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Research Article

FORMULATION AND EVALUATION OF CHLORPHENOXAMINE HYDROCHLORIDE RAPIDLY DISINTEGRATING TABLETS

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ABSTRACT
The aim of the present study was to develop rapid disintegrating tablets of Chlorophenoxamine hydrochloride which acts as antihistaminic, anticholinergic, antipruritic and antiparkinsonian agent. Chlorphenoxamine Hydrochloride is present in the market as conventional tablets with very low bioavailability due to first pass effect. To increase its bioavailability; rapidly disintegrating tablets of chlorophenoxamine hydrochloride to be dissolved and disintegrate quickly in the mouth cavity and reach to the systemic circulation more quickly than conventional tablets. Rapid disintegrating tablets of Chlorophenoxamine hydrochloride were prepared by using different superdisintegrants such as Aci-Di-Sol, crosspovidone and sodium starch glycolate with two different concentrations 2.5 mg and 5 mg. The blend was examined for angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The compressed tablets were evaluated for drug content, friability, disintegration time *in-vitro*, wetting time and dissolution rate. The flowability tests and the quality control tests for tablets were done and good results were obtained for all formulae. *In vitro* dissolution studies showed the release in the following descending order of superdisintegrants: Crospovidone > Croscarmellose sodium > Sodium Starch Glycolate. Selection of the best formula was done and it was found that F6 the formula which contains Crosspovidone 5 mg showed the fastest disintegration time in 16 seconds and drug release about 100 % in 8 minutes. The accelerated stability study was done for formula F6. It was concluded that Crosspovidone at a concentration of 5 mg is suitable for preparing rapid disintegrating tablets of Chlorophenoxamine hydrochloride.
Keywords: Rapid disintegrating tablets, chlorophenoxamine hydrochloride, flowability tests, direct compression, superdisintegrating agents, accelerated stability study.

INTRODUCTION

The oral route of administration is the most important method of administering drugs for systemic effects. Nevertheless it is probable that at least 90 % of all drugs used to produce systemic effects are administered by the oral route. The main problem of conventional tablets in our life is dysphagia especially in pediatric and elderly due to physiological changes in patients. To overcome this problem we must make rapid or fast disintegrating tablets which dissolve upon contact with saliva in buccal cavity. Rapid disintegrating tablets are those solid dosage forms when put on tongue, disintegrate or dissolve instantaneously, releasing the drug within a few seconds without the need of water. Its aim is to designing dosage forms, convenient to be manufactured and administered; free of side effects, offering immediate release and enhanced bioavailability to achieve better patient compliance.[1] Orally rapid disintegrating tablets contain a wide range of pharmaceutical actives ingredients covering many therapeutic categories, so it is good application for pediatric and geriatric treatments. It has many advantages of solid dosage forms, such as good stability, accurate dosing, easy manufacturing, small packaging size and easy handling by patients and also has the advantages of liquid formulations, such as easy administration and no risk of suffocation resulting from physical obstruction by a dosage form. Drugs may be absorbed in the buccal, pharyngeal, and gastric regions because the tablets disintegrate inside the mouth. Thus, rapid drug therapy intervention and increased bioavailability of drugs is possible.[2] Chlorphenoxamine hydrochloride is chemically 2-[1-(4-chlorophenyl)-1-phenylethoxy] ethyl} dimethylamine hydrochloride is indicated for the prevention and treatment of motion sickness, irradiation sickness, post-operative vomiting, nausea and vomiting of pregnancy and drug-induced nausea, symptomatic treatment of nausea and vertigo due to Meniere's disease and other labyrinthine disturbances and anesthetic pre-medication[3]. It is slowly absorbed with low bioavailability due to first pass effect in the liver. Due to its anticholinergic properties the drug should not be given to patients with glaucoma or prostatic enlargement. In particularly sensitive patient's drowsiness, dizziness and blurred vision or dryness of mouth may occurs sometimes.[4]

MATERIALS AND METHODS

Chlorphenoxamine dihydrochloride was obtained as a gift from Epico Company, Cairo, Egypt. Sodium Starch Glycolate, Crosscarmellose Sodium, Crospovidone were obtained from Cid Company, Cairo; Egypt. Disodium Hydrogen Phosphate, Potassium dihydrogen Phosphate and mannitol were purchased from Sigma Company, Cairo, Egypt. All other chemicals/solvents used were of analytical grade.

