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Development and Evaluation of Chlorpheniramine Maleate Orally Disintegrating Tablets

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ABSTRACT

Introduction: Orally Disintegrating Tablets (ODTs) have garnered significant attention in the pharmaceutical industry, particularly for medications with delayed dissolution and low oral bioavailability. These tablets offer advantages, especially for patients with swallowing difficulties, both young and elderly, and those who may face dehydration during extended periods on the road. This study focuses on the use of super-disintegrants as part of a novel approach to manufacturing ODTs containing chlorpheniramine maleate (CPM), with additional consideration given to the impact of sweeteners on the formulation.

Objective: The primary objective of this work is to create CPM-ODTs using a direct compression method, emphasizing fast disintegration qualities to enhance patient compliance. The study aims to assess various parameters, including drug content, hardness, friability, disintegration time, wetting duration, water absorption ratio, and *in vitro* release of drugs, to evaluate the performance of the manufactured tablets.

Methods: The method employed in this study involves the use of two super-disintegrants, namely sodium starch glycolate and croscarmellose sodium, in the formulation of CPM-ODTs. The direct compression method is utilized, and the tablets are subjected to a comprehensive analysis to measure their key characteristics and performance. Stability analysis is also conducted on the final trial formulation to ensure both chemical and physical sustainability.

Results: The results of the study reveal that the formulation incorporating 10mg Croscarmellose Sodium (CCS) exhibits the quickest disintegration time and the fastest drug release among the tested formulations. Additionally, stability analysis demonstrates that formulation ODT6, which includes 10 mg CCS, sucralose, and menthol powder, is both chemically and physically sustainable.

Conclusion: In conclusion, the use of super-disintegrants, specifically CCS, in the direct compression method for CPM-ODTs proves to be effective in achieving fast disintegration and drug release. The optimized formulation (ODT6) with 10 mg CCS, sucralose, and menthol powder is identified as both chemically and physically sustainable, indicating its potential for further development as a patient-friendly oral medication.

1. INTRODUCTION

Due to its ease of administration and manufacture, oral administration is thought to be the most popular method, and tablets are the most popular solid dosage form [1]. Since its initial release on the market in the 1980s, ODT's made a great deal of interest and have become one of the most alluring oral drug delivery technologies [2]. Due to its amazing impact on patient compliance, ODTs have grown dramatically over the past ten years and benefit patients who have difficulty swallowing. Numerous people experience deglutition issues, dysphagia, or difficulty swallowing, according to reports [3, 4]. Appealing taste and flavour, ease of use as well as swallowing, with the need for quick action in

Journal of Chemical Health Risks
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specific applications are the main factors influencing ODT indent growth. It could additionally contribute to increased safety and effectiveness in clinical settings [5]. Mouth dissolving products is solid dosage forms for oral use that are intended to dissolve and disperse throughout the oral cavity prior to drug release, regardless of the site of absorption [6]. ODTs are uncoated tablets that are meant to be fed into the mouth and quickly dissolve before being ingested, according to the European Pharmacopoeia [7]. They must dissolve within three minutes. ODTs are defined as solid dosage forms containing medical chemicals that dissolve quickly, typically in a couple of seconds, once placed over the tongue in a document issued by the Food and Drug Administration, Centre for the Evaluation and Research of Drugs (CDER) [8]. On the contrary hand, the USP as well as the FDA have stricter regulations that require ODTs to dissolve within 30 seconds [9]. Some advantages of ODT's are it is easily accessible and self-administrable. It needs a moist environment to dissolve the drugs and sustainable formulations can be developed with reduced side effects. ODTs can be given to paediatric, geriatric and psychiatric patients. Few limitations of ODT products are it is hygroscopic in nature and highly fragile, so a specialized packaging is necessary for effective stability of the product [11]. Sometimes it faces some permeability issues in oral mucosal barrier and gives an occasional mouth feeling. Chlorpheniramine maleate, an antihistaminic, is used to treat the itching associated with chicken pox as well as symptoms of hay fever, cold rashes, allergy, watery eyes, itchy eyes, cough, runny nose, and sneezing. A natural chemical called histamine, which is produced by our bodies during an allergic reaction, is blocked by chlorpheniramine maleate. Furthermore, it inhibits acetylcholine and aids in the drying of various bodily fluids. Desmethyl and di-desmethyl chlorpheamine, the first-pass metabolites of chlorpheniramine maleate, reduce their bioavailability. Fast-dissolving tablets, however, prevent first-pass metabolism and increase medication bioavailability [12]. Thus, these tablets experience instantaneous dissolving and speedier activity within minutes. ODTs, however, prevent first-pass metabolism and increase medication bioavailability. Thus, these tablets experience instantaneous dissolving and speedier activity within minutes [13].

2. MATERIALS AND METHODS

2.1 Materials used for preparation of ODTs:

Chlorpheniramine maleate was supplied as gift sample from Aristo Pharmaceutical Pvt Ltd. Mannitol and microcrystalline cellulose (PH-112) was used as diluent supplied by Loba chemie Pvt. Ltd. Sodium starch glycolate and croscarmellose sodium was used as superdisintegrants, supplied by Loba Chemie Pvt. Ltd. and Qualikem Laboratories Ltd. Menthol powder is used as flavouring agent and sucralose is used as sweetening agent to mask the bitterness of the drug. Sunset yellow colour is added to give a pleasant appearance of the tablet. Talc and magnesium stearate is used as glidant and lubricant is supplied by Loba Chemie Pvt. Ltd.

2.2 Methods:

- **Preformulation Study:** Identification of Drug

ATR-IR Spectroscopy: The infrared spectrum of Chlorpheniramine malate was recorded by using an ATR-IR spectrophotometer. A small quantity of sample was placed in a spectrophotometer to record its IR spectra.

Determination of melting point: One crucial factor in determining of a drug's purity is its melting point, which is measured using a melting point apparatus. The melting point of chlorpheniramine maleate is 130-135°C [14, 15].

Physicochemical Properties: Studying the physicochemical characteristics of the bulk drug is important to manufacture the medicinal ingredient into a dosage form. The physical properties comprise of colour, odour, taste, solubility, pH and Loss on drying of drug.

