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Preparation and Evaluation of Oro Dispersible Tablet of Diphenhydramine Hydrochloride by Sublimation Method

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ABSTRACT:
Oro dispersible tablets of Diphenhydramine Hydrochloride using different super disintegrating agents and a subliming agent through the sublimation method. This work is intended to prepare a solid oral dosage form that disintegrates quickly in the mouth, providing ease of administration and improving patient acceptability. The formulation approach is based on enhancing the disintegration characteristics by selecting suitable excipients and applying an effective preparation technique. Diphenhydramine hydrochloride Oro dispersible tablets were successfully formulated using the sublimation method with camphor as subliming agents. A combination of croscarmellose sodium and crospovidone acted effectively as super disintegrants. The sublimation technique produced tablets with increased porosity, leading to significantly reduced in vitro disintegration time, dispersion time, and wetting time. In vitro drug release studies demonstrated that over 90% of the drug was released within 2 minutes across all formulations. Among them, F3 and F4 were identified as the most stable and effective formulations. To confirm the therapeutic effectiveness of these formulations, further studies on bioavailability, preclinical, and clinical evaluations are required.

Keywords: Orodispersible tablet, croscarmellose, crospovidone, diphenhydramine hydrochloride.

I. INTRODUCTION:

Fast disintegrating solid dosage forms have become very popular in the last few years. This area is now growing quickly in the pharmaceutical industry. The main reason for this growth is the many benefits these dosage forms offer — such as being easy to take for people who have trouble swallowing, allowing faster absorption of the drug in the body, giving more comfort to the patient, and helping improve patient compliance with treatment. [1,2]

Oro dispersible tablets (ODTs) are a modern drug delivery method designed to improve patient acceptance. These tablets break down quickly in the mouth and can be taken easily without the need for water or chewing. This system is especially helpful for people who have difficulty swallowing solid dosage forms like tablets and capsules. These formulations are particularly useful for children and elderly patients. Studies show that around 50% of people suffer from dysphagia (trouble in swallowing), which often leads to poor medication compliance and less effective treatment. [3]

The United States Food and Drug Administration (FDA) defines an Oro dispersible Tablet (ODT) as a solid dosage form that contains a medicinal substance or active ingredient and breaks down quickly, usually within seconds, when placed on the tongue. Generally, the disintegration time for ODTs ranges from a few seconds to about one minute. Some drugs are absorbed through the mouth, throat (pharynx), and oesophagus as saliva carries them to the stomach. In such cases, the drug's bioavailability is much higher compared to regular tablet forms. Oro dispersible tablets are also known by other names such as Orally Disintegrating Tablets, Mouth Dissolving Tablets, Fast Disintegrating Tablets, Fast Dissolving Tablets, Rapid Dissolving Tablets, Porous Tablets. However, among all these terms, the United States Pharmacopoeia (USP) prefers the term "Oro dispersible Tablets" for tablets that quickly disperse in the mouth, usually within 3 minutes before swallowing.[4]

Diphenhydramine hydrochloride is an antihistamine medicine commonly used to treat symptoms of allergies, hay fever, and the common cold. These symptoms include skin rashes, itching, watery eyes, itchy eyes, nose or throat, coughing, runny nose, and sneezing. It is also helpful in preventing and treating nausea, vomiting, and dizziness caused by motion sickness. Additionally, Diphenhydramine hydrochloride can be used as a

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sleep aid to help people relax and fall asleep. This drug works by blocking a natural chemical in the body called histamine, which is released during an allergic reaction. Its ability to reduce symptoms like watery eyes and runny nose comes from blocking another natural chemical made by the body, known as acetylcholine. [5]

Diphenhydramine hydrochloride is a histamine H1 blocker that is used for several purposes such as an antiemetic (to prevent vomiting), antitussive (to relieve cough), and for treating skin conditions like dermatoses and itching (pruritus). It is also used for allergic (hypersensitivity) reactions, as a sleep aid (hypnotic), for Parkinson's disease symptoms, and as a common ingredient in cold medications. It helps relieve symptoms related to vertigo or Meniere's disease, nausea and vomiting, motion sickness, and insect bites. The main aim of this study was to prepare or dispersible tablets of diphenhydramine hydrochloride using excipients like crospovidone, croscarmellose sodium, mannitol, and dicalcium phosphate by applying the sublimation technique. [6]

II. MATERIALS AND METHOD:

Table no 1: List of Materials

Sl No.	Materials
1	Diphenhydramine Hydrochloride (API)
2	Croscarmellose Sodium
3	Crospovidone Iodine
4	Camphor
5	Starch
6	Mannitol
7	Dicalcium Phosphate
8	Magnesium Stearate
9	Talc

To prepare mouth-dissolving tablets of Diphenhydramine hydrochloride using the sublimation technique, accurately weighed amounts of the drug, camphor, mannitol, dicalcium phosphate, and starch were first blended and passed through sieve no. 40 to ensure uniform particle size.