Equipment

Spectrophotometer, UV-1601 PC (Shimadzu, Kyoto, Japan), Electric balance (Sartorius GmbH, Gottingen, Germany), Single Punch Tablet Press machine (model TDP shanghaitlanhe), pharmaceutical machinery factory, China), Dissolution apparatus II, USP standard (Scientific) Pharma Test, Germany), Tablet Hardness Tester, Pharmatest Type PTB301, (Germany), Tablet Friability Test Apparatus (VEEGO), model: FT-2D, (India), Tablet Disintegration Test Apparatus, (VEEGO) model: VTD-3D, (India), Magnetic stirrer (Thermolyne Corp., USA), PH- Meter (CG 820 Schott-Gerate GmbH, Germany),Ultra Sonicator (Decon

laboratories, Hove, UK) and Tablet Thickness apparatus planimeter, (India).

Methodology

Calibration Curve of Chlorphenoxamine hydrochloride in phosphate buffer pH 6.8 by spectrophotometric method

A mass of 12.6 mg of Chlorphenoxamine hydrochloride dissolved in 10 ml phosphate buffer pH6.8 in 100 ml volumetric flask then completes the volume to 100 ml with phosphate buffer pH 6.8, from this stock solution 20 ml was taken to 100 ml volumetric flask and diluted to 100 ml with phosphate buffer pH 6.8. Samples of 1, 2, 3, 4, 5, 6 and 7 ml from the previous stock solution were taken and were diluted to 10 ml with phosphate buffer pH 6.8. These diluted samples were corresponding to 2.62, 5.04, 7.56, 10.08, 12.6, 15.12, and 17.64 µg/ml of Chlorphenoxamine hydrochloride. The absorbance was measured spectrophotometrically at wave length 254 nm. The blank was carried out using phosphate buffer pH 6.8. A procedural constant (k) was calculated from the reciprocal of the slope of the best fitting line representing the calibration curve.

Formulation of Chlorphenoxamine hydrochloride powder blends and the flowability tests evaluation

Six formulae of rapidly disintegrating tablets were prepared. All formulations contain Chlorphenoxamine hydrochloride: different types of superdisintegrants were used such as Crosscarmellose Sodium (Ac-Di-Sol), Crosspovidone and Sodium Starch Glycolate. Each superdisintegrant was added in different a concentration 2.5 mg and 5 mg as shown in Table 2. All the ingredients were passed through mesh 60. Required quantity of each ingredient was taken for each specified formulation and all the ingredients were co grind in a mortar and pestle. Mannitol is used as directly compressible diluent. The powder blend was evaluated for their flow properties such as bulk density, tapped density, angle of repose, Carr's compressibility index and Hausner's ratio[5].

Compression of tablets

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied to preparation of ODTs because of the availability of improved excipients especially superdisintegrants and sugar based excipients[5]. Direct compression method was carried out for all tablet formulations from F1 to F7 using 8 mm punch machine. Tablets ingredients were accurately weighed. These powders were then passed through 20 mesh sieve.

Evaluation of rapidly disintegrating tablets of Chlorophenoxamine hydrochloride

Friability test

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. The friabilator was used for this purpose. Preweighed sample of tablets was placed in the friabilator, which was then operated for 100 revolutions. Tablets were dusted and reweighed. Compressed tablets should not lose more than 1 % of their weigh[6].

Weight variation test

Weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual tablet weight to the average one, determinations were carried out in triplicate[7,8].