- **Analytical methods:**

Determination of absorption maxima of CPM:
Standard CPM stock solution was prepared in a 100 ml volumetric flask using pH 6.8 phosphate buffer as per IP recommendations. The appropriate volume of aliquot 40µg/ml from working CPM stock solutions was transferred to a 50 ml capacity volumetric flask. Using a pH 6.8 phosphate buffer as a blank, 40 µg/ml of chlorpheniramine maleate was scanned in the spectrum mode from 200 nm to 400 nm to obtain absorption maxima of (λ_{max}) as obtained in Fig 3 [16].

Development of Standard Curve: Seven dilutions were made from standard CPM stock solution at different strengths of working range and checked the absorbance at λ_{max}=261nm using a pH 6.8 phosphate buffer as a blank. Plotting the absorption against various solution strengths (Fig 4) allowed for the determination of linearity and correlation (Table 5) [17, 18].

- **Drug excipient compatibility:**

ATR-IR Spectroscopy: A study on the compatibility of drugs and excipients was conducted by combining equal amounts of drugs and all excipients. Then, this mixture was placed in a marked, tightly sealed container and stored in a stability chamber for 15 days at a temperature of 40°±2°C and 75±5% RH. This container's physical characteristics, color, and ATR-IR analysis were checked after 15 days [19].

Journal of Chemical Health Risks
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JCHR (2023) 13(4s), 468-481 | ISSN:2251-6727

Differential Scanning Calorimetry Analysis: DSC thermograms of pure drug Chlorpheniramine Maleate and physical mixture were obtained by placing approximately 2-4 mg of sample in an aluminium pan that was heated between -50°C and 300°C at a rate of 20°C per minute. DSC provides information regarding the physical properties like the degree of drug crystallinity and the amorphous nature of the samples [13].

Table 1. Formulation Trials of Chlorpheniramine Maleate ODTs

Ingredients (mg/Tablet)	**ODT_1**	**ODT_2**	**ODT_3**	**ODT_4**	**ODT_5**	**ODT_6**
Chlorpheniramine Maleate	4	4	4	4	4	4
Mannitol	10	10	10	10	10	10
MCC- pH 112 (Qs)	45	42.5	40	45	42.5	40
SSG	5	7.5	10	-	-	-
CCS	-	-	-	5	7.5	10
Menthol	3	3	3	3	3	3
Sucralose	8	8	8	8	8	8
Sunset Yellow	1	1	1	1	1	1
Talc	2	2	2	2	2	2
Magnesium Stearate	2	2	2	2	2	2
Total (mg)	**80**	**80**	**80**	**80**	**80**	**80**

- **Formulation Method:**

Chlorpheniramine Maleate ODTs were prepared by Direct Compression method using Sodium Starch Glycolate and Croscarmellose Sodium as a super-disintegrant. The composition of the Chlorpheniramine Maleate ODTs is given in Table 1. The following procedures were used to prepare the granules:

Step 1: Sifting: Microcrystalline Cellulose (pH-112), and Mannitol were passed through a #30 sieve and Chlorpheniramine maleate was sifted through a #60 sieve. Sodium Starch Glycolate and Croscarmellose Sodium were passed through the #40 sieve. Menthol Powder and Sucralose were sifted through the #60 sieve and Sunset Yellow passed through the #100 sieve. Magnesium stearate and Talc were shifted through #60 and #40 sieves respectively.

Step 2: Blending: At first MCC and Mannitol take in a mortar and then triturate with the pestle for about 15 min. Then Chlorpheniramine maleate mix with the diluent mixture followed by the geometric dilution method for about 30min. After that, add superdisintegrants and blend properly for 15min. Next, add menthol powder and sucralose and continue the mixing for about 15min. Then, the whole mixture was mixed with the sunset yellow colour followed by geometric dilution to prevent the unequal distribution of colour for 20min.

Step 3: Lubrication: Before compression dry mixing granules and lubricate using talc and magnesium stearate for 10 min.

Step 4: Compression: After that tablets were compressed in an 8-station single rotary tablet press (Digicon Pharma Machinery, Ahmedabad, India). Compressed the tablets as per the given parameters (Table 2).

Table 2. Punch tooling and description

Parameter	**Standard**
Punch	6.5mm circular flat punches with a bevelled edge having scored in the upper punch tip and plane surface in the lower punch tip.
Description	Uncoated tablets that are light yellow in colour, round-shaped, bevelled edges with the break line on one side and the plain on another side.

- **Pre-Compression Parameter:**

The angle of Repose: The fixed funnel method was used to estimate the angle of repose (θ). The funnel's height was modified such that its tip touched the top of the granules mound. The funnel was opened so that the granules could freely pour out over the surface. The granular cone's diameter was measured, and the formula below was used to determine its angle of repose [20].

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

Where, h and r are the height and radius of the cone

Bulk Density: The three-tap method was used to estimate the bulk density of powder (g/cc). A 100 ml

Journal of Chemical Health Risks
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graduated cylinder was carefully filled with 10 g of powder. At intervals of two seconds, the cylinder was dropped three times from a height of one inch onto a hardwood surface. It is calculated by using the given formula [21]:

Bulk Density= $\frac{M}{Vb}$

Where, M is the mass of the powder, and Vb is the Bulk Volume of the powder.

Tapped Density: By mechanically tapping a graduated measuring cylinder containing the powder sample, the tapped density (TD) is produced. Tap the same powder sample 10, 500, and 1250 times, then read the associated volumes V_{10}, V_{500}, and V_{1250} to the closest graded unit. V_{1250} is the tapped volume if the difference between V_{500} and V_{1250} is less than or equal to 2 ml [22].

$$\textbf{Tapped density (TD)} = \frac{\text{weight of powder blend}}{\text{Minimum volume occupied by cylinder}}$$

Compressibility Index: The simplex approach of evaluating the free flowing nature of powdery substances, elasticity, which serves as a sign of how readily a powder substance flow, was calculated using the compressibility index (I). The following formula is employed to compute it [23]

$$\textbf{CI (\%)} = \frac{TD-PD}{TD} \times 100$$

Where, TD=Tapped Density, PD=Poured Density, CI=Carr's compressibility index.

