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COMPARATIVE STUDY OF PREFORMULATION AND IN VITRO EVALUATION OF SUSTAINED RELEASE MARKETED FORMULATION OF TRIHEXYPHENIDYL HCL TABLETS

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ABSTRACT

The present investigation highlighted the study and evaluation of marketed formulation of Trihexyphenidyl Hcl. To achieve this goal, various marketed formulation of Trihexyphenidyl Hcl was evaluated with respect to the various quality parameters, (Uniformity of weight, Hardness, Drug Content, In-vitro Disintegration test and In-vitro Dissolution test). It was observed that Trihexyphenidyl Hcl (tablets) was pharmaceutically equivalent. In present study the comparative dissolution study of three marketed formulations i.e. Bexol (Intas Laboratories Pvt Ltd.), Hexylent (Talent Healthcare Ltd), Pacitane (Wyeth Pharmaceuticals Ltd.), was being carried out. All the formulations showed excellent drug release profile. The present study gives an idea about its release so that it will be useful for further development concerned with the improvement of patient compliance.

KEYWORDS: Anti- Parkinson, Parkinson, In vitro evaluation, Trihexyphenidyl Hcl tablet, Sustained release.

INTRODUCTION

Parkinson's disease (PD) is a progressive, neurodegenerative disorder with cardinal motor features of tremor, bradykinesia ,and rigidity.[1] this disease affects more than 1 million Americans older than 50 years of age with the incidence increasing significantly with age.[2] the term "Parkinsonism" describes the motor syndrome of bradykinesia, rigidity, tremor and balance and gait problems.[3] secondary parkinsonism, which has a different etiology and pathology than PD ,is the predominant clinical manifestation of a number of disorders including brain tumours near the basal ganglia, head trauma, and progressive supranuclear

palsy. Secondary Parkinsonism can also be caused by toxins and drugs, antipsychotic agents. Parkinson's disease and secondary Parkinsonism are characterized by striatal dopamine deficiency. In PD, the degeneration of dopamine-containing neurons in the substantia nigra leads to the formation of lewy bodies. Lewy bodies are not present in secondary Parkinsonism the nigral striatal pathway may be impaired and nigral cell loss or loss of striatal cellular elements may occur.[4]

Contraindications/warnings: A boxed warning appears in the tolcapone (tasmar) prescribing information of three fatal cases of acute, fulminant liver failure had been reported.[5] Patients must sign an informed respond to start the therapy with tolcapone. The warning states that "the actual incidence of hepatocellular injury appears to be 10 to 100-fold more high than the background incidence in the general population.[6] If patients do not have a retort to tolcapone in three weeks, therapy should be stopped.[7] Concomitant use of non-selective MAO inhibitors with levodopa/carbidopa (parcopa, sinemet, sinemet cr) can be resulting in hypertensive crisis; simultaneous use of these agents is contraindicated.[8] The MAO must be discontinued two weeks prior to starting levodopa/carbidopa. Carbidopa/ Levodopa also contraindicated in patients with narrow-angle glaucoma.[9] the benztropine, trihexyphenidyl and anti-cholinergics should not be given to patients with narrow angle glaucoma. Benztropine should be used carefully in patients with benign prostatic hypertrophy as it can exacerbate urinary retention. Including, the manufacturer considers dementia, tardive dyskinesia and prostatism contraindicated to the use of this drug.[10]

With potentially fatal reactions that have occurred in patients receiving mao inhibitors concomitantly with meperidine, the use of rasagiline (azilect) and selegiline (generic, zelapar) with meperidine is contraindicated.[11] For same reasons, these two drugs should not be used concurrently with methadonen or tramadol; and this contraindication is often extended to other opioids.[12] Selegiline and Rasagiline are contraindicated for use with sympathomimetic amines due to the potential for serious hypertensive responses.[13]

MATERIAL AND METHOD

Table. 1: Marketed formulation of Trihexyphenidyl Hcl.