Content uniformity

Five tablets were powdered and blended then the blend equivalent to 1 mg of Chlorphenoxamine hydrochloride was weighted and dissolved in suitable quantity of phosphate buffer pH 6.8 solution. Solution was filtered and diluted and drug content was analyzed spectrophotometry at 254 nm[7,8].

***In-vitro* disintegration time**

The disintegration time of tablet was measured in water (37 ± 2^0C) according to USP disintegration test apparatus. Three trials for each were performed[9].

Wetting time

A piece of tissue paper folded twice was placed in a small petri dish (ID 6.5 cm) containing 6 ml of pH 6.8 (simulated saliva fluid). A tablet was put on the paper and the time for complete wetting was measured. Three trials for each were performed[10].

***In vitro* dissolution studies**

The dissolution test has been carried out for all the formulations. The *in vitro* drug release is performed using USP dissolution apparatus-II, 24 type paddle apparatus using 100 ml of phosphate buffer pH 6.8 (50 rpm) at 37 ± 0.5ºC. 5 ml of the samples were withdrawn at predetermined time intervals of 2, 4, 6, 8, 10, 12 minutes and replaced with the fresh medium of phosphate buffer pH 6.8. The samples were filtered through 0.45 mm membrane filter, suitably diluted and analyzed spectrophotometry at 254 nm[11].

Accelerated stability studies for optimized formulae F6

It is a method that will help rapid prediction of long term stability of drug. The stability studies of formula F6 were carried out at 40 ºC, 50 ºC and 60 ºC and 75 % ± 5 % RH (relative humidity) where, tablets were wrapped in aluminium foils and placed in petri dishes using a stability chamber for 3 month. The effects of temperature and time on the physical characteristics of the tablet after the period of 3 months were evaluated for assessing the stability of the prepared formulations. The different parameters that studied were disintegration time, weight variations, drug content and dissolution rate[12].

Table 1: The relation between concentration and absorbance of Chlorphenoxamine hydrochloride in phosphate buffer pH 6.8 at 254 nm by spectrophotometric method

Concentration of Chlorophenoxamine hydrochloride (µg/ml)	Absorbance
10	0.009
20	0.131
30	0.245
40	0.32
50	0.371
60	0.445
70	0.507
80	0.6

Table 2: The composition of the rapidly disintegrating tablets of Chlorphenoxamine hydrochloride prepared by direct compression method

Formulae Composition	F1	F2	F3	F4	F5	F6	F7
Chlorophenoxamine HCl (mg)	20	20	20	20	20	20	20
Mannitol (mg)	70	70	70	70	70	70	70
Crosspovidone (mg)	----	-----	----	------	2.5	5	------
Ac Di Sol (mg)	2.5	5	------	-----	-----	-------	-----
Sodium Starch glycolate (mg)	-----	-----	2.5	5	------	--------	------
Aspartame (mg)	7.5	5	7.5	5	7.5	5	10
Talc (mg)	5	5	5	5	5	5	5
Total weight (mg)	105	105	105	105	105	105	105

Table 3: The evaluation of the powder flowability of different formulations of Chlorphenoxamine hydrochloride rapidly disintegrating tablet

Formulae	Angle of Repose (Θ) ± SD (n = 3)	Bulk Density (gm/cm^3) ± SD	Tapped Density (gm/cm^3) ± SD	Compressibility Index (%) ± SD	Hausner's Ratio± SD
F1	28.8 ± 0.09	0.37 ± 0.01	0.43 ± 0.12	23 % ± 0.11	1.20 ± 0.11
F2	27.7 ± 0.07	0.38 ± 0.02	0.41 ± 0.29	20 % ± 0.23	1.01 ± 0.12
F3	30.1 ± 0.08	0.32 ± 0.05	0.49 ± 0.16	14 % ± 0.14	1.16 ± 0.11
F4	31.2 ± 0.07	0.39 ± 0.04	0.47 ± 0.07	16 % ± 0.09	1.19 ± 0.09
F5	33.4 ± 0.06	0.40 ± 0.08	0.52 ± 0.14	22 % ± 0.06	1.28 ± 0.09
F6	32.01 ± 0.05	0.41± 0.02	0.54 ± 0.28	22 % ± 0.08	1.29 ± 0.09