Hausner's Ratio: The Hausner ratio is a proximate indicator of powder flow easiness. The following formula is used to compute it [20].

$$\textbf{Hausner Ratio} = \frac{TD}{PD}$$

- **Post-Compression Parameter:**

Weight Variation: Twenty tablets were chosen at random, and each one was weighed. The weight of the tablets was calculated on average. The weight of each tablet's deviation from the average weight was calculated. The weight variation test standard followed IP (NMT 10%) [24].

Tablet Thickness: The thickness of the tablets in mm was measured by using digital vernier callipers. Randomly, 20 tablets are taken, and measure the thickness [13].

Tablet hardness: Tensile strength or crushing load is a measurement of the capacity to endure the mechanical stress of handling during production, packing, and transportation. Using a Monsanto Hardness Tester (Vinsyst Technologies), the crushing load for ODTs of various batches was calculated by compressing the tablets in a diametric direction in kg/cm^2. 10 tablets are taken and the average was calculated [13].

Friability: The measurement of stress and abrasion resistance is called friability. The following approach was done to assess the friability using the Roche Friabilator. 6.5 gm tablets were precisely weighed and put in the tumbling device, which rotates at 25 rpm and drops the tablets across 6 inches with each rotation. The weight of the tablets was measured after 100 revolutions to calculate the percentage of weight reduction. The friability calculation formula is presented as Eq. [25].

$$\textbf{Friability (f)} = \frac{Wi-Wf}{wi} \times 100\%$$

Where, Wi is the initial weight and Wf is the final weight of the tablets.

Disintegration time: Utilizing a digital Tablet Disintegration Tester and 900 ml of pH 6.8 phosphate buffer at 37±0.5° C, the *in vitro* disintegration time of prepared ODTs was calculated. The average time for these six tablets to completely disintegrate was calculated by randomly selecting six tablets from each batch [26].

Wetting time: The technique was used to determine the duration of tablet wettability. A piece of Whatman filter #41 paper that had been folded once diametrically was placed in a small petri dish (6.5 cm internal diameter) filled with 8 ml of water, a tablet was placed on the paper, and the amount of time it took for the paper to completely wet were recorded as shown in **Fig 1** [27].

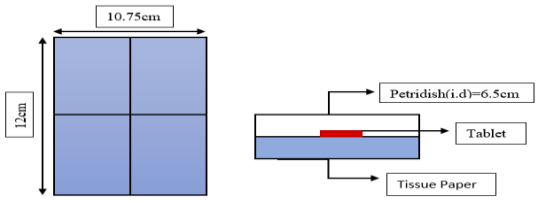

Fig 1. Method for the measurement of the wetting time of a tablet [28]

Water absorption ratio: The identical process used for the wetting time test was used for this one. In this test, the tablet's original weight was recorded before it was placed on a Petri dish. The tablet was fully wetted before being weighed [28].

Journal of Chemical Health Risks
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JCHR (2023) 13(4s), 468-481 | ISSN:2251-6727

***In vitro* dispersion test:** Two tablets were dropped into distilled water in a 100 ml flask, stirred, and the *in vitro* dispersion time was recorded. Using a mechanical stirrer, stirring was carried out for 10 minutes at a speed of 500 RPM. Then, this solution is passed using a 710 µm sieve [29].

***In vitro* drug release studies:** *In vitro* drug release studies of CPM-ODTs are done by using USP Apparatus-II (Paddle Type). In this study, only one dissolution media is used which is 500 ml, pH 6.8 phosphate buffer. Randomly choose 6 tablets from each formulation and placed each tablet in the vessel and maintained the paddle's rotation at a speed of 50 rpm and temperature of 37°± 0.50 °C. For the measurement of the *in vitro* drug release pattern from the ODTs, at the end of each minute, 5ml aliquots from each vessel were pipetted out, and this process continued for up to 5 minutes. Then the withdrawn aliquots were filtered through Whatman Filter Paper No. 41 before being analysed at 261 nm with a SHIMADZU UV Spectrophotometer [30, 31].

Assay: From each batch, three tablets were chosen at random, crushed, and the mixture equaling 5.0 mg of CPM was precisely weighed and put into a 100 ml volumetric flask. 20 ml of phosphate buffer (pH 6.8) was added while stirring continuously, and make up the volume was 100 ml using the same. The solutions were filtered and subjected to spectrophotometric analysis at 261nm [13].

3. RESULTS AND DISCUSSION:

- **Identification of the Drug: ATR-IR Spectroscopy of Drug:**

The drug sample was subjected to scanning from 4000 cm^{-1} to 400 cm^{-1} by using this ATR-IR spectrophotometer and the IR spectrum is obtained as depicted in **Fig. 2**

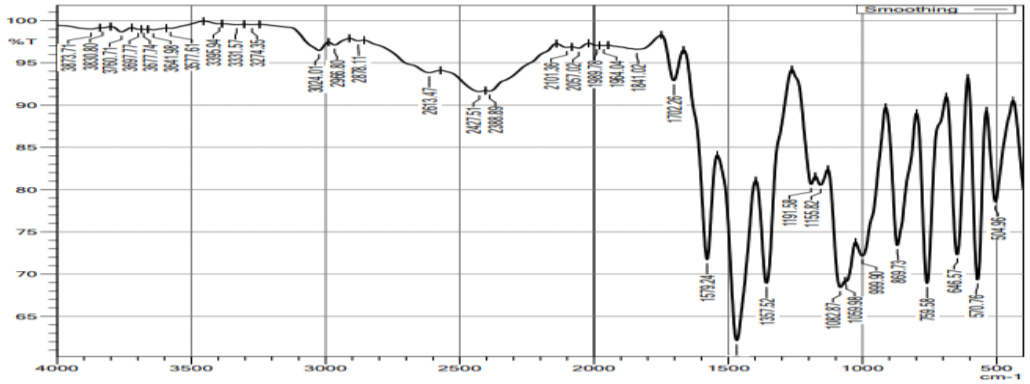

Fig 2. ATR-IR spectra for Chlorpheniramine Maleate

Chlorpheniramine Maleate's major functional groups have distinctive peaks in the IR spectra. **Table 3** shows the peak values seen at various wave numbers along with the functional group that these peak values belong to. Major peaks are identical to Chlorpheniramine Maleate's functional group. Hence, the sample was confirmed as CPM.