S. No.	Brand Name	Manufacturer	Dosage form
1	Bexol	Sun Pharma ltd.	Tablet (2mg)
2	Hexylent	Torrent Pharma Ltd	Tablet (2mg)
3	Pacitane	Vibra (Cadila Pharmaceuticals Ltd.)	Tablet (2mg)

Method

Preformulation study

The following preformulation studies of Trihexyphenidyl Hcl were carried out

I. Melting point

II.Fourier Transform Infrared (FTIR) spectroscopy

III Loss on drying

IV.Assay of drug

V Assay of drug

VI. Partition Coefficient

Evaluation marketed formulation (Trihexyphenidyl Hcl)

I. Weight variation

II. Hardness

III. Friability

IV. Disintegration

V. Dissolution

Preformulation Studies

Melting Point

Melting point of the Trihexyphenidyl Hcl was determined by using digital melting point apparatus. (MEPA. Lab India Apparatus) and the melting point of Trihexyphenidyl Hcl was found to be **336°C**

Fourier transforms infrared (FTIR) spectral studies

Infrared spectra of the Trihexyphenidyl Hcl were recorded on a FT-IR spectrophotometer (Agilent Technologies, India)Measurements were attempted with the accumulation of 3 scans and a resolution of 4 cm^{-1} over the range of 400 to 4000 cm^{-1}. The technique is based upon the simple fact that a chemical substance shows marked selective absorption in infrared region. After absorption of IR radiations, the molecules of a substance vibrate at many rate of vibration, giving rise to closed packed absorption bands which was called an IR absorption spectrum which may extend over a wide wavelength range.

Trihexyphenidyl Hcl

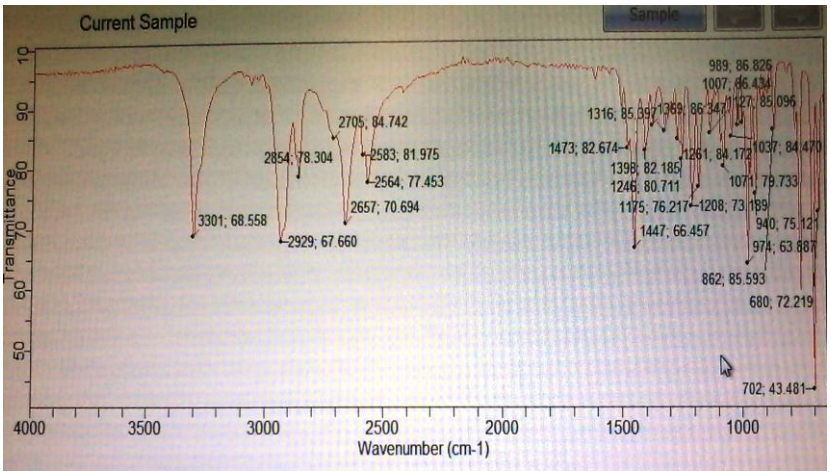

Fig. 1: FTIR spectra of Trihexyphenidyl Hcl.

Table. 2: IR bends of Trihexyphenidyl Hcl.

Functional group	Bandscm^{-1}
N-H stretching	3301
C-H	2929
C=C	1447
C-H bend benzene	680
C-H bend benzene	665

Loss on drying: The Test is designed to measure the amount of water and volatile matters in a sample when the sample is dried under specified conditions.

1.0 g of drug was weighed accurately. It was placed in a tray dryer (Oven) at 105^{o}c for 4 hrs. After 4 hrs. The drug was reweighed. (Within limits as it should be less than 0.5% in case of).

Table. 3: Effect of loss on drying of different Anti-Parkinson agents.

S. No	Drugs
1	Trihexyphinydil Hcl

Spectroscopic Estimation of Anti-Parkinson Agents

Trihexyphenidyl Hcl

Preparation of standard stock solution: Standard solution of Trihexyphenidyl Hcl was prepared by dissolving 100 mg of drug in 100 ml of methanol (solution A,1000 µg/ml), Further 10 ml of the solution A was diluted to 100 ml with methanol(solution B, 100µg/ml). Solution B was used as the standard stock solution.

