloride from tablets containing 5.0, 10.0, 15.0,
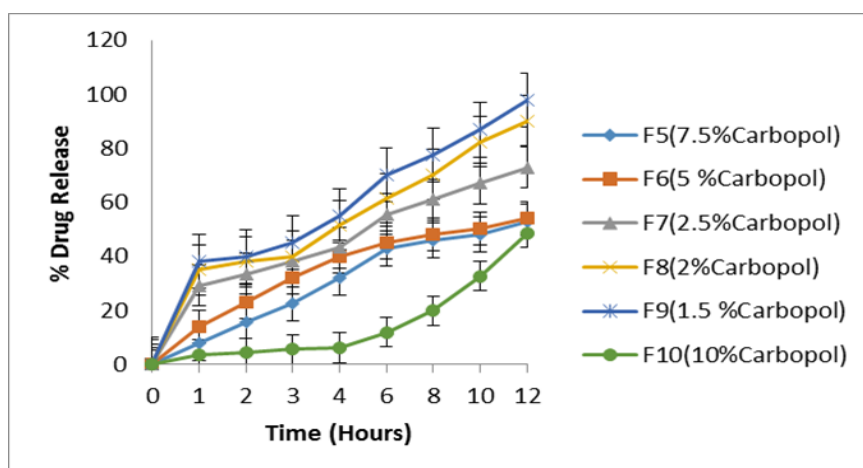and 20.0% Eudragit RLPO® as a sustained release polymer

Figure 7: The release profiles of Trihexyphenidyl Hydrochloride from tablets containing Carbopol®971P as the sustained release polymer

Table 2: Physical Properties of the Trihexyphenidyl HCl Prepared tablets

Actual Drug Content (%) (± S.D) n=20	Formula No.	Mean wt. (mg) (± S.D) n=20	Mean Thickness (mm) (± S.D) n=20	Friability (% loss) n=20	Mean Hardness (KP) (± S.D) n=10
99.3 (±0.54)	F1	149.2 (±0.001)	2.7 (±0.35)	0.09	5.0 (±0.12)
98.5 (±0.49)	F2	148.6 (±0.004)	2.69 (±0.22)	0.10	5.3 (±0.22)
97.8 (±0.81)	F3	150.9 (±0.008)	2.75 (±0.15)	0.21	5.5 (±0.31)
98.2 (±0.40)	F4	152.3 (±0.06)	2.8 (±0.27)	0.05	5.9 (±0.16)
97.5 (±0.35)	F5	147.9 (±0.04)	2.65 (±0.33)	0.07	5.5 (±0.78)
97.9 (±0.65)	F6	149.9 (±0.03)	2.7 (±0.29)	0.14	5.1 (±0.13)
99.3 (±0.43)	F7	148.3 (±0.002)	2.7 (±0.17)	0.27	5.3 (±0.43)
98.1 (±0.52)	F8	150.5 (±0.007)	2.75 (±0.12)	0.22	5.0 (±0.15)
97.5 (±0.33)	F9	151.9 (±0.008)	2.8 (±0.15)	0.16	5.4 (±0.67)
98.8 (±0.68)	F10	148.6 (±0.03)	2.68 (±0.23)	0.08	5.2 (±0.18)

N.B: The value between parentheses in this table and subsequent ones represent the standard deviation of three reading

Table 3: Dissolution of Trihexyphenidyl Hydrochloride Tablets containing different concentration of Eudragit RLPO ®as sustained release polymer

Time (hr) Formula Eudragit RLPO ® (%w/w)	% Released THP after time (hrs)							
	1	2	3	4	6	8	10	12
F1 5%	81.6 (±0.37)	87 (±0.53)	87.5 (±0.48)	88 (±0.19)	93.5 (±0.22)	95 (±0.13)	98 (±0.35)	100 (±0.28)
F2 10%	71 (±0.29)	84 (±0.37)	86.3 (±0.26)	88.49 (±0.08)	88.6 (±0.15)	90 (±0.44)	94 (±0.60)	100 (±0.53)
F3 15%	66 (±0.15)	78 (±0.45)	80.5 (±0.33)	83.6 (±0.28)	85.4 (±0.05)	88 (±0.27)	91 (±0.35)	99.83 (±0.19)
F4 20%	63.4 (±0.23)	74.6 (±0.17)	80.7 (±0.21)	83.7 (±0.25)	85 (±0.06)	87.8 (±0.18)	92 (±0.42)	100 (±0.20)

In view of the above results, formulations F8 and F9 represent an optimal dissolution requirement of THP extended release tablets of the USP 38 (2015).