Next, super disintegrants were thoroughly incorporated into the blend to promote rapid disintegration. Finally, magnesium stearate and talc were added as lubricant and glidant, respectively. The final powder mixture was then compressed into tablets.

Following compression, the tablets were subjected to drying in a hot air oven at 60°C until a constant weight was achieved. This step ensured the complete sublimation of the volatile component (camphor), thereby creating a porous structure in the tablet for faster disintegration. The formulation details are presented in **Table No.2**

Figure No 1: Formulations

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Table 2: Formulation design of mouth dissolving tablets of Diphenhydramine hydrochloride by sublimation technique.

Ingredients(mg)	F1	F2	F3	F4
Diphenhydramine Hydrochloride	25	25	25	25
Crospovidone	--	--	30	20
Croscarmellose Sodium	20	30	--	--
Starch	20	20	20	20
Mannitol	130	130	130	130
Dicalcium Phosphate	83	73	73	83
Camphor	10	10	10	10
Magnesium Stearate	6	6	6	6
Talc	6	6	6	6
Total Weight (mg).	300	300	300	300

Evaluations:

Pre formulation Study

This study involves evaluating the physical and chemical properties of the Active Pharmaceutical Ingredient (API) and excipients before formulation. These properties affect the stability, safety, and effectiveness of the final dosage form.

Bulk Density

Bulk density refers to the ratio of the mass of a powder to the total volume it occupies without any external pressure or tapping. It provides insight into how powders will pack and settle in containers or capsules.

Formula: Bulk Density (ρb) = (Weight of Microcapsules (g) / Bulk Volume (ml)

Tapped Density

Tapped density is determined after mechanically tapping a measuring cylinder containing the powder sample. This process settles the particles and reduces the volume, resulting in a denser form of the powder. It reflects the compressibility and packing ability of the material.

Figure no 2: Bulk density apparatus

Formula: Tapped Density (ρt) = Weight of Microcapsules (g) / Tapped Volume (ml)

Carr's Index

Carr's Index is a commonly used measure to evaluate the flowability and compressibility of powder. It is derived from the difference between tapped and bulk density. A lower value indicates better flow properties of the powder.

Formula: Carr's Index = [(Tapped Density - Bulk Density) / Tapped Density)] × 100

Hausner Ratio

Hausner Ratio is an important parameter that indicates the flow characteristics of powders. A higher Hausner Ratio means poor flow, which

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can affect the uniformity of dosage. A value close to 1 indicates good flowability.

Formula: Hausner Ratio = Tapped Density / Bulk Density

Table no 3: Carr's index, flow property, Hausner Ratio

Sl. No.	% Carr's Index	Flow Property	Hausner Ratio
1	<10	Excellent	1.00 - 1.11
2	11-15	Good	1.12 - 1.18
3	16-20	Fair	1.19 - 1.25
4	21-25	Passable	1.26 - 1.34
5	26-31	Poor	1.35 - 1.45
6	32-37	Very Poor	>1.45
7	>37	Extremely Poor	-

Angle of Repose

Angle of Repose is the angle formed between the horizontal surface and the slope of a powder heap when it is allowed to fall freely. This angle indicates the flow property of the powder – the smaller the angle, the better the flowability.

Formula: $\theta = \tan^{-1}(h/r)$, where 'h' is the height of the pile and 'r' is the radius of the base.

Table no 4: Angle of repose, flow property

Angle of Repose (θ)	Flow Property
<25	Excellent
25-30	Good
31-40	Satisfactory
41-50	Poor
>51	Very Poor

Evaluation of Tablets:

Weight Variation Test

This test is performed to ensure the uniformity of tablet weight during production. It involves calculating the average weight of randomly selected tablets and comparing each individual tablet weight with this average. The deviation should not exceed ±5% from the average weight as per pharmacopeial standards. A consistent tablet weight indicates good manufacturing control. [7]

Formula: % Weight Variation = ((Average Weight - Individual Weight) × 100) / Average Weight

Thickness Test

This test is used to determine the thickness of tablets, which helps ensure a uniform size of dosage forms. The thickness is usually measured using instruments like a Vernier Calliper. Uniform thickness indicates consistent tablet compression and helps in proper packaging and handling.