Table 3. Interpretation data for ATR-IR spectra of Chlorpheniramine Maleate

IR Absorption Bands(cm^{-1})		Bond	Functional Group
Observed Peak	**Characteristics Peak**		
3331.57, 3395.94, 3577.61	3300-3500	C-H Stretch	Alkanes
3274.35	3200-3400	N-H Stretch	1° Amines
3024.01	3010-3100	=C-H Stretch	Alkenes
2101.36, 2388.89, 2427.51, 2427.51, 2613.47	2100-2600	-C=C-	Alkynes
1470	1400-1500	CH_2 Scissoring	Amides
1357.52, 1470, 1579.24	1550-1300		

Physicochemical Properties: Different physicochemical properties of Chlorpheniramine Maleate are evaluated which are given below in **Table 4.**

Journal of Chemical Health Risks
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JCHR (2023) 13(4s), 468-481 | ISSN:2251-6727

Table 4. Physical Properties of CPM

Colour	CPM is a white crystalline powder that is observed by the naked eye.
Odour	It is odourless.
Taste	It is bitter.
Solubility	It is freely soluble in water.
pH	1mg of chlorpheniramine maleate, accurately weighed, was added to a 100ml volumetric glass flask then diluted to a 1%w/v solution with distilled water. The solution's pH was then checked with a digital pH meter, and it was found to be 4.7.
Melting Point	The melting point of Chlorpheniramine maleate is 132.60°C determined by Systronics (India) Limited (SYS 973 Plus). The range of Chlorpheniramine Maleate is reported melting points is 130°C to 135°C
Loss on Drying	The percentage loss on drying of the drug was found to be 0.35% after 4 hours at 105°C. The drug passes the test for loss on drying within the I.P.-specified limits (NMT 0.5 %).

- **Analytical Methods:**

Determination of absorption maxima of Chlorpheniramine Maleate:

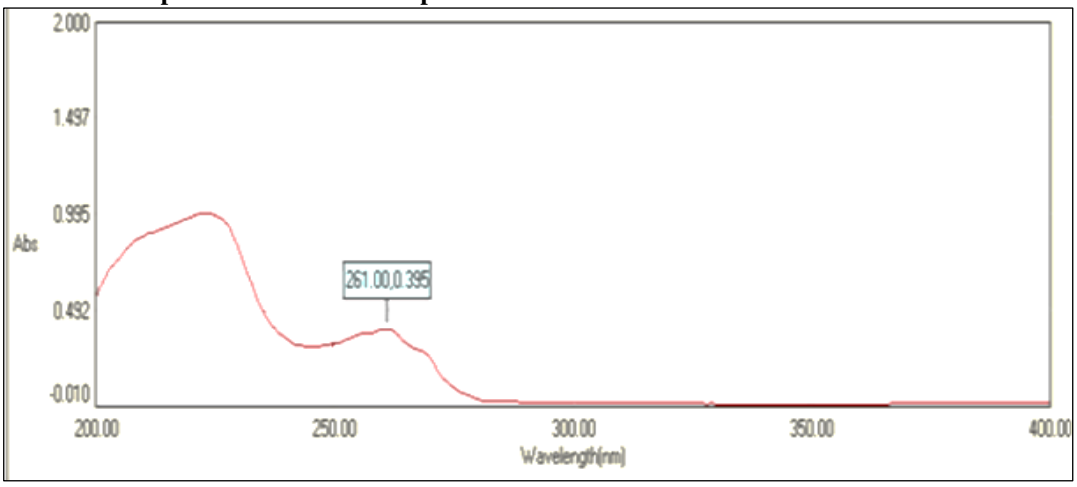

Fig 3. UV Spectrum for λ_{max} of Chlorpheniramine maleate

Table 5. Absorbance of CPM at different concentrations

Concentration (µg/ml)	Absorbance at 261 nm
2	0.054
4	0.089
6	0.123
8	0.165
10	0.201
12	0.239
14	0.276

Journal of Chemical Health Risks
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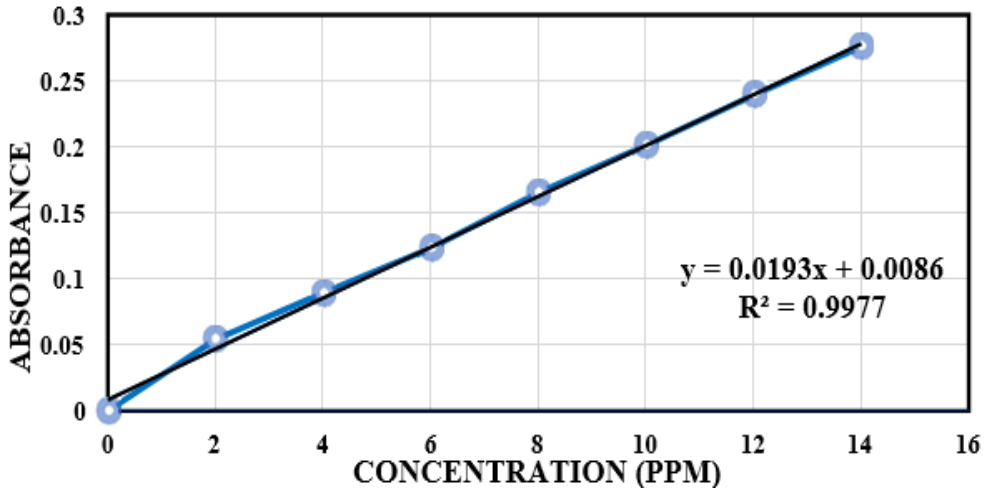

Fig 4. Standard curve of Chlorpheniramine maleate

• **Drug excipients compatibility:**

ATR-IR Spectroscopy:

Physical mixtures of the drug and all excipients were subjected to scanning from 4000 cm^{-1} to 400 cm^{-1} by using this ATR-IR spectrophotometer and the IR spectrum is obtained in **Fig 5** after 15 days study at of 40°±2°C/75±5% RH. Using the ATR-IR peak matching approach, the drug, and excipients compatibility of the two physical mixtures containing sodium starch glycolate and croscarmellose sodium was assessed. The drug-excipient spectra of both physical mixtures at Initial condition and after 15 days storage at 40°±2°C/75±5% RH had all the key peaks that are present in the spectrum of a pure drug. This indicates that the drug maintains its typical structure and hence confirming that there had been no chemical interaction or complexation between the drug and excipients.