Different kinetic models were performed to ascertain the release mechanism of THP from F8 and F9. It was found that, the best fit was achieved by zero order model table 4for F8.

3.5. Stability study of THP tablets

The aim of stability test is to ensure how the quality of a proprietary medicinal product varies as functions of environmental factors. Stability testing was done to establish the storage conditions and shelf life for the manufactured products [29, 30].

For further study of stability testing of the prepared THP extended release tablets via the effect of different conditions as well as different packaging materials, we select F8 containing 2 % Carbopol 971P® which gave the optimum dissolution profile and complying official requirements according to USP 38 [1]. **(Figure 8)** shows the standard calibration curve HPLC assay of Trihexyphenidyl Hydrochloride.

(Table 5) shows the results of stability testing of THP in formulation F8 stored in Sachet, PVDC/PVC/Alu and PVC/Alu, after storage for 180 days at 40 °C/75 % RH. It is obvious that, the percent remaining of drug after 180 is 95.6 %, 95.32 % and 95.278 %, respectively. The percent remaining of drug after 180 days was found to be 96.13 %, 95.9 % and 95.45 %, respectively.

Dissolution behavior after storage is an important parameter of the product. Factors such as formulation components and storage conditions can affect the dissolution stability of drug products [31, 32]. Iin vitro drug release profiles for all time points for the temperatures studied are shown in **Tables (6-7)**.

Actually it is difficult to compare graphs quantitavely because of the varying degrees of fluctuation. Therefore, the dissolution profiles were compared by using the two fit factors (f1 and f2) reported [34].The fit factors (f1 and f2) are two indices that compare the dissolution profiles of a reference formulation to that of a test formulation .however, these fit factors permit the systematic comparison of dissolution profiles at different time points. The dissolution profile of fresh tablets was considered as reference profile, while in the dissolution profile of sample tablets collected at the end of six months storage at elevated temperature was considered as the test profile. The f1 and f2 values were computed by the following equations [33]:

$$f1 = \sum_{t=1}^{n=t} (R_t - T_t) / \sum R_t \times 100$$

$$f_2 = 50 + \log \{[1 + (1/n) \sum^n W_t (R_t - T_t)^2]^{-0.5} X100\}$$

Where R_t is the cumulative percent released for the reference assay at time point $_t$, T_t is the cumulative percent released for the test assay at time point $_t$, n is the number of time points , and W_t is an optional weight factor which is applied to the value or values that are deemed more important than others .It is a value of 1 if all values are treated equally .The average difference between the reference and the test profiles is represented linearly by the test fit factor , *f1*and exponentially by the fit factor , *f2*.Fit factor , *f1* is 0 when the test and reference profiles are identical and increases proportionally with dissimilarity between the two profiles . Fit factor *f2* is 100 when the test and reference profiles are identical and increases proportionally with dissimilarity between the two profiles [33].

Further insight into the stability study, per se necessities the undertaking of parallel physical parameters as well as the dissolution studies of the stored tablets. It was found that, the color of the tablets stored at 40 °C /75 % RH was slightly changed from off white to heavy off white at the end of the period of study. Also the weight of some tablets was found to be slightly increased after six months especially in case of PVC/Alu, followed by less extent for PVDC/PVC/Alu and minimal extent with sachet (table 8). This increase in weight may be attributed to moisture uptake by the formula. The results revealed that, the tablets packed in PVC/ Aluminum blisters enveloped in aluminum sachet is the most stable one with the lowest rate of degradation .Tablets packaged in PVC / PVDC / Aluminum blisters have better stability and lower rate of degradation than those tablets packed in PVC / Aluminum blisters.