Table 4: The evaluation parameters of different formulations of chlorophenoxamine hydrochloride rapidly disintegrating tablets

Formulae	Thickness (mm) (± S.D) (n = 10)	Friability (%) (± S.D) (n = 10)	Weight variation (mg) (± S.D)	Wetting time (sec) (± S.D) (n = 3)	Drug content (%) (± S.D)	In-vitro Disintegration time (sec) (± S.D)
F1	2.25 ± 0.08	0.88 % ± 0.02	104 ± 0.03	160 ± 1.30	98 % ± 0.12	42 ± 0.11
F2	2.27 ± 0.01	0.77 % ± 0.09	105 ± 0.02	53.33 ± 2.42	105 % ± 0.03	23 ± 0.01
F3	2.27 ± 0.02	0.80 % ± 0.07	106 ± 0.04	72.33 ± 1.59	95 % ± 0.33	60 ± 0.23
F4	2.30 ± 0.03	0.71 % ± 0.21	105 ± 0.04	58.8 ± 1.95	96 % ± 0.21	59 ± 0.45
F5	2.25 ± 0.07	0.43 % ± 0.41	106 ± 0.04	36.66 ± 1.88	94 % ± 0.03	22 ± 0.26
F6	2.29 ± 0.03	0.66 % ± 0.11	107 ± 0.01	13 ± 2.40	95 % ± 0.27	16 ± 0.33
F7 (Plain tablets)	2.30 ± 0.08	0.55 % ± 0. 13	105 ± 0.03	160 ± 1.30	96 % ± 0.22	120 ± 0.16

Table 5: The *in-vitro* release and the cumulative amount released of Chlorophenoxamine hydrochloride rapidly disintegrating tablets

Time (minutes)	Cumulative amount released of Chlorophenoxamine hydrochloride drug.						
	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
2	30 ± 0.02	40 ± 0.08	33 ± 0.23	45 ± 1.30	50 ± 2.3	50 ± 0.12	10 ± 1.82
4	45 ± 0.04	60 ± 0.12	46 ± 1.4	55 ± 1.81	70 ± 2.1	75 ± 1.6	20 ± 0.35
6	60 ± 0.54	77 ± 0.32	55 ± 0.9	65 ± 1.62	88 ± 0.1	98 ± 0.99	19 ± 0.78
8	90 ± 0.56	98 ± 0.46	70 ± 0.45	70 ± 0.45	98 ± 0.99-	100 ± 0.87	22 ± 0.99
10	98 ± 0.34	100 ± 0.67	75 ± 0.11	75 ± 0.11	-	-	32 ± 1.92
12	100 ± 0.05	-	80 ± 0.23	88 ± 0.23	-	-	35 ± 1.41

Table 6: Accelerated Stability Studies of formulation F6 in $40^{o}C \pm 2^{o}C$ (75 ± 5 % RH) for 3 months

Time (days)	Thickness (mm)	Weight gain (mg)	% drug content	Disintegration time (sec)	Wetting time (sec)
30	0.227	104	99.9 %	15	10
60	0.228	105	99.95	16	11
90	0.225	105	100 %	14	10