Assay of Trihexyphenidyl Hcl

For determination 1 ml of stock solution was diluted to 10 ml and this 10µm/ml solution was Scanned in the range from 200 to 400 nm using Agilent Technologies Spectrophotometer. Determination of λ_{max} 250.0 nm

Salt name	**wavelength**
Trihexyphenidyl Hcl	250.0 nm

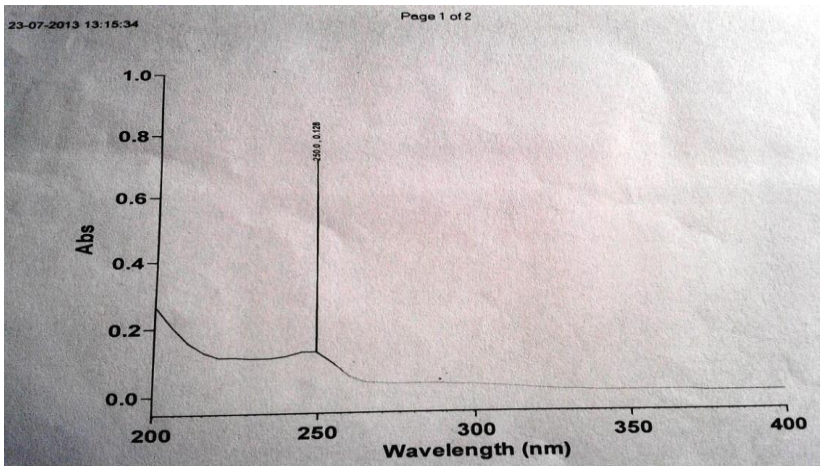

Fig. No. 2: Determination of λ_{max} of Trihexyphenidyl Hcl.

Table. 4: Standard Calibration Curve of Trihexyphenidyl Hcl.

Conc. (µg/ml)	Absorbance
0	0
0.1	0.019
0.2	0.0285
0.3	0.0384
0.4	0 .0475
0.5	0 .0584
0.6	0.0673
0.7	0.0772
0.8	0.0844
0.9	0.0921
1	0.102

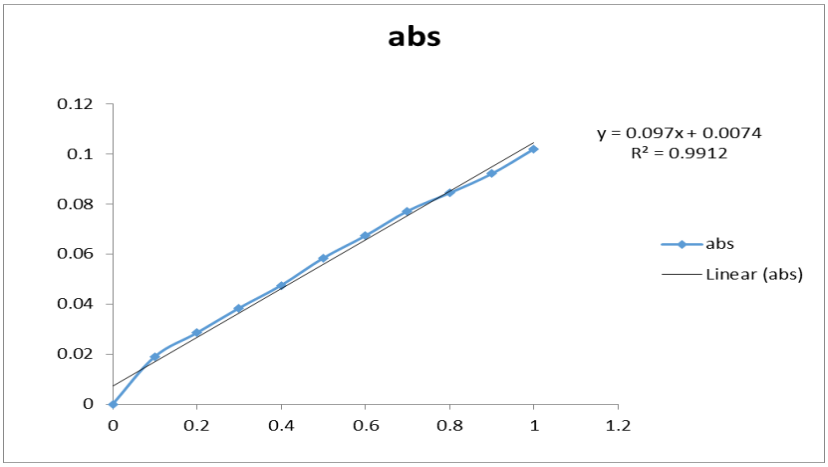

Fig. 3: Standard curve of Trihexyphenidyl Hcl in water at 250nm.

Solubility

A substance is said to be soluble if more than 0.1 g of that substance dissolves in 100 mL solvent. If less than 0.1 g dissolves in 100 mL solvent, the substance is said to be insoluble or, more exactly, sparingly soluble .

Determination of solubility

Table. 5: solubility of Trihexyphenidyl Hcl.

S. No.	Salt name	Solubility
1	Trihexyphenidyl Hcl	Slightly soluble in ether and benzene, slightly soluble in water. Soluble in methanol.

Partition Coefficient

The partition coefficient (P) is defined as the ratio of the equilibrium concentrations (ci) of a dissolved substance in a two-phase system consisting of two largely immiscible solvents. In the case n-octanol and water

$$\mathbf{Po/w} = \frac{\mathbf{Concentration\ of\ drug\ in\ n-Octanol}}{\mathbf{Concentration\ of\ drug\ in\ water}}$$

Method: 100 mg of drug weighed accurately and transferred to a volumetric flask containing 2o ml of n –octanol and 20 of water. The mixture was shaken on magnetic stirrer. After 24 hrs Both phases of mixture were separated using separating funnel and examine using UV spectrophotometer at 250.0nm for Trihexyphenidyl Hcl.

