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Original Research Article

FORMULATION AND EVALUATION OF TRIHEXYPHENIDYL HYDROCHLORIDE IMMEDIATE RELEASE TABLETS

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ABSTRACT

The main objective of this research work was to formulate and evaluate the immediate release tablets of Trihexyphenidyl HCL 5mg, an M1 muscarinic acetylcholine receptor antagonist. It blocks cholinergic activity in CNS, which is responsible for the symptoms of Parkinson's disease. The tablets are prepared by direct compression method and wet granulation method. The formulations was optimized by incorporating varying composition of sodium starch glycollate and pregelatinised starch as super disintegrant, lactose and microcrystalline cellulose as diluent, povidone K-30 as binder and magnesium stearate agent as lubricant. All the excipients are tested for compatibility with drug, which revealed that there was no physical and chemical interaction occurred. The Preformulation parameters such as bulk density, tapped density, compressibility index and Hausner ratio were analyzed. The thickness, hardness, friability, weight variation, disintegration time and drug content uniformity was evaluated for core tablets. The effect of these variables on drug release also studied. The *In-vitro* drug release studied was performed in the USP dissolution apparatus-II (paddle) using pH 4.5 acetate buffer as dissolution media at 100rpm. The cumulative amount of drug release at different intervals is estimated using HPLC method. Based on the evaluation result the formulations F-8 containing MCC and SSG (6%) showed 98.5% release in 30 mins and so it was optimized as best formulation.

Key words: Trihexyphenidyl, Immediate release, Super disintegrants, Wet granulation, Parkinson'disease.

INTRODUCTION

In the present study the novel drug delivery systems are developed for expanding markets/indications, extending product life cycles and generating opportunities. Oral administration is the most popular route for systemic effects due to its ease of ingestion, pain, avoidance, versatility and most importantly patient compliance.[1] For many drug substances conventional immediate release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with an acceptable level of safety to the patient. These IR preparations are primarily intended to achieve faster onset of action for drugs such as analgesics, antipyretics, and coronary vasodilators. Other advantages include enhanced oral bioavailability through transmucosal delivery and pre gastric absorption, convenience in drug administration to dysphasic patients, especially the elderly and bedridden, and new business opportunities.[2] Anticholinergics or antimuscarinics are most often used to help control some of the common side-effects which can occur with some antipsychotic (neuroleptics or major tranquillisers) drugs e.g. tremor or shaking, stiffness or movement problems.[3] Trihexyphenidyl is a selective M1 muscarinic acetylcholine receptor antagonist. It is able to discriminate between the M1 (cortical or neuronal) and the peripheral muscarinic subtypes (cardiac and glandular). Trihexyphenidyl partially blocks cholinergic activity in the CNS, which is responsible for the symptoms of Parkinson's disease. Trihexyphenidyl is rapidly absorbed on oral administration from gastrointestinal tract. The onset of action is within 1 hour after oral dosing. The peak activity is noted after 2 to 3 hours.[4]

OBJECTIVES

The objective of the present study was to formulate and to evaluate the immediate release tablets of Trihexyphenidyl HCL by using different super disintegrants and to estimate the preformulation, pre compression and post compression properties of the various formulations.

MATERIALS AND METHODS

Materials

Trihexyphenidyl Hcl was received as gift sample. Mico crystalline cellulose (PH 101 and PH 102) from Brahmar cellulose Pvt Ltd., Cuddalore, PVP K-30, Sodium starch glycollate from S.D Fine Chem., Mumbai, Aerosil and pregelatinised starch were obtained from Signet chemical corporation Pvt Ltd.Mumbai, Magnesium stearate and Lactose were obtained from Vijilak pharma,

Mumbai. All the reagents and chemicals used were of analytical grade.

Methods

Preformulation studies may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe and effective dosage forms. Ideally the Preformulation phase begins early in the discovery process such the appropriate physical, chemical data was available to aid the selection of new chemical entities that enter the development process during this evaluation possible interaction with various inert ingredients intended for use in final dosage form were also considered in the present study.[5]

Preparation of Trihexyphenidyl HCl immediate release tablet

First five batches prepared by direct compression method by following procedure. Trihexyphenidyl is sifted through mesh # 40 and collected in double lined polybag. Lactose monohydrate, microcrystalline cellulose PH 102 and pregelatinised starch sifted through mesh # 40 and added to the material. Aerosil is sifted through mesh # 40 and added to the material of step-2 and mixed for 10 minutes. Lubrication: Magnesium stearate sifted through mesh# 40 and added to the material and mixed for 5 minutes and collected in double lined polybag. Remaining seven batches were prepared by wet granulation method by following procedure.