(Table 8): Physical properties of the prepared tablets for F8 (containing 2.0% Carbopol 971P®) in different Packaging materials at 40 °C after 15, 60, 120 and 180 days

Using the results of THP content of prepared tablets stored at different temperatures in different packaging materials by Arrhenius equation we can calculate estimated shelf life time of formulations F8 and F9 in different packaging materials as shown in table 9-10. The calculated shelf lives indicated that tablets packaged in PVC enveloped in sachet has the longest shelf life followed by tablets packaged in PVDC blisters, and tablets packaged in PVC blisters has the shortest shelf life time.
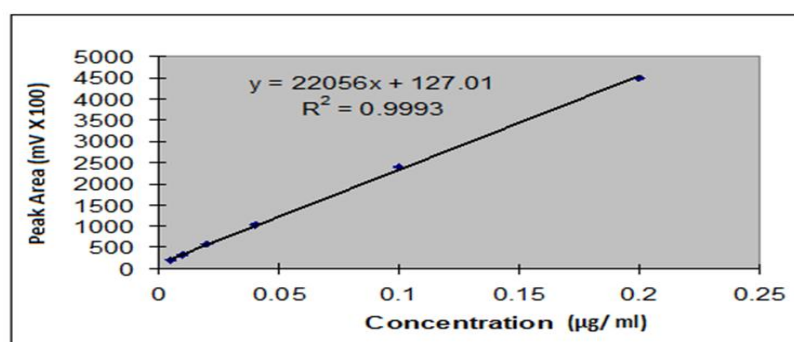

Figure 8: Standard calibration curve of THP in solvent mixture at 254 nm (r = 0.9993 intercept = 22056   slope = 127.01

Table 4: Dissolution Kinetics calculations of different models for F8.

	Zero	First	Second	Diffusion	Hixon	Baker
A	28.27578	1.963019	-0.00302	4.963288	0.309867	-0.02513
B	5.273995	-0.07249	0.006745	23.77232	0.171523	0.022823
R	0.994954	-0.97581	0.897396	0.984061	0.98921	0.974416
K	5.273995	-0.16695	0.006745	23.77232	0.171523	0.022823
t(1/2)	9.480478	-4.15105	1.482548	4.423814	5.57456	2.409851

Where,
A=Intercept   B=Slope   R= Correlation Coefficient   K= Release rate constant

Table 5: Stability of Trihexyphenidyl Hydrochloride in the selected F8 formulae stored in different packaging materials at 40.0 ºC and 75.0% R.H.

Storage time (days)		THP assay (% of label claim)		
		Sachet	PVC/PVDC/ALU	PVC/ALU
0		98.1	98.1	98.1
15		97.79	97.62	97.63
30		97.66	97.46	97.45
45		97.45	97.32	97.30
60		97.23	96.98	96.98
75		97.06	96.81	96.78
90		96.78	96.62	96.589
120		96.43	96.24	96.20
150		96.02	95.78	95.712
180		95.6	95.32	95.278
Zero order	R	0.999202	0.996184	0.99678
	A	98.0552	97.9384	97.9422
	B	-0.01363	-0.01456	-0.0149
First order	R	0.999222	0.996367	0.996976
	A	1.9914	1.99097	1.990992
	$Bx10^5$	-6.1	-6.5	-6.7
Mechanism of Degradation		First Order	First Order	First Order
$K \times 10^5$		14.081	15.057	15.4

R= Correlation Coefficient
A=Intercept
B=Slope

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Table 6: Dissolution of Trihexyphenidyl Hydrochloride from tablets of F8 in different packaging materials at 40, 35 and 30 °C after 15 days