Table. 6: Partition coefficient of Trihexyphenidyl Hcl.

S. No.	Drug	Partition coefficient
1	Trihexyphenidyl Hcl	4.21

Formulation of Trihexyphenidyl Hcl

Table. 7: Marketed formulations.

S. No.	Brands name	Marketed formulation code	Strength
1	Bexol	Th1	2mg
2	Hexylent	Th2	2mg
3	Pacitane	Th3	2mg

Evaluation parameter Trihexyphenidyl Hcl

I. Weight variation
II. Hardness
III. Drug Content Uniformity
IV. Friability
V. Disintegration
VI. Dissolution study

Weight variation

To study mass difference twenty tablets of the promoted design was weighed using Dwijo electronic balance. Twenty tablets was weighed and average weight was calculated. The individual tablets was weighed and compared with average mass. Not more than two of the individual weights differ from the average weight of tablets by more than 5% As per Indian pharmacopoeia, 2011.

Table. 8: Weight variation of Anti-Parkinson agents.

S.no.	Brand's code	Acceptance criteria(gm)	Observation (Highest wt. /lowest wt.)	%variation (upper limit, lower limit)
1	Th1	0.132±0.0099	0.14,0.13	+6.060, -1.5
2	Th2	0.099±0.007425	0.09,0.09	0.00
3	Th3	0.1195±0.008962	0.12,0.119	+0.418, -0.418

Hardness of tablet: The hardness was determined using Monsanto hardness tester. The average of the six determinations was firm and defined as "Hardness factor". The force was dignified in kilograms per centimetre square.

Table. 9: Hardness of dosage forms.

S. No	Marketed formulation code	Hardness(kg/cm^2)
1	Th1	0.2
2	Th2	0.3
3	Th3	0.3

Drug Content

Estimation of drug content Trihexyphenidyl Hcl

20 tablets were weighed accurately and powdered. The powder was equivalent to 100mg of Trihexyphenidyl Hcl was transferred to 100mL volumetric flask and made the volume to mark with distilled water. Then filtered through Whatman filter paper No. 41. 5 ml. of the filtrate was transferred into a 50 ml. volumetric flask and made the volume up to the mark with buffer solution. Aliquots of the sample were removed and diluted to 10 ml. with buffer solution. The absorbance was determined at 250 nm against the buffer solution as blank. The different marketed formulations of different manufacturers were used for study. The drug of all brand's tablets were shown in the following table:

Table. 10: Drug content of Trihexyphenidyl Hcl.

S. No.	Brand's code	Drug content(mg)
1.	Th_1	95.10
2.	Th_2	93.50
3.	Th_3	94.23

Disintegration Test

Test regulates whether dosage forms like tablets, capsules, boluses pessaries and suppositories disintegrate within a given time when placed in a liquid medium under the suggested experimental conditions.

Fig. 4: In-vitro disintegration test apparatus.

Table. 11: Disintegration time of dosage form.

S. No.	Brand code	Disintegration time
1	Th1	1.19 min.
2	Th2	1.23 min.
3	Th3	54 sec.

Friability

It is the fixed of tablets to powder, chip or fragment and this can mark the taste appearance, consumer acceptance of the tablet and also add to tablet's weight variation or content uniformity problems. Friability is the damage of weight of tablet in the container/package, due to elimination of fine particles from the surface. This in process excellence control test is performed to certify the skill of tablets to tolerate the astonishments during transportation, processing, handling and shipment. Permitted friability limit is 1.0 %.

Table. 12: Friability of dosage forms.

S. No.	Brand code	Friability (%)
1	Th1	0.00
2	Th2	0.00

Dissolution Study of Anti-Parkinson agents

Fig. 5: Dissolution test apparatus.