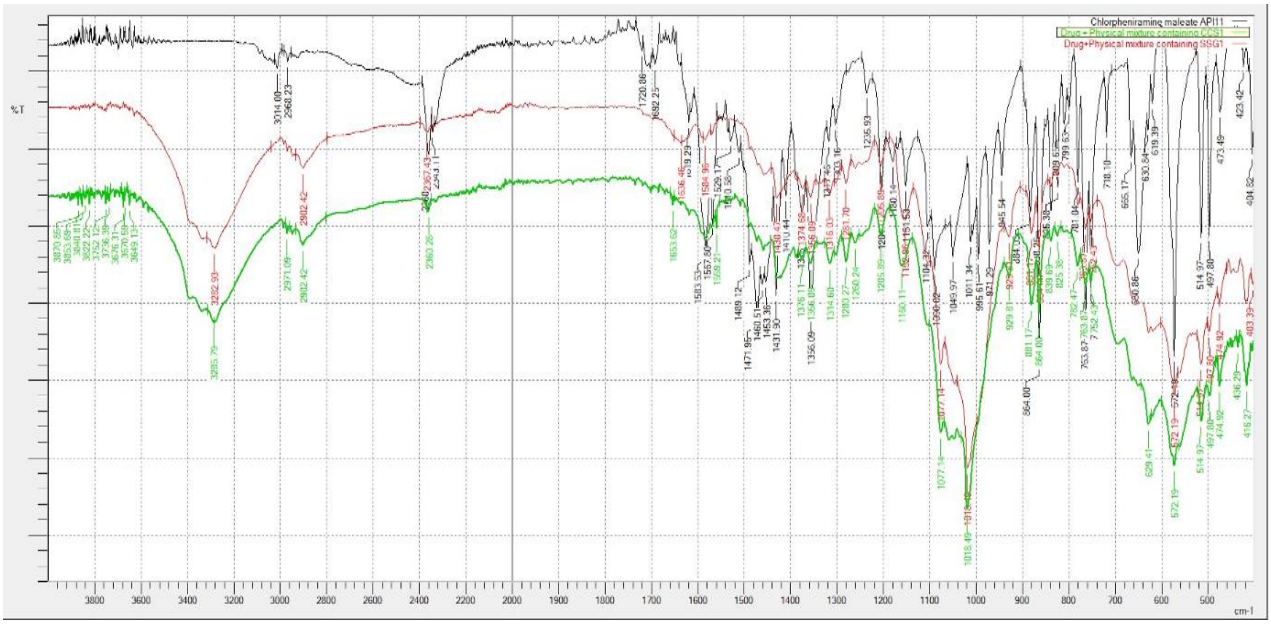

Fig 5. Drug excipient compatibility study after 15 days storage at 40° ±2°C /75% ± 5%RH

DSC Thermal Analysis:

DSC thermograms of the pure drug Chlorpheniramine Maleate and the physical mixture are shown in **Fig 6.** TA Instruments Trios, version V4.4.1.41651, was used for data analysis.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2023) 13(4s), 468-481 | ISSN:2251-6727

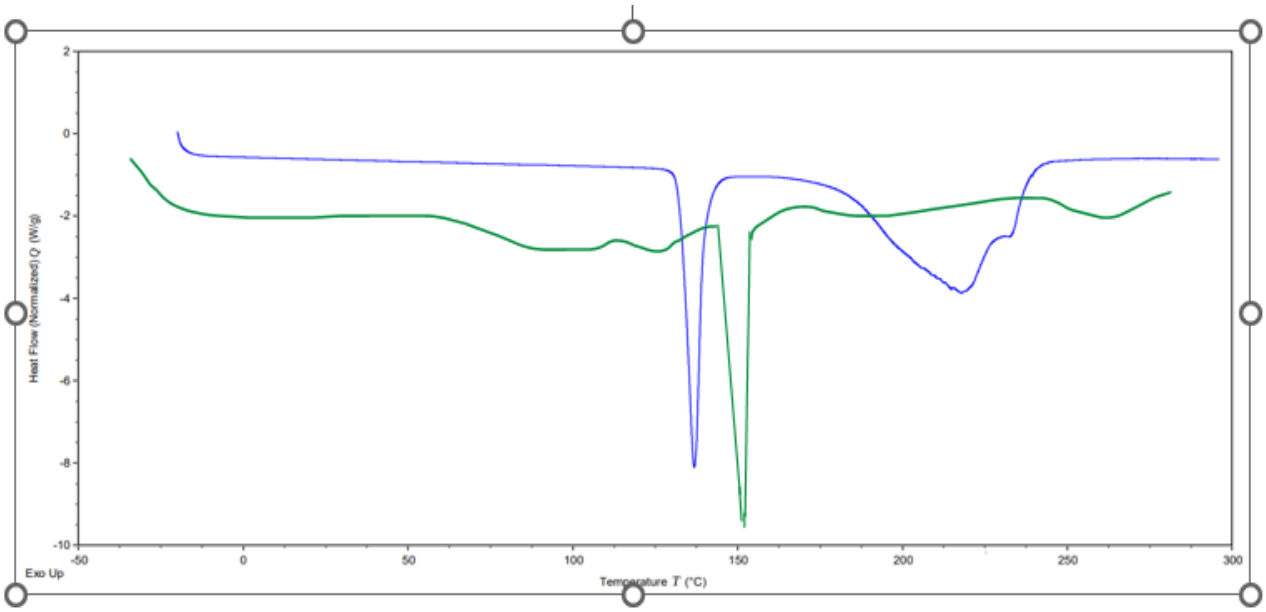

Fig 6. DSC thermogram of Chlorpheniramine Maleate (Blue colour) and Drug excipient Physical mixture (Green colour)

- **Pre-Compression Parameter:**

The flow property of 6 different formulations is shown in **Table 6**. The obtained angle of repose (Ɵ) was found between 27.63° to 28.96°, indicating that the ODTs powder blends have good flow characteristics and may be utilized for direct compression. Powder blends' bulk and tapped densities ranged from 0.46-0.48 gm/cc and 0.55-0.56gm/cc, respectively. The powder blend has a good flow characteristic, as shown by Carr's index, which varied from 14.28 to 16.36%. Whereas, Hausner's Ratio for the ODT1 formulation is 1.19 indicating fair flow properties but ODT2 to ODT6 formulation's Hausner's Ratio belongs between 1.16-1.17 which indicates good flow characteristics.

