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FORMULATION & EVALUATION OF ORAL DISPERSIBLE TABLETS OF CHLORPHENIRAMINE

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ABSTRACT

Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly patient compliance. The most popular solid dosage forms are the Fast disintegrating tablets and Chlorpheniramine was chosen a choice drug candidate. Since it is drug prescribed especially in elderly patients as antihypertensive and also it is given in the conditions of heart failure an Chlorpheniramine heart attack. The drug is bitter taste in nature and produces noncompliance to patient's especially geriatric patients. It concluded that INDION 204 resin were useful for masking the taste as well as enhancing the solubility of the drug. Super disintegrants were helpful in formulation of the Oral Dispersible tablets. Crosscarmellose sodium was used as superdisintegrants in formulations. The oral disintegrating tablets of Chlorpheniramine with sufficient mechanical strength, acceptable taste and smaller disintegration time were achieved employ-ing suitable superdisintegrants and other excipients at optimum concentration. Stability studies revealed that there was no significant change in drug content and dissolution profile of oral disintegrating tablets. FTIR studies revealed that there was no shift in peaks, indicating there is no interaction between Chlorpheniramine and other ingredients used. Among three superdisintegrants used, Crosspovidone showed better performance in disintegration time when compared to sodium starch glycolate and Crosscarmellose sodium. So the formulation of F4 was found to be best among all other formulations, because it has exhibited faster wetting time, good taste and faster disintegration time when compared to all other formulations.

KEYWORD: Chlorpheniramine, Oral Dispersible tablets, superdisintegrants & Crosscarmellose sodium.

1. INTRODUCTION

It is an innovative tablet technology in which the dosage form containing active pharmaceutical ingredients disintegrates rapidly, usually in seconds, without the need for water, offering optimal patient comfort. The European Pharmacopoeia defines orodispersibles as a tablet that can be put in the mouth where it disperses rapidly before swallowing. Researchers have formulated the ODT for several categories of drugs, which are used for therapy in which a rapid maximum plasma concentration is required to obtain the desired drug response. These include neuroleptics, cardiovascular agents, pain relievers, allergy medications, and erectile dysfunction medications.

1.1. Superdisintegrants

Disintegrating agents are substances that are generally included in tablet formulations to facilitate the breakdown of compacted mass when placed in a fluid environment. Promote moisture penetration and dispersion of the matrix of the tablet. In recent years, numerous new agents known as"super-disintegrants" have been developed. These new substances are more effective at lower concentrations with greater disintegration efficiency and mechanical resistance. In contact with water, super-disintegrants swell, hydrate, change volume or shape and produce a disruptive change in the tablet. The superdisintegrant effective provide better compressibility, compatibility and not have any negative impact on the mechanical strength of the formulations containing drugs of high dose.

1.2. Super- disintegrating mechanism: swelling[1]

Perhaps the most widely accepted mechanism of action for disintegrating tablets is bloating. High porosity tablets exhibit poor disintegration due to the lack of proper swelling force. On the other hand, sufficient swelling force is exerted on the Low porosity tablet.

1.3. Porosity and capillary action (Perspiration)

Disintegration by capillary action is always the first step. When we place the tablet in a suitable aqueous medium, the medium penetrates the tablet and replaces the air adsorbed on the particles, weakening the intermolecular bond and breaking the tablet into fine

particles. The water intake by the tablet depends on the hydrophilicity of the drug / excipient and conditions of tablet formation. For these types of disintegrating maintenance of the porous structure, a low interfacial tension to the aqueous fluid is required which aids in disintegration by creating a hydrophilic network around the drug particles.

1.4. Advantages of ODT

- Ease of administration to patients who cannot swallow, such as the elderly, stroke patients, and bedridden patients; patients who should not swallow, such as patients with kidney failure; and that they refuse to swallow, as pediatric, geriatric and psychiatric patients.
- Compliance of the patient for bedridden patients and people with disabilities who travel and are busy and do not have immediate access to the water.
- Sentimiento good feeling of ownership of the mouth MDDDS helps to change the basic view of drugs.
- Convenience of administration and precise dosage compared to liquid formulations.
- Benefit from liquid drugs in the form of a solid preparation.
- Absorption drug of the pre - gastric area, p. The mouth, pharynx, and esophagus can cause a rapid onset of action.
- The absorption pregástricamente can result in improved bioavailability, reduced dosage and one improvement in the clinical performance reduce side effects.

1.5. Limitations[3,4]

- tablets generally have insufficient mechanical strength. Therefore, careful handling is required during the manufacturing process.
- Tablets can leave an unpleasant and / or grainy taste in the oral cavity if not formulated correctly.
- Dosis medicines with higher doses are difficult to formulate in FDT, for example, rifampicin (600 mg), ethambutol (1000 mg), etc.