Study of Trihexyphenidyl Hcl

Th1 tablet

Dissolution studies was studied using 8 station USP dissolution test apparatus type -2 (lab India) using 900 ml dissolution medium maintained at 37.0 ± 0.5˚c at stirring rate 100 rpm. All brand tablets were evaluated 900 ml distilled water for the following 45 min samples, measuring 5 ml were withdrawn at different time intervals 5, 10, 15, Sink condition was maintained for the whole experiment. Withdrawn sample was clarified in filter paper (What

man filter paper 41). After filter samples were analysed at 250 nm (UV–visible spectrophotometer) using distilled water as blank. The cumulative percentage drug release was intended.as per Indian pharmacopoeia.

Table. 13: %CDR of dosage forms.

S. No.	Time	Abs	conc.	In 5ml	In 900ml	CR	%CDR
0	0	0	0	0	0	0	0
1	5	0.912	0.90566	0.004528	0.815094	0.815094	40.75472
2	10	1.016	1.008937	0.005045	0.908044	0.908044	45.40218
3	15	1.132	1.124131	0.005621	1.011718	1.011718	50.5859
4	20	1.264	1.255214	0.006276	1.129692	1.129692	56.48461
5	25	1.356	1.346574	0.006733	1.211917	1.211917	60.59583
6	30	1.476	1.46574	0.007329	1.319166	1.319166	65.95829
7	35	1.578	1.567031	0.007835	1.410328	1.410328	70.51639
8	40	1.678	1.666336	0.008332	1.499702	1.499702	74.9851
9	45	1.812	1.799404	0.008997	1.619464	1.619464	80.97319

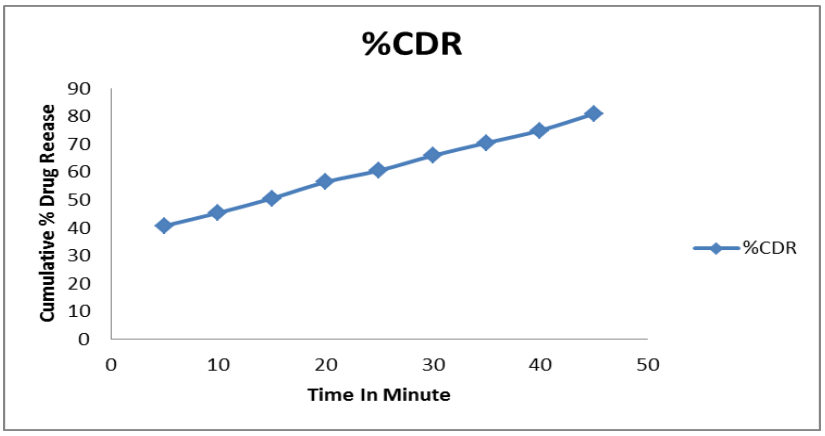

Fig. 6: dissolution profile of Th1 tablet.

Th2 tablet

dissolution was studied using 8 station USP dissolution test apparatus type -2 (lab India) using 900 ml dissolution medium maintained at 37.0 ± 0.5˚c at stirring rate 100 rpm. All brand tablet was assessed 900 ml distilled water for the following 45 min samples, measuring 5 ml was withdrawn at different time intervals 5, 10, 15,,, Sink condition was maintained for the whole experiment. Withdrawn sample was filtered in filter paper (what man filter paper 41). After filter sample was analysed at 250 nm (UV–visible spectrophotometer) using distilled water as blank. The cumulative percentage drug release was calculated as per Indian pharmacopoeia.

Table. 14: %CDR of dosage forms.

S. No.	Time	Abs	conc.	In 5ml	In 900 ml	CR	%CDR
0	0	0	0	0	0	0	0
1	5	0.912	0.90566	0.004528	0.815094	0.815094	40.75472
2	10	1.098	1.090367	0.005452	0.981331	0.981331	49.06653
3	15	1.186	1.177756	0.005889	1.05998	1.05998	52.99901
4	20	1.269	1.260179	0.006301	1.134161	1.134161	56.70804
5	25	1.39	1.380338	0.006902	1.242304	1.242304	62.11519
6	30	1.51	1.499503	0.007498	1.349553	1.349553	67.47766
7	35	1.598	1.586892	0.007934	1.428203	1.428203	71.41013
8	40	1.701	1.689176	0.008446	1.520258	1.520258	76.01291
9	45	1.967	1.953327	0.009767	1.757994	1.757994	87.8997