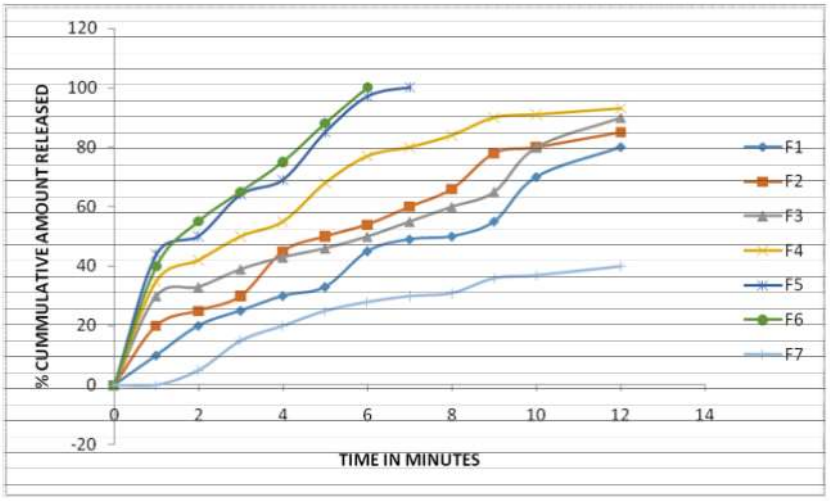

Figure 2: The dissolution of chlorophenoxamine hydrochloride from different formulations of rapidly disintegrating tablets

Table 7: Accelerated Stability Studies of formulation F6 in 50°C ± 2°C (75 ± 5 % RH) for 3 months

Time (days)	Thickness (mm)	Weight Gain (mg)	% drug content	Disintegration time (sec)	Wetting time (sec)
30	0.227	105	100 %	14	9
60	0.228	106	99	15	10
90	0.225	104	97	16	10

Table 8: Accelerated Stability Studies of formulation F6 in 60°C ± 2°C (75 ± 5 % RH) for 3 months

Time (days)	Thickness (mm)	Weight Gain (mg)	% drug content	Disintegration time (sec)	Wetting time (sec)
30	0.224	105	100 %	16	9
60	0.227	107	98 %	17	10
90	0.225	105	96 %	18	10

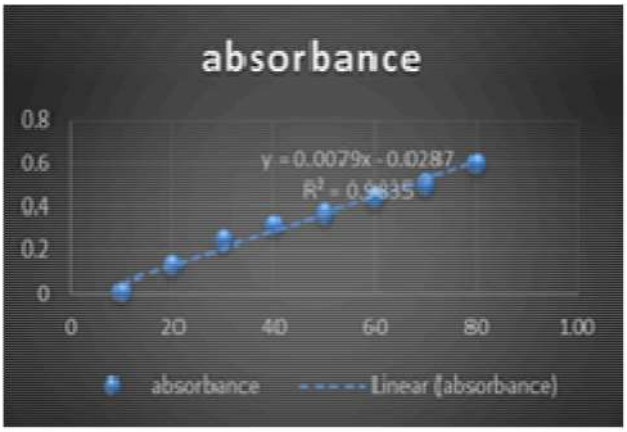

Figure 1: Calibration curve of Chlorphenoxamine hydrochloride in phosphate buffer pH 6.8 at 254 nm by spectrophotometric method

RESULTS AND DISCUSSION

Calibration curve of Chlorphenoxamine hydrochloride in phosphate buffer pH 6.8 by spectrophotometric method

Table 1 and Figure 1 showed the standard calibration curve of Chlorphenoxamine hydrochloride in phosphate buffer pH 6.8. Chlorphenoxamine hydrochloride exhibited a maximum absorbance at 254 nm measured spectrophotometrically. Linear regression analysis was carried out and showed that Chlorphenoxamine hydrochloride can obey Beer's Lambert Law within the range of concentrations used (10-80 µg/ml) in the tested solvent used. The value of correlation coefficient was found to be 0.9835.

Preparation of the different formulations of Chlorphenoxamine hydrochloride rapidly disintegrating tablets

Six patches of Chlorphenoxamine hydrochloride rapidly disintegrating tablets were prepared with different concentrations of superdisintegrant and plain patch F7 with no superdisintegrants as shown in Table 2. The powder blend for each formula was evaluated for their flow properties such as bulk density, tapped density, angle of repose, Carr's compressibility index and Hausner's ratio. The flowability of all the formulations' blends were determined as mentioned before. Bulk density was found in the range of 0.3-0.4 g/cm^3 and the tapped density between 0.416-0.526 g/cm^3. Using these two densities data Hausner's ratio and Carr's

compressibility index were calculated. The powder blends of all formulations had Hausner's ratio 1.25 1.29 indicates good flow property. The good flowability of the powder blend was also evidenced with angle of repose (range of 28- 32) indicating good flowability. The results were shown in Table 3.