Hardness Test

The hardness test is used to evaluate the mechanical strength of a tablet. It measures the force required to break or crush the tablet, which helps determine its resistance to physical stress during packaging, transport, and handling. The Monsanto Hardness Tester is commonly used for this purpose, and the hardness is expressed in units like kg/cm².

Friability Test

This test checks how well tablets can resist breaking or chipping when subjected to mechanical stress. The test is carried out using a friabiliator, in which tablets are rotated at 25 rpm for 4 minutes. After rotation, the weight loss is measured. A friability value of less than 1% w/w is considered acceptable, indicating good tablet strength.

Formula: % Friability = ((Initial Weight - Final Weight) × 100) / Initial Weight

Invitro Disintegration Test

Conventional disintegration test (DT) apparatus may not accurately measure the disintegration time of mouth dissolving tablets (MDTs), as it uses a large volume of water and rapid movement. However, in the mouth, only a small amount of saliva (less than 6 ml) is present.

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Since MDTs are designed to disintegrate quickly in the limited saliva without chewing, a modified method is used. In this method, 6 ml of pH 6.8 phosphate buffer is taken in a 25 ml measuring cylinder, maintained at 37±2°C. The tablet is placed in it, and the time taken for complete disintegration is recorded.

Water Absorption Ratio

To evaluate water uptake, a small Petri dish (internal diameter: 6.5 cm) was filled with 6 ml of water. A tissue paper was folded twice and placed at the bottom of the dish. A pre-weighed tablet was gently placed on the folded tissue, and the time taken for the tablet to become completely wet was noted.

After complete wetting, the tablet was carefully removed and reweighed. The water absorption ratio (R) was then calculated using the following formula:

R= (Wa - Wb / Wb) × 100

Wb represents the initial weight of the tablet (before absorbing water)

Wa represents the final weight of the tablet (after water absorption)

Invitro Dissolution Study

The dissolution behaviour of Diphenhydramine Hydrochloride from the or dispersible tablet was evaluated using 900 ml of phosphate buffer (pH 6.8) as the dissolution medium. The study was carried out using a USP dissolution apparatus equipped with a paddle stirrer, operated at 50 revolutions per minute (rpm). The temperature of the dissolution medium was carefully maintained at 37 ± 0.5°C throughout the test.

Each test was performed using a single tablet containing 25 mg of Diphenhydramine Hydrochloride**.** At specified time points — 0.5, 1.0, 1.5, 2.0, 2.5, 3.0 and 3.5 minutes, 5 ml samples of the dissolution medium were collected. These samples were analysed for drug content by measuring absorbance at **269 nm** using a UV spectrophotometer. After each withdrawal, the same volume of fresh phosphate buffer was added to maintain sink conditions.

Finally, the percentage cumulative drug release was calculated from the collected dissolution data to assess the release profile of the formulation [8].

III. RESULTS AND DISCUSSION:

Pre-formulation studies were carried out for all formulation blends and the results were found to be within I.P. limits, as shown in **Table 5**.

The bulk density ranged from 0.63 to 0.71 g/cm³**,** and tapped density from 0.81 to 0.91 g/cm³. Based on these values, the Hausner's ratio was calculated and found to be less than 1.32**,** indicating good flow properties. The Carr's compressibility index ranged from 17.54% to 20.31%**,** suggesting fair flowability. These findings were further supported by angle of repose values between 16.38° and 22.46°, which are well below 40°, confirming good powder flow.

All tablets appeared white, round, smooth-surfaced, and were free from cracks, pinholes, or depressions**.** Due to good flow properties of the blend, tablets showed uniform weight with acceptable variation as per I.P. standards. Tablet thickness ranged from 4.53 mm (F4) to 5.33 mm (F1)**.** The hardness was between 3.6 – 4.4 kg/cm², reflecting sufficient mechanical strength. Friability loss was less than 1%**,** indicating good durability**,** that already mentioned in **Table No 6** and **figure no 3.**

Table No.5: Pre formulation study evaluation data with (mean±SD, n=3)

Formulation	Bulk Density (ρb)	Tapped Density (ρt)	Carr's Index	Hausner's Ratio	Angle of Repose (θ)
F1	0.69±0.003	0.91±0.005	19.91±0.09	1.31±0.001	20.74±236
F2	0.71±0.001	0.88±0.001	21.32±0.05	1.23±0.003	22.38±124
F3	0.63±0.005	0.81±0.003	20.13±0.12	1.28±0.006	21.89±155
F4	0.65±0.001	0.86±0.005	19.12±0.11	1.32±0.008	16.38±084