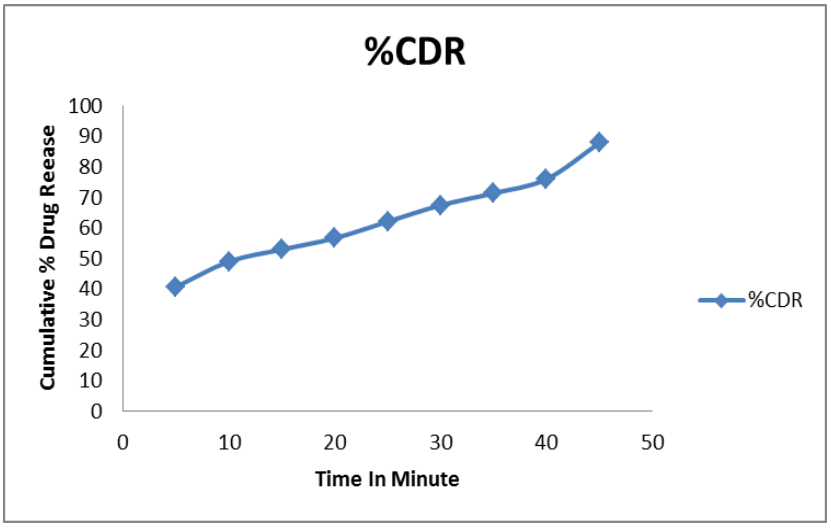

Fig. 7: dissolution profile of Th2 tablet

Th3 tablet

dissolution was studied using 8 station USP dissolution test apparatus type -2 (lab India) using 900 ml dissolution medium preserved at 37.0 ± 0.5˚c at stirring rate 100 rpm. All brand tablet was assessed 900 ml distilled water for the following 45 min samples, measuring 5 ml was withdrawn at dissimilar time intervals 5, 10, 15,,. Sink condition was maintained for the whole experiment. Withdrawn sample was filtered in filter paper (what man filter paper 41). After filter sample was examined at 250 nm (UV–visible spectrophotometer) using distilled water as blank. The cumulative percentage drug release was intended as per Indian pharmacopoeia.

Table. 15: %CDR of dosage forms.

S. No.	Time	Abs	conc.	In 5ml	In 900ml	CR	%CDR
0	0	0	0	0	0	0	0
1	5	0.956	0.949355	0.004747	0.854419	0.854419	42.72095
2	10	1.089	1.08143	0.005407	0.973287	0.973287	48.66435
3	15	1.167	1.158888	0.005794	1.042999	1.042999	52.14995
4	20	1.211	1.202582	0.006013	1.082324	1.082324	54.11619
5	25	1.367	1.357498	0.006787	1.221748	1.221748	61.08739
6	30	1.411	1.401192	0.007006	1.261072	1.261072	63.05362
7	35	1.595	1.583913	0.00792	1.425521	1.425521	71.27607
8	40	1.698	1.686197	0.008431	1.517577	1.517577	75.87885
9	45	1.805	1.792453	0.008962	1.613208	1.613208	80.66038

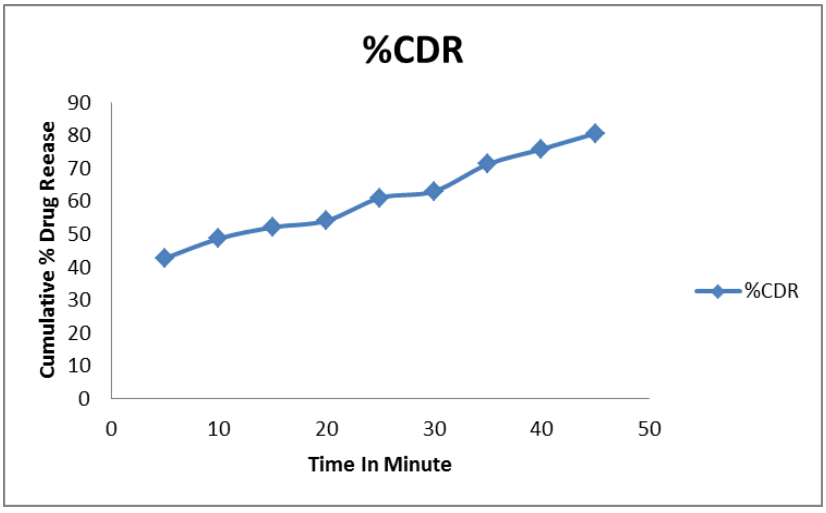

Fig. 8: dissolution profile of Th3 tablet.