Table 6. Different Pre-compression Parameters of ODTs Powder Blends

Formulation	**ODT_1**	**ODT_2**	**ODT_3**	**ODT_4**	**ODT_5**	**ODT_6**
Angle of Repose(Ɵ)	28.96°	27.63°	28.02°	28.09°	27.95°	28.23°
Bulk Density(gm/cc)	0.46	0.48	0.48	0.47	0.48	0.48
Tapped Density(gm/cc)	0.55	0.56	0.56	0.55	0.56	0.56
Carr's Index (%)	16.36	14.28	14.28	14.54	14.28	14.28
Hausner's Ratio	1.19	1.16	1.16	1.17	1.16	1.16

- **Post-Compression Parameter:**

Weight Variation:

Due to the permissible limit of 10%, every batch of orally disintegrating tablets had deviations below that level. Each formulation's average weight values are essentially uniform and meet the specification. So, the test for weight variation was passed by all formulations.

Journal of Chemical Health Risks
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JCHR (2023) 13(4s), 468-481 | ISSN:2251-6727

Fig 7. Appearance of ODTs Formulation

Tablet Thickness:
In **Table 7**, the thickness for all batches is shown. Different batches of orally disintegrating tablets ranged in thickness from 2.01 to 2.15 mm. In **Fig 7**, the thickness of six tablets of ODT6 formulation is displayed.

Tablet Hardness:
In **Table 7,** the results of each formulation's hardness in tabular form. Orally disintegrating tablets ranged in hardness from 2.06 to 2.11 kg/cm^2 which was within the specifications. So, all six formulation batches passed the hardness test. In **Fig 7**, **the** six ODT6 formulation tablets' hardness as shown.

Friability:
In **Table 7,** the friability test results of all batches is shown. All the batches demonstrated friability in the range of 0.21 to 0.33 percent, which is below the permitted maximum of 1.0 percent. Thus, the friability test was passed by all six batches.

Disintegration Time:
The disintegration time of the tablets is the most crucial factor that must be optimized during the formulation of an orally disintegrating tablet. The tablet underwent a disintegration test in purified water. According to the Indian Pharmacopoeia 2018, the maximum time until an orally disintegrating tablet disintegrates is NMT 30 seconds. Superdisintegrants, croscarmellose sodium, batch numbers ODT5 and ODT6 (7.5 mg and 10 mg per tablet, respectively) show disintegration time of 26 seconds and 15.16 seconds respectively which matched the specification. So ODT5 and ODT6 out of six formulations passed disintegration testing

Wetting Time:
All six formulations' wetting times were measured and are shown in **Table 7** below. The wetting time of ODT5 and ODT6 formulations are 56sec and 29sec respectively. The wetting time was rapid in Croscarmellose sodium followed by Sodium starch glycollate. In this instance as well, it was seen that the time required for wetting decreased as disintegrant concentration reduced as shown in **Fig 8**.

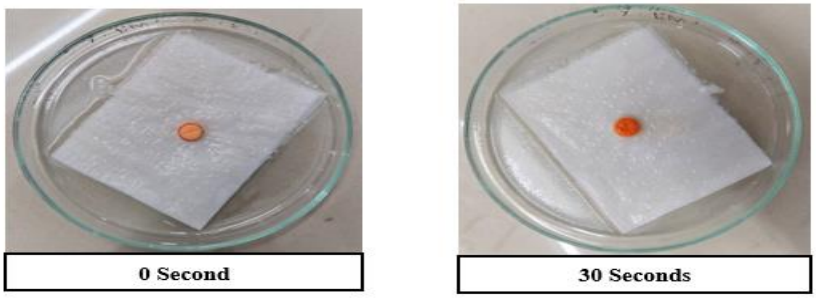

Fig 8. Wetting Time of the tablet of ODT6 batch

Water Absorption Ratio:
The capacity of disintegrants to expand in the presence of minimal water was determined using the water absorption ratio, a crucial criterion. The range of water absorption ratio of the six formulations is in the range of 30.1 to 79.2% (**Table 7**). With an increase in sodium

Journal of Chemical Health Risks
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JCHR (2023) 13(4s), 468-481 | ISSN:2251-6727

starch glycollate concentration, followed by croscarmellose sodium, the water absorption ratio rises. Here, croscarmellose sodium in the ODT6 batch shows the highest water absorption, 79.2%.

***In vitro* dispersion test:**

In vitro dispersion tests of six formulations were performed. By continuous stirring the tablets of every batch were properly dissolved in distilled water. When this solution passes through a 710µm sieve, no particle from any formulation batch was left on the sieve. As a result, the "*in vitro*" dispersion test was passed by all of the batches.

Assay:

An assay of the tablet of each formulation was performed and the results are shown in **Table 7**. The assay results of six batches are within the acceptable limit. The six formulation batches of Chlorpheniramine Maleate ODT were evaluated, and the results were within acceptable limits. According to IP 2007, the permitted limit for the assay of Chlorpheniramine Maleate tablets is between 95 and 105 percent.