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Table No.6: Evaluation Study data of Oro dispersible Tablet with (mean±SD, n=3)

Formulation	Weight Variation(mg)	Thickness test (mm)	Hardness Test (Kg/cm^2)	Friability Test(%w/w)
F1	298.5±2.66	5.33±0.57	4.1±1	0.36±0.03
F2	297.05±2.88	4.76±0.25	4.0±1	0.31±0.01
F3	299.4±1.69	4.80±0.05	4.03±0.05	0.16±0.01
F4	296.8±2.91	4.53±0.25	4.13±0.05	0.23±0.01

Table no 7: Dissolution Rate Profile of Diphenhydramine Hydrochloride Oro dispersible tablet with the Standard Curve Equation: (Y=0.0083x +0.0597**).**

Time (min)	Abs(nm)	Con (µg/ml)	Loss(5ml) Con(µg/ml)	Con(µg/ml) in D M (Con xVolume)	Cum Drug Con(µg/ml) (loss Con+ DM Con)	Total Drug Release(mg) (Cum Drug Con/1000)	% Drug Release	%Cumulative Drug Release
0	0.065	0.63	0	0.63x900= 567	0+567= 567	0.567	2.26	2.26
0.5	0.084	2.92	0.63x5= 3.15	2.92x900= 2628	3.15+2628= 2631.15	2.631	10.52	12.78
1.0	0.095	4.25	2.92x5= 14.6	4.25x900= 3825	14.6+3825= 3839.6	3.839	15.35	28.13
1.5	0.103	5.21	4.25x5= 21.25	5.21x900= 4689	21.25+4689= 4710.25	4.710	18.84	46.97
2.0	0.115	6.66	5.21x5= 26.05	6.66x900= 5994	26.05+5994= 6020.05	6.020	24.08	71.05
2.5	0.126	7.98	6.66x5= 33.3	7.98x900= 7182	33.3+7182= 7215.3	7.215	28.86	99.91

Tablet No.8: Cumulative % of drug for Formulation 1, 2, 3 and 4: On the Basis of Above Dissolution Rate Profile, we have the date of the entire 4 Formulations respectively

Sl No	Formulation	Cumulative % of Drug (%)
1	**F1**	1.83, 12.31, 25.71, 42.35, 62.91 and 88.71
2	**F2**	1.89, 10.65, 25.65, 43.42, 72.61 and 89.33
3	**F3**	2.26, 12.78, 28.13, 46.97, 71.05 and 99.91
4	**F4**	1.98, 11.02, 25.38, 42.86, 69.75 and 91.56

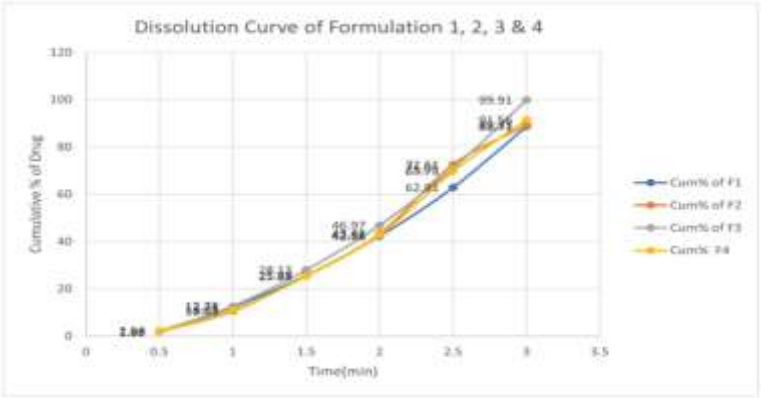

Figure no 3: Dissolution Rare Profile Curve of Tablet

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IV. CONCLUSION:

Diphenhydramine hydrochloride Oro dispersible tablets were successfully formulated using the sublimation method with camphor as subliming agents. A combination of croscarmellose sodium and crospovidone acted effectively as super disintegrants.

The sublimation technique produced tablets with increased porosity, leading to significantly reduced in vitro disintegration time, dispersion time, and wetting time. In vitro drug release studies demonstrated that over 90% of the drug was released within 2 minutes across all formulations. Among them, F3 and F4 were identified as the most stable and effective formulations.

To confirm the therapeutic effectiveness of these formulations, further studies on bioavailability, preclinical, and clinical evaluations are required.

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Conflict of interest: No conflict of interest.

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