RESULT AND DISCUSSION

Preformulation study: The Preformulation study of Anti-Parkinson agents was performed by various physico-chemical parameters including description, solubility, partition coefficient, loss on drying, melting point.

Table. 16: Preformulation study.

S. No	Marketed formulation	Parameters						
		Colour	Melting point	FTIR	Loss on drying	Assay	Solubility	Partition coefficient
1	Th1	creamy-white	336°C	C=C C=C C=O (CH_3 bending)	0.1	250nm,slope 1.007	Slightly soluble in water. Soluble in methanol	4.21

Table 17: Calibration curve data of Trihexyphenidyl Hcl.

Conc. (µg/ml)	Absorbance
0	0
0.1	0.019
0.2	0.0285
0.3	0.0384
0.4	0 .0475
0.5	0 .0584
0.6	0.0673
0.7	0.0772
0.8	0.0844
0.9	0.0921
1	0.102

Calibration curve for Trihexyphenidyl Hcl: Calibration curve of both drugs was carried out with UV-Vis Spectrophotometer, Cary-60 UV-Vis Spectrophotometer, Agilent technologies.

Calibration Curve of Trihexyphenidyl Hcl

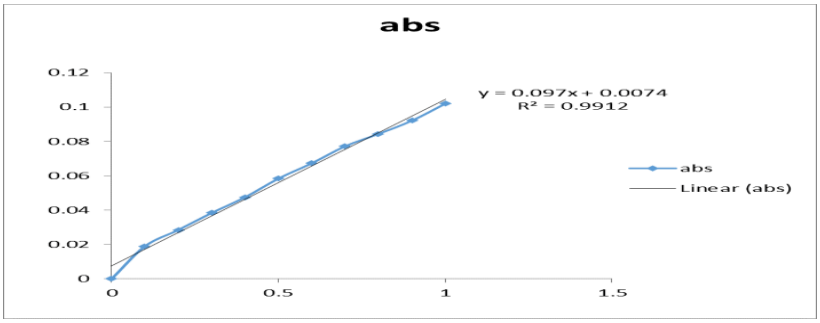

Fig. 9: Standard curve of Trihexyphenidyl Hcl in 0.01N Hcl at 250nm.

Determination of dissolution study

Table. 18: Data for cumulative drug release of different anti- Parkinson formulation (tablet).

Time (min)	% CDR (Th1)	% CDR (Th2)	% CDR (Th3)
0	0.0	0.0	0.0
5	40.75472	40.75472	42.72095
10	45.40218	49.06653	48.66435
15	50.5859	52.99901	52.14995
20	56.48461	56.70804	54.11619
25	60.59583	62.11519	61.08739
30	65.95829	67.47766	63.05362
35	70.51639	71.41013	71.27607
40	74.9851	76.01291	75.87885
45	80.97319	87.8997	80.66038