Sifting

Sift through mesh # 40 and collected in double lined polybag. Sift granulac, microcrystalline cellulose PH 101, Sodium starch glycolate through mesh # 40 and added to the material. Sift magnesium stereate and aerosil through mesh # 40 and collected in double lined polybag.

Dry mixing

Dry mix the contents for 10 minutes.

Granulation

Granulate the mix by adding purified water to that. Mix the mass to get uniform dough mass

Drying

Dry the wet mass in tray dryer at an inlet air temperature of 50 ± 5 °C till the moisture content is NMT 2% (measured using a halogen moisture balance).

Sifting & Milling

Sift the dried granules using #18 sieve and collect the under size and retained granules separately. Pass the materials retained on #18 sieve.

Lubrication

Add the material into Octagonal blender, mix for 5 minutes at 12rpm and collect the material in a cleaned SS container lined with double poly bags.

Compression

Compress the lubricated blend using 9.0 mm round Shaped Punches and dies, debossed with N, T on either side of score

line and 5 on other side. Composition of Trihexyphenidyl HCL immediate release tablets given in table no. 1

EVALUATION PARAMETERS

ORGANOLEPTIC PROPERTIES:

Colour A small quantity of trihexyphenidyl powders were taken in butter paper and viewed in well-illuminated place.

Taste and odour Very less quantity of trihexyphenidyl was used to get taste with the help of tongue as well as smelled to get odour.

Determination of melting point

Melting point of the drug sample was done by open capillary method. Drug was taken in glass capillary whose one end was sealed by flame. The capillary containing drug was dipped in liquid paraffin inside the melting point apparatus. Melting point was the first indication of purity of the sample since the presence of relatively small amount of impurity can be detected by a lowering as well as widening in the melting point range.[6]

Solubility study:

It is important to know about solubility characteristic of a drug in aqueous system, since they must possess some limited aqueous solubility to elicit a therapeutic response. The solubility of drug was recorded by using various descriptive terminology specified in Indian pharmacopoeia, 2007.[7]

Loss on drying

The accurately weighed 1gm of sample was transferred in glass-stoppered, shallow weighing bottle and accurately weighed the bottle. The bottle was transferred in oven and substance was dried at 105°C for 3 hours. The bottle was removed from oven and reweighed, loss on drying was calculated by following equation,

$$\text{LOD} = \frac{\text{Initial weight of substance} - \text{Final weight of substance}}{\text{Initial weight of substance}} \times 100$$

Drug Excipient Compatibility Studies

Compatibility study was carried for pure Trihexyphenidyl HCL and combination of Trihexyphenidyl HCL with excipients. Fourier transfer infra red (FTIR) spectroscopic (shimadzu, Japan) studies were carried out by approximately diluting the sample with dried potassium bromide (1:100) and acquiring infrared (IR) spectrum in the range of 400 to 4000cm^{-1} .[8]

Determination of percentage purity of drug:

The expected range for individual active ingredient is to be within 97%–102% of the labelled amount.

PRECOMPRESSION PARAMETERS:

Bulk density

Density is a term obtained by dividing weight of powder by volume of powder. It was given as g/cm3. Apparent bulk density was determined by pouring presieved drug excipients blend into a graduated cylinder and measuring the volume and weight. It was determined by following equation.[9]

$$\rho b = m / V_b$$

Where, ρb = Bulk density,

m = Mass of powder, V_b = Volume of powder

Tapped density

It was determined by placing a graduated cylinder containing a known mass of drug and excipients blend on mechanical tapping apparatus, which was operated for a fixed numbers of taps until the powder bed volume has reached a minimum using the weight of a blend in a cylinder and from this minimum volume, the tapped density was computed. It was determined by following equation.

$$\rho t = m / Vt$$

Where, ρt = Tapped density, m = Mass of powder,

Vt = Tapped volume.

Compressibility Index

Compressibility was indirectly related to the relative flow rate, cohesiveness and particle size distribution of the powder. Powders with compressibility values lesser than about 20% have been found to exhibit good flow properties.Tapped (ρt) and apparent (ρb) bulk density measurements can be used to estimate the compressibility of a material11.

$$CI (\%) = (\rho t - \rho b) / \rho t * 100$$

Where, ρb = Bulk density, ρt = Tapped density

Hausner's ratio It was the ratio of bulk volume to tapped volume or tapped density to bulk density. It was a measure used to describe compressibility of powder89.

$$\text{Hausner's ratio} = \rho t / \rho b$$

Where, ρt = Tapped density, ρb = Bulk density

Angle of repose

The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. Angle of repose is maximum angle possible between pile of powder and horizontal plane.[10]

$$\theta = \tan^{-1} h/r$$

Where, h = Height of pile of powder,

r = The radius of the base of conical pile.