Quality control tests of rapidly disintegrating tablets (F1 – F7)

The mixed blend of drug and excipients were compressed using single punch tablet machine to produce biconvex tablets weighing 105 mg each with 8 mm punch for compression, a minimum of 50 tablets were prepared for each batch. Tablets were prepared using direct compression technique. All the formulations exhibited white colour odourless and biconvex in shape with smooth surface. Since the powder material was free flowing; tablets were obtained of uniform weight due of uniform die fill with acceptable weight variations. The average weight of the rapidly disintegrating tablets prepared by direct compression method was 104 mg ± 0.004 to 105 mg ± 0.003. The friability of all formulations was found to be less than 1.0 % and hence the tablets with lower friability may not break during handling on machines and or shipping. The drug content was found in the range of 98 % ± 1.910-105.3 % ± 2.002 (acceptable limit). Disintegration time is very important for RDTs which is desired to be less than 60 seconds for orally disintegrating tablets. This rapid disintegration assists swallowing and also plays a role in drug absorption in buccal cavity, thus promoting bioavailability. Disintegration time of prepared RDTs was in the range of 16.83 sec ± 1.46 to 120 sec ± 0.23 seconds. The disintegration time (D.T) is higher for F7 control (150 sec) while F6 showed fast disintegration time of 16.80 seconds as showed in Table 4. Wetting time is used as an indicator from the ease of the tablet disintegration in buccal cavity. It was observed that wetting time of tablets was in the range of 13 sec ± 2.40 to 160 sec ± 1.30 seconds as shown in Table 5. *In vitro* dissolution studies of the prepared rapid disintegrating tablets were performed in pH 6.8 using USP dissolution apparatus type 2 was shown in Table 5 and Figure 2. The dissolution rate was found to increase linearly with increasing concentration of superdisintegrant. This was marked by decreased disintegration time values for tablet formulation containing higher proportions of superdisintegrants.

Accelerated stability studies of formula F6 rapidly disintegrating tablets

Formula F6 which is the best formula chosen contains 5 mg crosspovidone rapidly disintegrating tablet was stored at 40°C, 50 °C and 60°C ± 2°C (75 ± % RH) for 3 months in a stability chamber, the samples were withdrawn at different time intervals after 15 days, 30 days, 45 days, 60 days, 75 days and finally 90 days. The quality control tests of F6 at 40°C and 75 ± 5 % RH after three months showed that; the weight of the tablet was ranged from 105 mg ± 0.564 to 104 mg ± 0.324, friability was ranged from 0.034 % ± 0.043 to 0.045 % ± 0.033, the drug content was 98 % after 15 days while after 90 days it was 94 %, the wetting time ranged from 9 seconds ± 0.033 to 12 seconds ± 0.032, the *in-vitro* disintegration time was ranged from 16 seconds ± 0.042 to13 seconds ± 0.033 and finally about 86 % - 90 % of the drug released at the end of 8 minutes. All the results above were within the acceptable range as shown in Table 6, 7 and 8.

CONCLUSION

On the basis of the previous findings the following could be concluded the rapidly disintegrating tablets of Chlorphenoxamine hydrochloride drug can be successfully prepared by direct compression technique using selected superdisintegrants for the better patients' compliance and effective therapy. The blends of all formulations of rapidly disintegrating tablets showed free flowing powder and excellent flowability parameters. The formulation F6 containing crospovidone shows faster disintegration than other formulations and all the prepared Chlorphenoxamine Hydrochloride rapidly disintegrating tablets complied with the pharmacopieal requirements.

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