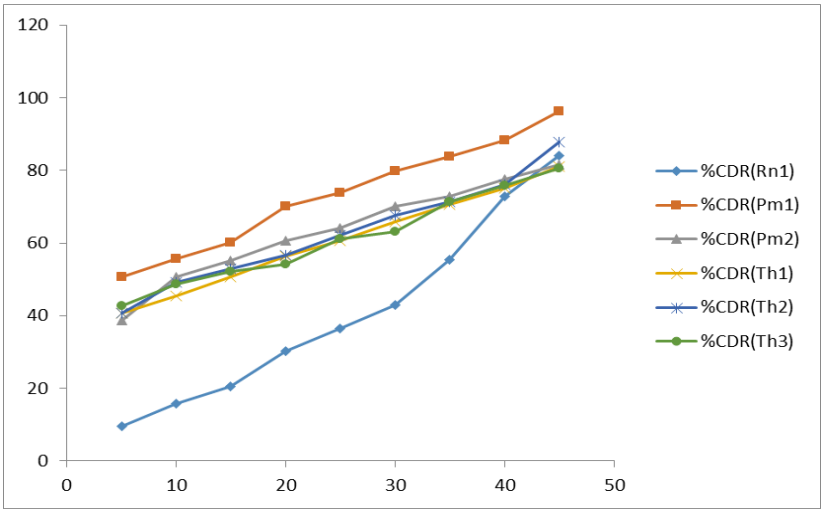

Fig. 10: % CDR curve of different marketed Trihexyphenidyl Hcl.

DISCUSSION

Standard Curve: In the preformulation study the standard curve of Trihexyphenidyl Hcl was obtained to check the purity of the drug sample. The λ-max of the sample drug was compared with that of the reference standard which is 205.0 nm Trihexyphenidyl Hcl respectively the calibration curve is performed by UV-Vis Spectrophotometer (carry-60 UV-Visible, Agilent technologies) and found satisfactory.

The FTIR: The Fourier Transform Infrared spectroscopy was performed by (cary-630 FTIR-Spectrophotometer, Agilent technologies). Spectra of the pure Trihexyphenidyl Hcl was carried out and there FTIR spectra of are given in figure 2.1 2.2 and figure 2.3 respectively.

Solubility: Determination of solubility of the pure drug Trihexyphenidyl Hcl in different solvent (i.e. methanol, ethanol and distilled water) was studied and it has been found that the drug shows its maximum solubility in methanol and freely soluble in distilled water.

Partition coefficient: Partition coefficient of the pure drug sample of Trihexyphenidyl Hcl is carried out with the help of UV-Vis Spectrophotometer at 205.0 nm respectively and we found that at equilibrium drug having low partition co-efficient value in water and maximum value in organic phase.

Evaluation of formulation (tablet)

Weight variation: According to the Indian Pharmacopoeia for those tablets which are less than 80 mg. the percentage deviation is 10% of average weight of 20 tablets. All tablets of

chosen marketed formulation were come under the limit of weight variation. So result is that, all marketed formulations are passed in weight test.

Hardness: In all the formulations, hardness test showed good mechanical strength. Hardness of the tablets was within the range of 0.0 to 4.0 kg.

Disintegration time: The formulations showed disintegration time between the ranges of 25 seconds to 7.50 minutes.

Friability: The friability of the all formulations was found to be 0%, indicated that tablets had a good mechanical resistance, so the tablets are passed in friability test.

Dissolution: Dissolution study was carried out in USP –II type dissolution apparatus (paddle type) with (DS-8000, LABINDIA). Dissolution study was performed at 100 rpm in 900ml (distilled water for Trihexyphenidyl Hcl) .The temperature was maintained at 37 ± 0.2^{o}C throughout the dissolution process. The absorbance of withdrawn sample was measured by UV-Vis spectrophotometric method at 205.0 nm (Promethazine Hcl). In-vitro dissolution studies showed that all marketed formulation released drug more than 90% within 45 minutes, but the percentage release of formulation F_L is greater than any other marketed formulation. The results are shown in figure 10.

CONCLUSION

The main purpose of research work is to evaluate the marketed formulation of Anti-Parkinson agents and find out that which tablet is more potent and shows best anti-Parkinson activity and passed from all the evaluation parameters according to the Indian Pharmacopoeia. all marketed formulation of Trihexyphenidyl HCl showed good results in various tests for drug release studies and all marketed brands showed values of parameters within acceptable limits (As per I.P.- 2010, U.S.P 2007). Comparative study of in vitro dissolution of different brands of Trihexyphenidyl HCl shows that highest Cumulative % drug release approx. **96.17**%.

The efficacy of Covance is very good so it is a very effective drug to prevent the patient from Parkinson disease. By the mean of this research work we conclude that Covance is more effective and the release of medicament from dosage form is better than any other formulation of Anti-Parkinson tablet among selected marketed brands, so the use of Covance is more effective in the treatment of Parkinson disease.

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