Time (hr) Formula	% Released THP after time (hrs)							
	1	**2**	**3**	**4**	**6**	**8**	**10**	**12**
F8 Sachet 40 °C	34.5 (±0.23)	37.5 (±0.41)	39.5 (±0.17)	51.1 (±0.09)	61 (±0.52)	69.77 (±0.20)	81.84 (±0.19)	89.6 (±0.27)
F8 PVDC 40 °C	34.6 (±0.05)	37.6 (±0.47)	39.6 (±0.33)	51.2 (±0.54)	61.1 (±0.55)	69.87 (±0.06)	81.94 (±0.16)	89.7 (±0.34)
F8 PVC 40 °C	34.7 (±0.10)	37.7 (±0.25)	39.7 (±0.14)	51.3 (±0.43)	61.2 (±0.60)	69.97 (±0.47)	82.03 (±0.17)	89.8 (±0.09)
F8 Sachet 35 °C	34.7 (±0.22)	37.7 (±0.10)	39.7 (±0.26)	51.15 (±0.40)	61.2 (±0.12)	70 (±0.70)	82.1 (±0.29)	89.8 (±0.38)
F8 PVDC 35 °C	34.8 (±0.05)	37.8 (±0.29)	39.8 (±0.34)	51.25 (±0.21)	61.3 (±0.61)	70.1 (±0.10)	82.2 (±0.05)	89.9 (±0.07)
F8 PVC 35 °C	34.9 (±0.14)	37.9 (±0.19)	39.9 (±0.54)	51.35 (±0.43)	61.4 (±0.06)	70.27 (±0.40)	82.34 (±0.71)	90.1 (±0.28)
F8 Sachet 30 °C	34.9 (±0.33)	37.9 (±0.10)	39.9 (±0.63)	51.5 (±0.74)	61.4 (±0.19)	70.17 (±0.42)	82.34 (±0.07)	90.1 (±0.14)
F8 PVDC 30 °C	34.8 (±0.22)	37.8 (±0.13)	39.85 (±0.52)	51.55 (±0.55)	61.3 (±0.08)	70.1 (±0.11)	82.34 (±0.41)	90.1 (±0.03)
F8 PVC 30 °C	34.7 (±0.02)	38.7 (±0.27)	39.7 (±0.18)	51.5 (±0.06)	61.4 (±0.04)	70.15 (±0.32)	82.34 (±0.66)	90.1 (±0.58)

PVC polyvinyl chloride
PVDC polyvinyl diene chloride

Table 7: Dissolution of Trihexyphenidyl Hydrochloride from tablets of F8 in different packaging materials at 40, 35 and 30 °C after 180 days.

Time (hr) Formula	% Released THP after time (hrs)							
	1	**2**	**3**	**4**	**6**	**8**	**10**	**12**
F8 Sachet 40 °C	31 (±0.44)	34 (±0.23)	36 (±0.51)	48 (±0.17)	58 (±0.19)	67 (±0.27)	78.2 (±0.16)	86.1 (±0.08)
F8 PVDC 40 °C	30.9 (±0.06)	33.9 (±0.12)	35.9 (±0.36)	47.9 (±0.24)	57.9 (±0.04)	66.9 (±0.29)	78.1 (±0.54)	86 (±0.40)
F8 PVC 40 °C	30.8 (±0.21)	33.8 (±0.27)	35.8 (±0.31)	47.8 (±0.51)	57.8 (±0.37)	66.8 (±0.48)	78 (±0.20)	86 (±0.31)
F8 Sachet 35 °C	33 (±0.15)	36 (±0.50)	38 (±0.14)	49 (±0.26)	59.25 (±0.19)	68.75 (±0.07)	80.5 (±0.10)	88.25 (±0.46)
F8 PVDC 35 °C	32.9 (±0.33)	35.9 (±0.13)	37.9 (±0.28)	48.9 (±0.15)	59.15 (±0.06)	68.65 (±0.20)	80.4 (±0.61)	88.15 (±0.58)
F8 PVC 35 °C	32.8 (±0.17)	35.8 (±0.58)	37.8 (±0.44)	48.8 (±0.34)	59.05 (±0.57)	68.55 (±0.08)	80.3 (±0.19)	88.05 (±0.24)
F8 Sachet 30 °C	34.2 (±0.12)	37.2 (±0.50)	39.3 (±0.09)	50.8 (±0.28)	60.7 (±0.31)	69.4 (±0.06)	81.6 (±0.23)	89.4 (±0.17)
F8 PVDC 30 °C	34.1 (±0.15)	37.1 (±0.16)	39.2 (±0.28)	50.7 (±0.37)	60.6 (±0.31)	69.3 (±0.11)	81.5 (±0.07)	89.3 (±0.17)
F8 PVC 30 °C	34 (±0.29)	37 (±0.07)	39.1 (±0.38)	50.6 (±0.46)	60.5 (±0.37)	69.2 (±0.17)	81.4 (±0.08)	89.2 (±0.06)