POST-COMPRESSION PARAMETERS:

Thickness

Thickness of the tablets was measured using a calibrated Vernier Caliper. Three tablets of each formulation were picked randomly and thickness was measured individually.

Weight variation

Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation was allowed in the weight of a tablet according to US Pharmacopoeia46. The following percentage deviation in weight variation was allowed. In all formulations, the tablet weight is 200 mg, hence 7.5% maximum difference allowed.[11]

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using SQC hardness tester. It is expressed in kg/cm2. Three tablets were randomly picked and hardness of the tablets was determined.

Friability

The friability of tablets was determined by using Roche friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (WI) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (WF). The % friability was then calculated by

$$\%F = 100\ (1-WF/WI)$$

% Friability of tablets less than 1% was considered acceptable.

Disintegration Time

The test was carried out on 6 tablets using tablet disintegration tester. Distilled water at 37°C ± 2°C was used as a disintegration media and the time in seconds taken for complete disintegration of the Tablets with no palable mass remaining in the apparatus was measured.[12]

Assay

Twenty tablets were weighed and grounded in a mortar with pestle to get fine powder; powder equivalent to the mass of one tablet was dissolved in 0.1N HCL by sonication for 10 min and filtered through 0.45µ PVDF filter paper. The drug content was analyzed spectrophotometrically at 210 nm using an HPLC.[13]

In vitro drug release of Trihexyphenidyl Immediate release tablets

The In vitro drug release studies of Trihexyphenidyl HCL tablets were determined using USP II rotating paddle type. The dissolution test was performed using 900 ml of 4.5 Acetate buffer release and was performed at 37°C ± 0.5°C, with a rotation speed of 100 rpm. The samples were filtered through 0.45µ PVDF filter paper and analyzed after appropriate dilution by HPLC at 210 nm.[14]

Stability Studies

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, light and enables recommended storage conditions, re test periods and shelf-lives to be established. Stability studies were carried out at accelerated condition (40˚ C ±2˚ C at 75% RH ±5%RH) for the optimized formulation for 3 months. The samples were withdrawn after Pre determined Period of 1 month, 2 month and 3 month. The samples were analyzed for its hardness, disintegration time, drug content

and *In-Vitro* drug released.[15]

RESULTS

Table.1.Formulation of Trihexyphenidyl HCL Immediate release Tablets

INGREDIENTS	Direct Compression					Wet Granulation						
	F1*	F2*	F3*	F4*	F5*	F6*	F7*	F8*	F9*	F10*	F11*	F12*
Trihexyphenidyl HCl	5	5	5	5	5	5	5	5	5	5	5	5
Avicel (PH 101)	-	120	150	160	181	-	-	-	-	-	-	-
Avicel (PH 102)	-	-	-	-	-	184	180	177	117	173	178	176
DCL-21	183	63	31	19	-	-	-	-	-	-	-	-
Granulac 200	-	-	-	-	-	-	-	-	60	-	-	-
Povidone K-30	-	-	-	-	-	4	4	4	4	4	4	4
Pregelatinised starch 1500	10	10	12	14	-	-	-	-	-	-	-	-
Aerosil	1	1	-	-	-	1	1	-	-	-	-	-
Magnesium stearate	1	1	2	2	2	1	1	2	2	2	1	3
Purified Water	-	-	-	-	-	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Sodium Starch Glycolate	-	-	-	-	12	5	8	12	12	16	12	12
Total	200	200	200	200	200	200	200	200	200	200	200	200

Table.2.Results of FTIR study

Wave number in cm^{-1}	Functional groups	Pure drug Trihexyphenidyl HCL	Physical mixture
700-900	C-H Bending	765.77 cm^{-1}	No interactions
1350-1480	C=C STRETCH	1354.09 cm^{-1}	
1760-1550	C=O Stretching	1594.23 cm^{-1}	
3000-2850	C-H STRETCH	2931.93 cm^{-1}	
3500-3200	O-H Stretching	3308.06 cm^{-1}	
3500-3300	N-H STRETCH	3431.51 cm^{-1}	