Table 7. Post-Compression Parameter Data

Parameters	Formulation Batch					
	ODT_1	**ODT_2**	**ODT_3**	**ODT_4**	**ODT_5**	**ODT_6**
Weight Variation (mg)	80.5±1.27	80.2±2.30	79.2±2.70	79.8±2.10	80±1.70	80.4±1.51
Thickness (mm)	2.01±0.08	2.04±0.05	2.09±0.08	2.07±0.05	2.03±0.07	2.15±0.02
Hardness (Kg/cm^2)	2.06±0.08	2.07±0.11	2.06±0.08	2.07±0.11	2.11±0.13	2.09±0.12
Friability (%)	0.21	0.25	0.29	0.33	0.26	0.28
Disintegration Time (Sec)	192.5±3.56	75.1±2.69	45±1.41	45.33±2.4	26±0.89	15.16±0.7
Wetting Time (Sec)	206.2±3.43	80.3±1.86	71.3±1.97	87.3±1.37	56.2±1.12	29.2±1.47
Water Absorption Ratio (%)	30.1±2.52	44.4±1.24	53.8±1.05	67.2±0.68	71.2±1.18	79.2±0.63
Assay (%)	97.32	101.99	99.55	97.14	102.38	98.65

- ***In vitro* Drug Release Study:**

Table 8. *In vitro* drug release of all formulations

Time (Min)	% Cumulative Drug Release					
	ODT_1	**ODT_2**	**ODT_3**	**ODT_4**	**ODT_5**	**ODT_6**
0	0	0	0	0	0	0
1	4.15±0.56	57.9±0.72	70.85±1.02	72.15±0.79	88.34±0.98	92.23±0.9
2	20.98±0.58	66.97±0.69	91.58±0.95	83.16±0.83	93.52±1.25	96.76±0.6
3	39.12±0.75	75.39±0.86	92.88±0.59	86.4±0.96	98.70±0.69	99.87±1.0

All values are expressed as mean ± SD (Standard deviation), n=3

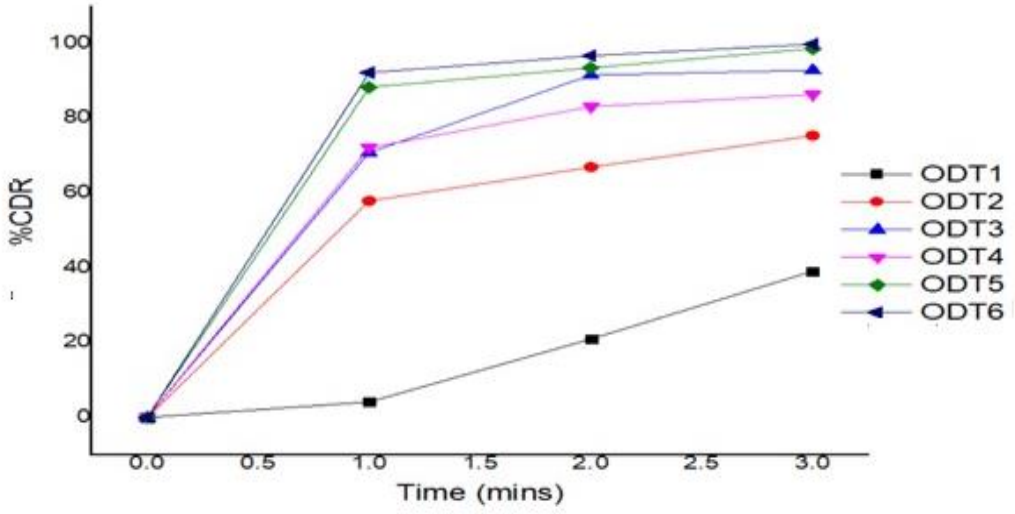

Fig 9. Percentage cumulative drug release study of formulation ODT1 to ODT6

- ***In vitro* drug release Kinetics:**

Journal of Chemical Health Risks
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JCHR (2023) 13(4s), 468-481 | ISSN:2251-6727

The *In vitro* drug release data (shown in Table 8 and Fig 9) of every optimized formulation of an orally disintegrating tablet containing chlorpheniramine maleate (ODT_6) was evaluated by an analysis of linear regression using several mathematical models in order to assess the goodness of fit:

a. Drug release rates cumulatively in relation to time (Zero order release model) (Fig 10)
b. First order kinetics: Log cumulative percentage of drug retained against time (Fig 11).
c. Higuchi model: cumulative percent release vs time squared (Fig 12).
d. Kors Meyer-Peppas model: Log cumulative percentage of drug released against. Log Time Fig 13).

The value of "n" in the Peppas concept describes a drug's release mechanism.