Table 8: Physical properties of the prepared tablets for F8 (containing 2.0% Carbopol 971P®) in different Packaging materials at 40 °C after 15, 60, 120 and 180 days

Time(Days)	Packaging type	Mean wt. (mg) (± S.D)	Moisture Content	Mean Hardness (KP) (± S.D)
Zero time (days)	-	149.2 ((±0.01)	2.50	5.0 (±0.12)
15	Sachet at 40 °C	149.2 (±0.02)	2.49	5.0 (±0.29)
	PVDC at 40 °C	149.0(±0.09)	2.51	5.2(±0.05)
	PVC at 40 °C	150.0(±0.03)	2.48	5.4(±0.29)
60	Sachet at 40 °C	149.6(±0. 18)	2.51	5.5(±13)
	PVDC at 40 °C	149.4(±0.01)	2.53	5.3(±0.15)
	PVC at 40 °C	150.4(±29)	2.50	5.2(±0.03)
120	Sachet at 40 °C	150.0(±0.06)	2.55	5.9(±0.13)
	PVDC at 40 °C	149.2(±0.42)	2.57	6.1(±37)
	PVC at 40 °C	151.2(±0.04)	2.54	5.6(±038)
180	Sachet at 40 °C	150.4((±32)	2.59	6.3(±0.42)
	PVDC at 40 °C	150.2(±0.02)	2.61	6.5(±37)
	PVC at 40 °C	151.2(±0.16)	2.58	6.0(±0.04)

Table 9: Estimated shelf lives of F8 (containing 2.0% Carbopol 971P®) and F9 (containing 1.5% Carbopol 971P®) tablets in different packaging materials

Formula / Packaging	F8 Shelf life in Years	F9 Shelf life in Years
Sachet	3.84	3.9
PVDC	3.7	3.83
PVC	3.6	3.75

Table 10: Calculated two fit factors (*f1* and *f2*) of F8 (containing 2.0% Carbopol 971P®) and F9 (containing 1.5% Carbopol 971P®) tablets in different packaging materials at 40 °C after 180 days.

	F8		F9	
	f1	*f2*	*f1*	*f2*
Sachet 40 °C 180 days	6	70	6	70
PVDC °C 180 days	7	70	6	70
PVC °C 180 days	7	70	6	69

f1 (difference factor) should be equal to or less than 15

f2 (similarity factor) should be equal to or higher than 50

4. Conclusion

The selected formula (F8) was found to be more stable in all packaging materials and at all stability conditions. This has been proved by the content of trihexyphenidyl hydrochloride in tablets which was found conforming the USP 38. In addition by using the fit factors f1 and f2 in case of dissolution profiles after time required for accelerated conditions. The shelf lives for F8 packaged in PVC blisters which have been calculated using Arrhenius equation were 3.6 and 3.75 years respectively.

From pharmacutical industrial point of view, the joint output of the two studies is thought to cover the information necessary for the formulation and stability of the extended release tablets of trihexyphenidyl hydrochloride hydrophilic matrices. This contribution has been coupled with growing interest to develop extended release tablets of trihexyphenidyl hydrochloride as an alternative of capsule with considering overcoming the problem of cost, labor and time compared with tablet manufacturing as well as compliance of elderly patients.

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