Table.3.Pre compression parameters

Formulation code	Bulk density* (gm/ml)	Tapped density* (gm/ml)	Compressibility index* (%)	Hausner's Ratio*	Angle of repose* (˚)
F1	0.441±0.01	0562±0.02	21.53±0.04	1.274±0.01	27.23±0.07
F2	0.459±0.01	0.590±0.01	22.71±0.03	1.257±0.01	28.26±0.15
F3	0.446±0.03	0.573±0.01	22.16±0.05	1.284±0.02	26.34±0.14
F4	0.451±0.01	0.581±0.00	22.37±0.04	1.288±0.01	26.23±0.07
F5	0.482±0.02	0.621±0.05	22.38±0.03	1.288±0.01	28.92±0.07
F6	0.383±0.01	0.498±0.01	23.09±0.03	1.300±0.02	28.32±0.31
F7	0.376±0.01	0.489±0.01	21.99±0.03	1.300±0.02	25.31±0.24
F8	0.378±0.02	0.490±0.02	22.85±0.03	1.296±0.00	24.61±0.28
F9	0.429±0.01	0.555±0.00	22.70±0.04	1.293±0.01	25.63±0.06
F10	0.380±0.01	0.485±0.01	21.64±0.02	1.276±0.01	24.59±0.17
F11	0.393±0.01	0.501±0.01	21.55±0.04	1.274±0.01	25.34±0.14
F12	0.400±0.02	0.517±0.01	22.63±0.01	1.292±0.01	23.63±0.06

***All values are expressed as mean ±S.D., n=3.**

Table.4.Post compression parameters

Formulation Code	Thickness * (mm)	Hardness* (kg/cm2)	Friability* %	Weight variation* %	Disintegration time(sec)*	Assay* (%)
F1	4.9±0.01	10.2±0.15	0.77±0.01	0.16±0.04	85	92.5±0.04
F2	4.56±0.01	9.4±0.14	0.04±0.04	0.22±0.017	73	94.6±0.012
F3	4.8±0.02	10.1±0.22	0.09±0.02	0.18±0.02	51	93.3±0.021
F4	4.56±0.02	7.1±0.16	0.12±0.01	0.17±0.03	73	94.7±0.034
F5	4.77±0.01	9.7±0.17	0.08±0.03	0.20±0.05	54	93.8±0.05
F6	4.45±0.02	5.23±0.06	0.26±0.05	0.16±0.06	39	97.3±0.012
F7	4.62±0.03	5.51±0.03	0.28±0.03	0.20±0.04	34	96.5±0.021
F8	4.16±0.04	4.76±0.12	0.31±0.02	0.19±0.04	21	100.4±0.019
F9	4.01±0.02	5.25±0.15	0.65±0.03	0.18±0.06	44	96.5±0.024
F10	4.21±0.04	4.96±0.12	0.55±0.02	0.20±0.04	28	98.6±0.036
F11	4.23±0.03	5.73±0.12	0.38±0.02	0.14±0.09	29	99.0±0.042
F12	4.45±0.05	5.51±0.15	0.42±0.01	0.21±0.05	34	97.1±0.032

***All values are expressed as mean ±S.D., n=3.**

Table.5.Comprehensive *In-Vitro* (%) drug released data of all formulations (F1-F12)

Time (Mins)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
5	30.4± 0.07	33.4± 0.12	30.6± 0.32	32.9± 0.46	42.5± 0.40	38.6± 0.07	38.5± 0.06	44.7± 0.79	36.4± 0.32	41.7± 0.79	37.1± 0.04	40.5± 0.40
10	60.3± 0.30	66.3± 0.67	59.9± 0.41	64.2± 0.44	73.7± 0.55	69.2± 0.21	68.2± 0.27	78.2± 0.23	68.3± 0.47	75.2± 0.23	67.1± 0.21	71.7± 0.55
20	73.5± 0.52	78.8± 0.49	78.1± 0.50	74.5± 0.28	88.9± 0.36	88.0± 0.45	89.8± 0.55	92.5± 0.33	79.8± 0.29	87.5± 0.33	88.7± 0.51	88.9± 0.36
30	89.7± 0.21	90.4± 0.54	90.8± 1.27	89.9± 0.48	95.2± 0.43	94.2± 0.24	94.5± 0.38	98.5± 0.62	90.4± 0.51	97.5± 0.62	96.5± 0.38	96.2± 0.43