1.5. Challenges in the formulation of ODT[5]

1. Mechanical resistance and disintegration time

The disintegration time will be delayed if the mechanical resistance is strong. Therefore, a good compromise between these two parameters is always essential.

2. Taste masking

Effective masking of the taste of bitter drugs should be done in such a way that the taste of the drug is not perceived in the oral cavity.

3. Feeling in the mouth

The particles generated after the disintegration of the ODT should be as small as possible. ODT should leave minimal or no residue in the mouth after oral administration. In addition, the addition of flavors and cooling agents such as menthol improves the sensation in the mouth.

4. Sensitivity to the conditions Environmental

ODT should generally exhibit low sensitivity to environmental conditions such as humidity and temperature.

5. Cost

The technology adopted for a ODT must be acceptable in terms of the cost of the final product.

1.6. The need for ODT development[6, 7-9]

The requirement for non - invasive delivery systems persists due to poor patient acceptance and compliance with the regimes of labor existing. The pediatric and geriatric populations are the primary targets, as both groups have had difficulty swallowing conventional tablets.

The factors related to the patient for the development of ODT include:

- avoids the risk of suffocation or suffocation during oral administration of conventional formulations due to physical obstruction, thus ensuring greater safety.
- Very old patients who may not be able to swallow a daily dose of antidepressant.
- An eight-year-old boy with allergies who wants a cheaper dosage form than antihistamine syrup.
- A woman of middle age who undergo radiation therapy for breast cancer may have too nauseated to swallow your H2 blocker.
- A schizophrenic patient in an institutional setting who may try to hide a conventional tablet under the tongue to avoid the daily dose of an atypical antipsychotic.

2. MATERIALS AND METHODS

Table 2.1.: List of chemicals used with their grade and supplier.

Sr. No	Materials	Grade	Supplied By
1	Chlorpheniramine	AR	Nitika Pharmaceutical Nagpur
2	Cross Carmellose Sodium	LR	Nulife Pharmaceuticals Pvt. Ltd. Pune
3	Direct compressible lactose	LR	Ozone International, Mumbai
4	Mg. Stearate	LR	Ozone International, Mumbai
5	Talc	LR	Research lab fine chemical industries Mumbai
6	Aspartame	LR	Research lab fine chemical industries Mumbai

Table 2.2: Details of equipment's used in the work.

Sr. No.	Instrument	Manufacturer	Model
1.	Electronic Weighing Balance	VIC, Mumbai	VB 601
2.	Tap Density Tester (U.S.P.)	VTAP/MATIC-II	VTAP-11
3.	Sieves	Jayant Scientific Industries	BC # 18, 22, 24
4.	Tablet punching machine	Cemach Machineries Limited	R & D TabletPress
5.	pH Meter	Equip-tronics	EQ-610
6.	Hardness tester	Monsanto type	MHT-20
7.	U.V. Spectrophotometer	Jasco, Japan	V-630
8.	IR Spectrophotometer	Shimadzu, Japan	Model-640
9.	Diffusion Cell Apparatus	Orchid Scientifics, Nashik	EMFDC-06

3. RESULT AND DISCUSSION

3.1. Preformulation Studies

3.1.1 IR Spectra

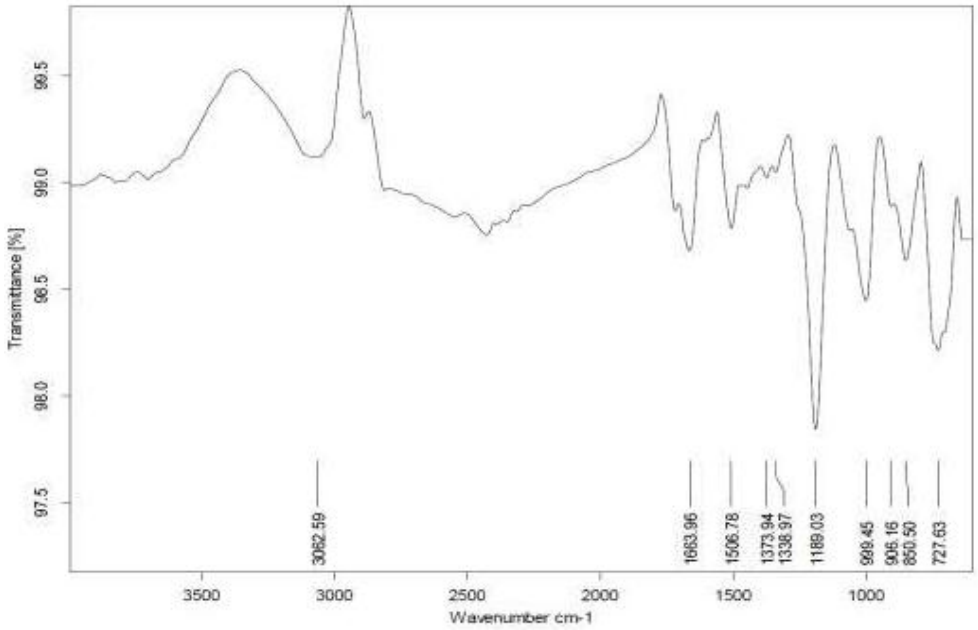

Fig 3.1: IR spectra of Chlorpheniramine API.