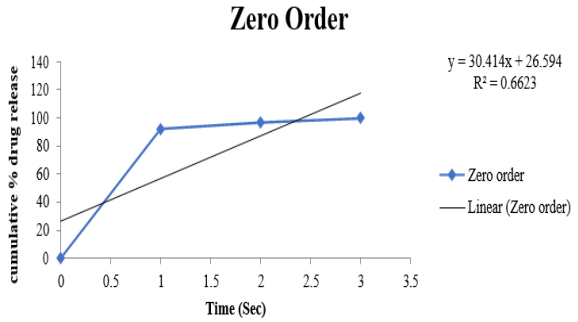

Fig 10. Zero order kinetics

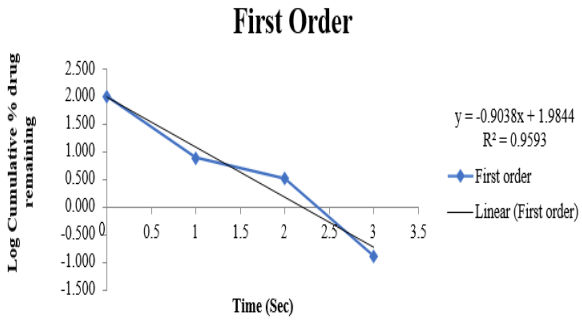

Fig 11. First order kinetics

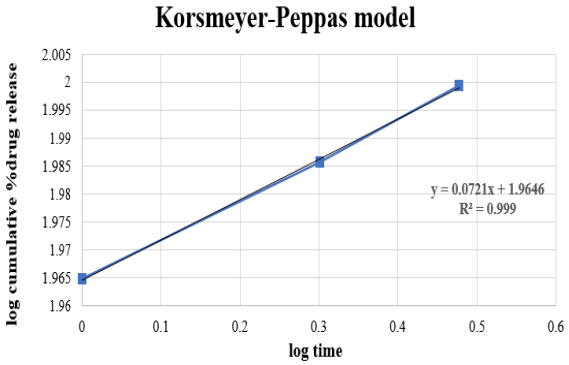

Fig 12. Higuchi model

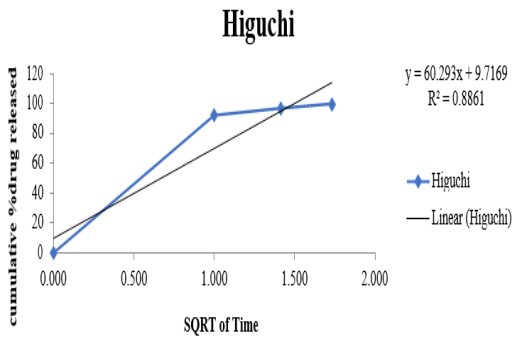

Fig 13. Korsmeyer Peppas model

With a coefficient of determination (r^2) of 0.9593, it can be inferred from the data above that formulation ODT6 reflects first-order kinetics. To comprehend the process how Chlorpheniramine maleate has been released from this formulation, the in-vitro release of drugs ODT6 data as log% CDR vs time was mapped to the Kors Meyer equation. In the optimized ODT6 batch, exponent "n" was found to have a value of 0.38. The Korsmeyer-Peppas model produces "n" values of 0.45, indicating that the formulation's Quasi-Fickian diffusion was used as the diffusion mechanism.

- **Stability Studies:**

According to recommendations from the International Conference on Harmonization (ICH), stability tests (Table 9) were conducted for the optimal formulation, ODT6. ODTs of ODT6 formulation were stored in a stability chamber for three months at 40°±2°C and 75±5 percent relative humidity after being wrapped in aluminium foil and placed in an amber-colored container. The ODTs were withdrawn and assessed for physical characteristics and *in vitro* drug release at intervals of 30 days (Fig 14).

Table 9. *In-vitro* dissolution data of formulation ODT_6 stability study batch

Time in mins	**%CDR of ODT_6 after Accelerated Stability Study for 3 months**			
	Initial	First Month	Second Month	Third Month
0	0	0	0	0
1	92.23	88.34	90.28	90.93
2	96.76	96.76	97.40	98.7
3	99.87	99.87	100.06	99.93

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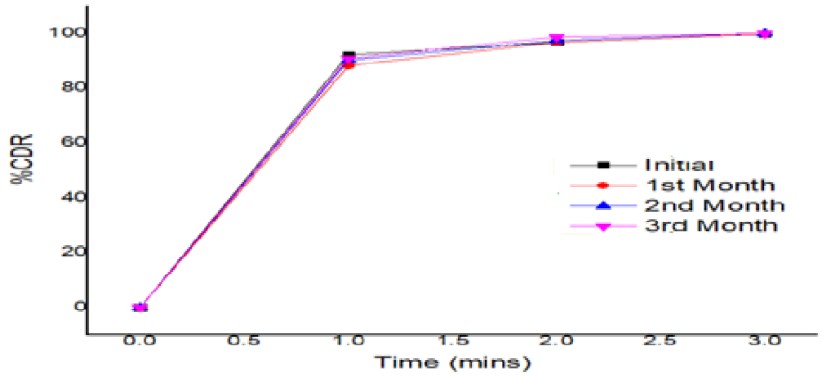

Fig 14. % CDR of ODT6 formulation during stability

Table 10. Physical Evaluation of ODT_6 Stability Study Batch All values are expressed as mean ± SD (Standard deviation), n=3

Interval	Weight Variation ± SD (mg)	Thickness ± SD (mm)	Hardness ± SD (Kg/cm^2)	Friability (%)	DT Time ± SD (Sec)	Assay ± SD (%)
First Month	81.1±1.73	2.19±0.03	2.75±0.62	0.35	12.8±1.17	97.28±0.58
Second Month	81.8±1.50	2.22±0.02	2.21±0.78	0.45	11.5±0.55	101.25±0.96
Third Month	82.3±1.78	2.25±0.02	1.50±0.95	0.63	10.3±0.52	99.87±0.98

Tablets utilized in the release study did not significantly alter. Based on the findings, it can be said that the orally disintegrating pills were stable for three months at the accelerated stability conditions of 40°C±2°C and 75%±5% RH. Even if its three-month stability is guaranteed, additional research in accordance with ICH requirements will be required to determine its shelf-life (Table 14).

CONCLUSION

The ODT6 formulation with the highest croscarmellose sodium concentration demonstrated the maximum capacity for hydration and swelling, with times of 29.2 secs and 79.20%, respectively. Formulations containing sodium starch glycollate disintegrated more slowly than croscarmellose sodium did. All formulae disintegrate times ranged from 192.5 to 15.16 seconds. The ODT6 formulation, which has the maximum quantity of croscarmellose sodium (10mg), was shown to have a relatively short disintegrate time. Within 3 minutes, it was discovered that the percent release of drugs for all six compositions ranged from 39.12% to 99.87%. With an increase in croscarmellose sodium concentration, there was an increase in drug release. The highest release of drugs was seen in the ODT6 formulation, at 99.87% in virtually the first three minutes. Chlorpheniramine Maleate's quick, pleasant, orally disintegrating tablets were developed in the current investigation. The following inferences are made from the studies completed and the results obtained above. Orally disintegrating tablets for chlorpheniramine maleate may be effectively made via the direct compression method with a variety of super-disintegrants as well as taste hindering agents. Results from Formulation ODT6, which was created using CCS 10 mg proportion, were encouraging. This formulation showed the highest ability for hydration and water absorption, the shortest disintegration time, and the highest percentage of drug release, all of which result in a rapid commencement of action and rapid relief from surprise allergic reactions. The ultimate ODT6 formulation also had a great tongue feel and a pleasing taste. All of the tablet evaluation criteria for the mouth-dispersing drug delivery system were met by this formulation. The ODT6 Formulation was therefore determined to be an optimized formulation between OD1 and ODT6. According to ICH criteria, accelerated stability testing of Optimized Formulation ODT6 revealed that it remained stable for three months at a temperature of 40°±2°C and a relative humidity of 75%±5%. Without a doubt, CPM-ODTs will quickly gain popularity because to their rapid onset of action, immediate relief, minimal side effects, nice mouthfeel, good stability, and enhanced patient compliance.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest

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