***All values are expressed as mean ±S.D., n=3.**

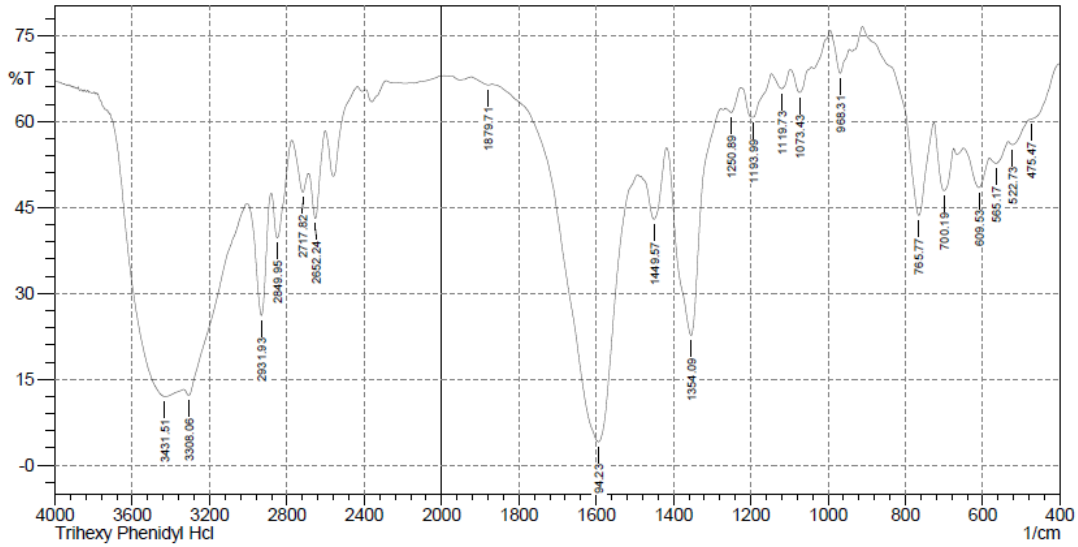

Fig.1.FT-IR spectra of pure drug

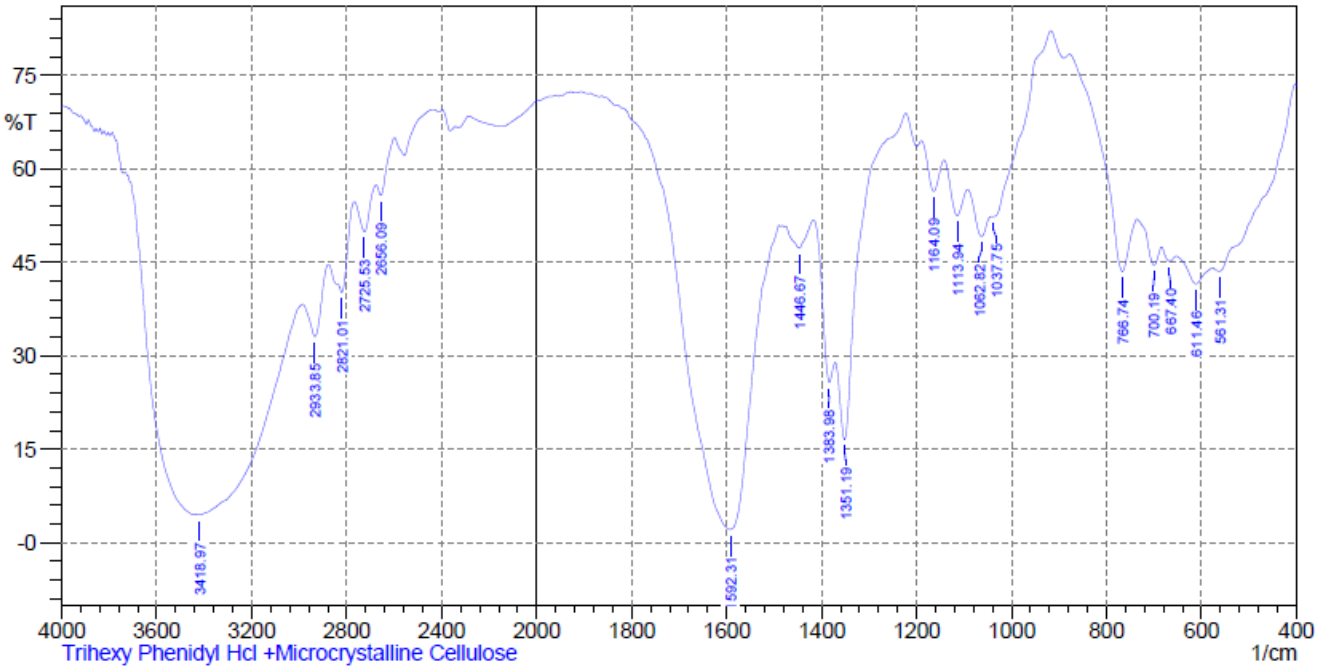

Fig.2.FT-IR spectra of Drug + Microcrystalline Cellulose

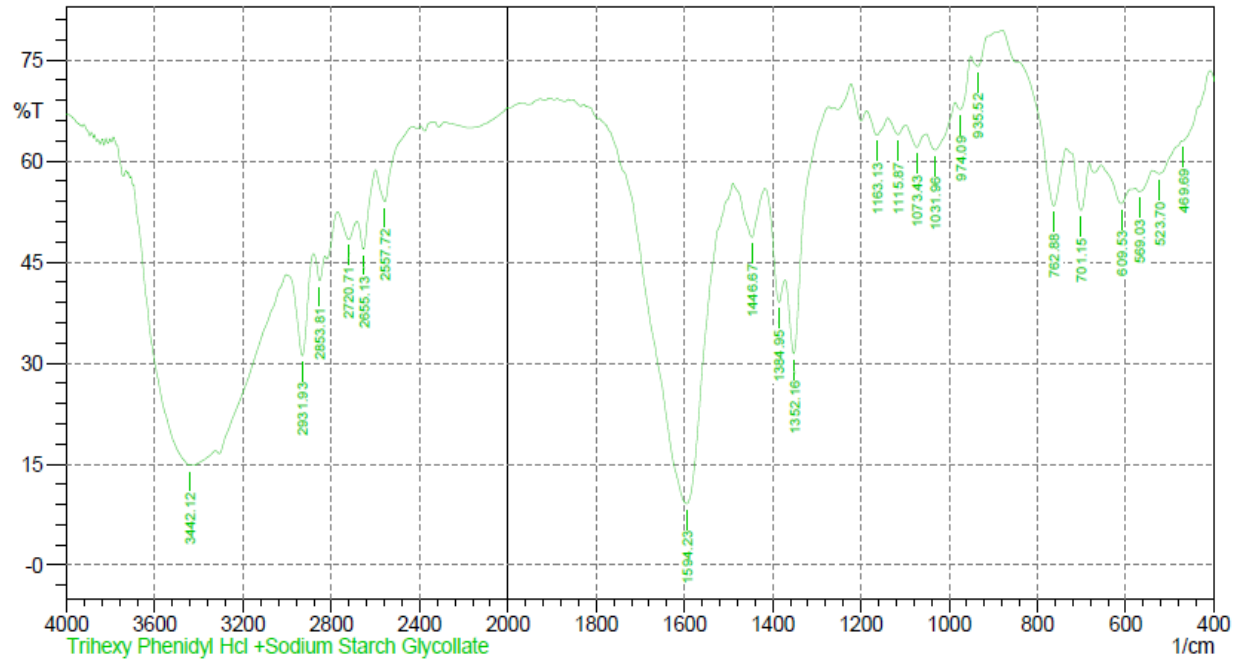

Fig.3.FT-IR spectra of Drug + Sodium starch glycollate

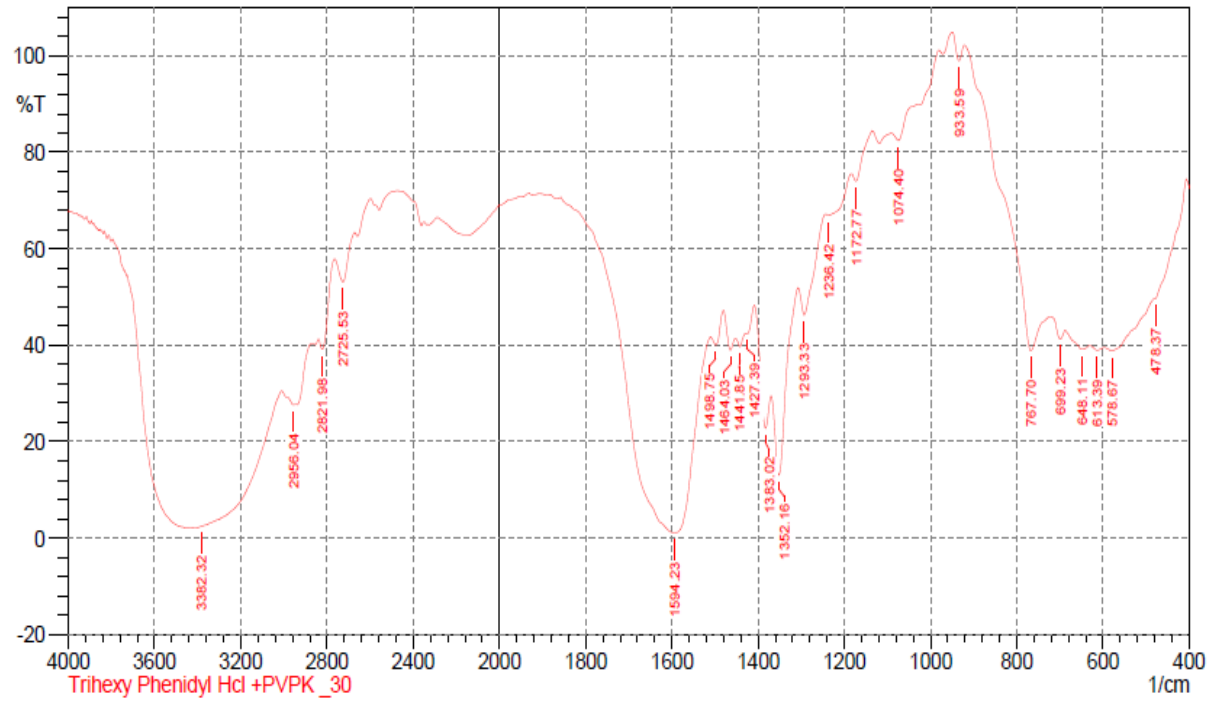

Fig.4.FT-IR spectra of Drug + Povidone K-30

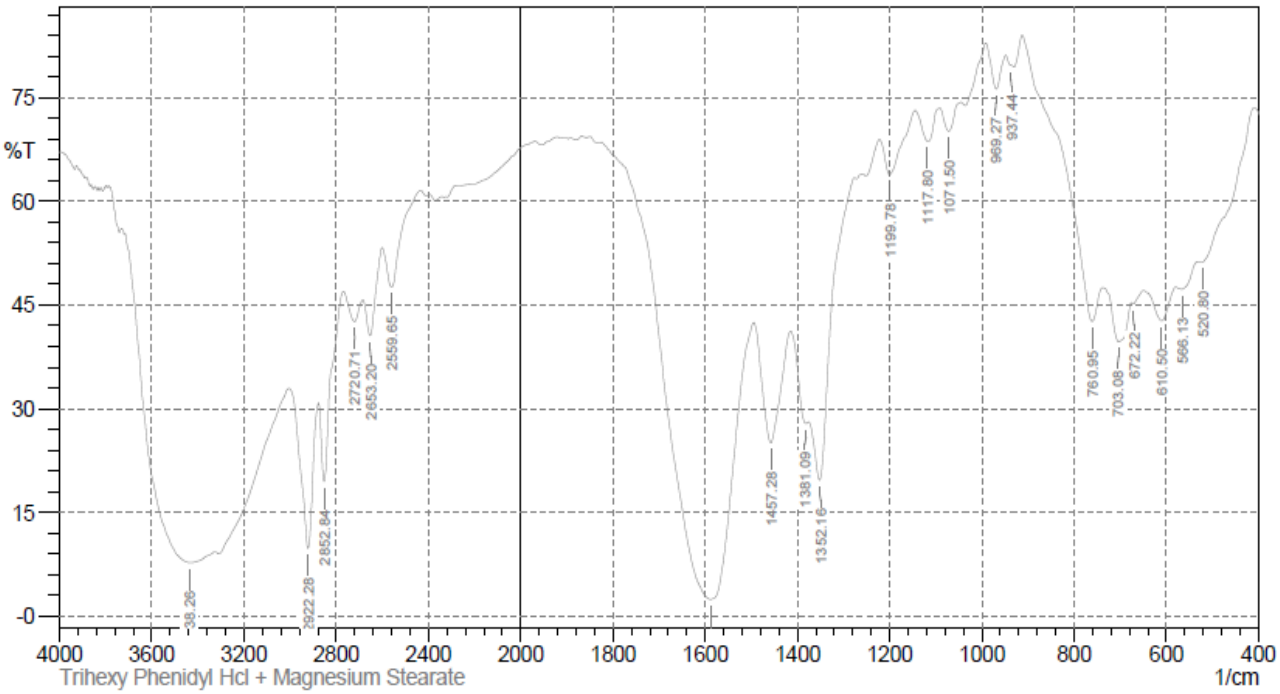

Fig.5.FT-IR spectra of Drug + Magnesium stereate

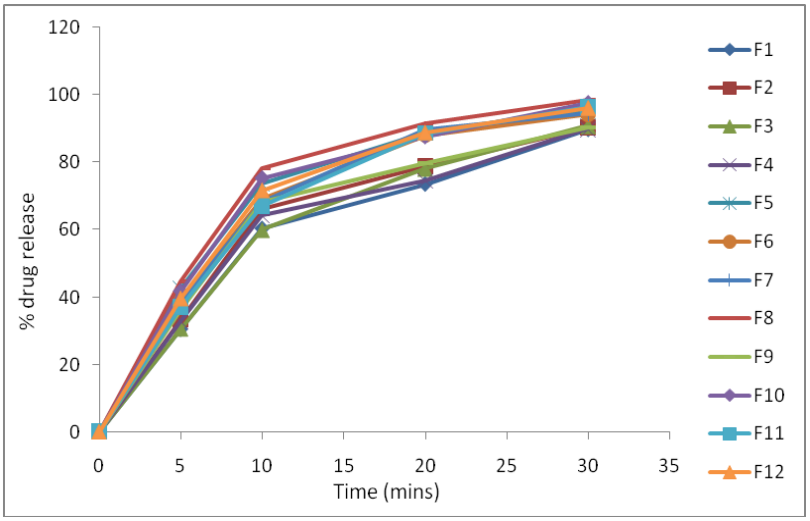

Fig.6.Plot of *in vitro* drug release study of formulations F1-F12

Pre compression parameter

DISCUSSION

The various formulations are prepared by using Pregelatinised starch and Sodium starch glycolate as super disintegrant in a various concentration. In the physical evaluation of API the colour was white; odour was characteristic odour and taste was bitter. The solubility of drug was sparingly soluble in distilled water and freely soluble in methanol and 4.5 pH acetate buffer. Melting point was found to be 256°C. Loss on drying is 2.5% and percentage purity was 100%.

Drug excipient compatibility studies

Drug excipients interaction was checked out by comparing the FTIR spectra of pure drug trihexyphenidyl HCL and FTIR spectra of the physical mixture of drug and excipients. The result of FTIR spectra of pure drug trihexyphenidyl and the physical mixture of drug and excipients were shown Table No.2 and Fig. 1 to Fig. 5 respectively.

The bulk density and tapped bulk density for all the formulation varied in range of 0.376 to 0.482 gm/cm3 and 0.485 to 0.621 gm/cm3. The values obtained lies within the acceptable range and with not much difference found between loose bulk density and tapped bulk density.

The percent compressibility and Hausner's ratio for all formulation was found within the range of 21.53% to 23.09% and 1.257 to 1.300 respectively. All the formulation shows acceptable compressibility and flow property showed in table no.3.

Post compression study

Tablets of all formulations (F1 to F12) were evaluated for different parameters such as thickness, hardness, weight variation, drug content and friability showed in table no.4.

Physical evaluation of tablets from all batches showed flat circular shape with no cracks with white color. The thickness of tablets ranged from 4.01 to 4.90mm. In

weight variation test, the Pharmacopoeia limit for percent of deviation for tablets having weight 100mg is ±7.5%. The average percent deviation of all tablets was found to be within the limit and hence all formulation passes the weight variation test. The hardness of tablets of all formulations was from 4.7 kg/cm2 to 10.2 kg/cm2. The friability of tablets of all formulations ranged from 0.04 to 0.77 %. The disintegration time of formulations was found between 21sec to 85 seconds. The content of drug formulations was found to be 92.50% to 100.40%.

In-vitro drug release studies

The In-vitro dissolution data of formulation showed in table no. 05 and figure no.06 formulation F1, F2, F3 and F4 containing 5-7% of Pregelatinised starch showed release rate 89.7% to 90.8% of drug respectively within 30 min. Formulation F5, F6 and F7 containing 3-6% sodium starch glycolate released 94.2% to 95.2% drug respectively within 30min. Formulation F8 containing SSG (6%) released 98.5% drug respectively within 30min. Formulation F9, F10, F11 and F12 containing 4-8% sodium starch glycolate released 90.4% to 97.5% drug respectively within 30min.The entire tablet released almost 85% of the drug within 30min, proving immediate release. Among all the formulated tablets formulation F8 containing Trihexyphenidyl with Sodium starch glycollate (6%) gave the highest cumulative percent released (98.5%) in 30min.

Stability Studies

The stability studies were carried out for the formulations F8 at 40 ± 2°C/75 ± 5% RH for 3 months. Table 8, shows the values of pre and post compression parameters after stability studies at different temperature and humidity conditions. The result indicated that the tablets did not show any prominent changes during the study period. This indicates that tablets are fairly stable at storage conditions.[15]

CONCLUSION

Development of immediate release tablet is to release the drug rapidly when it enters GIT. It may conclude that Trihexyphenidyl immediate release tablet would be a promising immediate release drug for an administration. In the formulation, the combination of cost effective and biocompatible excipient had been successfully used. Total 12 formulations were formulated by direct compression and wet granulation methods, among them formulation F8 concluded to be optimum containing Sodium starch glycollate (6%), indicating a promising potential of the trihexyphenidyl immediate release tablet as an alternative to the conventional dosage form.

i. FTIR studies revealed that there are no chemical interactions between trihexyphenidyl and the excipient used in the study.

ii. Stability studies of promising formulation indicated that there were no significant changes in drug content and in vitro dissolution.

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