Table No. 3.1.: Assignments for the Infrared Absorption Bands of Chlorpheniramine (API).

Frequency (cm^{-1})	Assignments	Frequency (cm^{-1})	Assignments
3062	Acid O–H stretching	1373	–CH3 bending
1663	C=C stretching	999	C–O stretching
1506	–CH2 bending	721	C-Cl stretching

3.1.2. IR spectra of Chlorpheniramine + Excipients

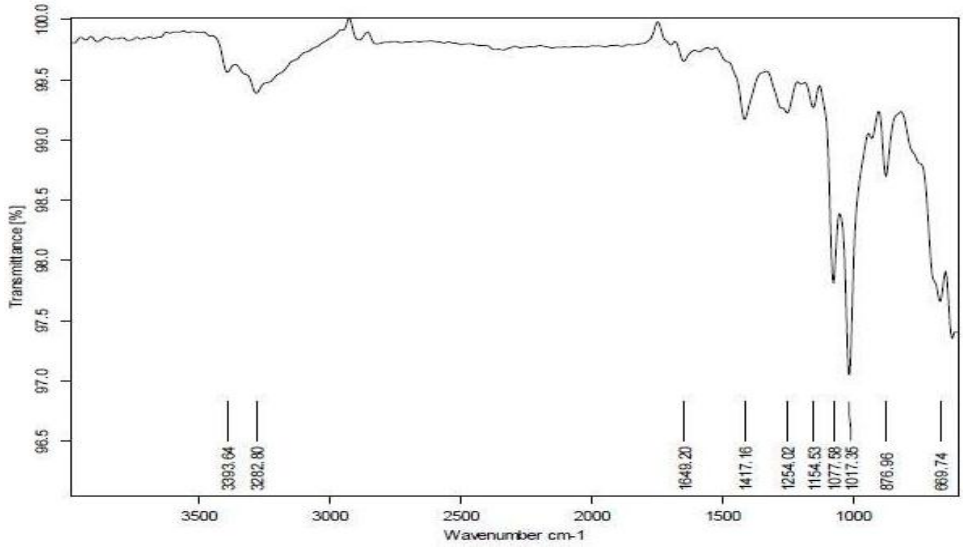

Fig. 3.2.: IR spectra of Chlorpheniramine + Excipients.

3.1.3. DSC of Chlorpheniramine API

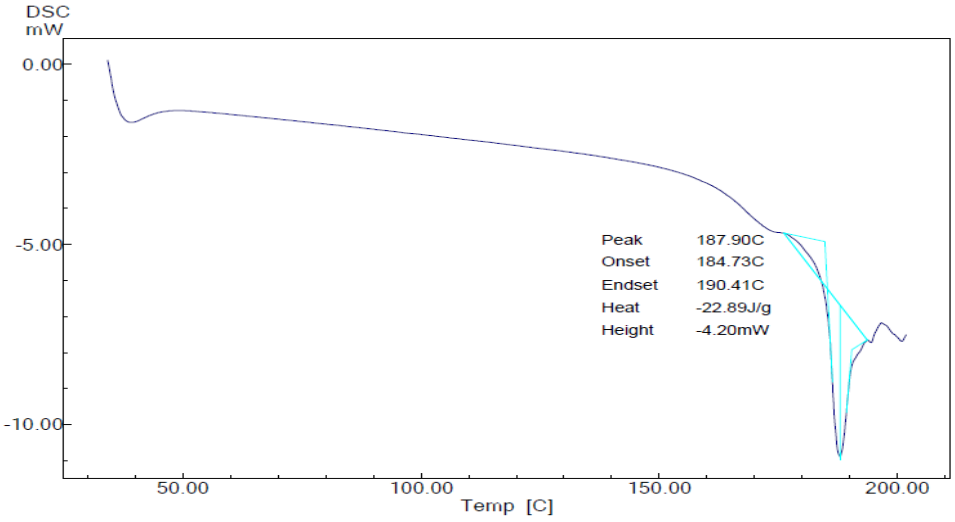

Fig.9.3: DSC of Chlorpheniramine API.

3.1.4. DSC of Chlorpheniramine +excipients

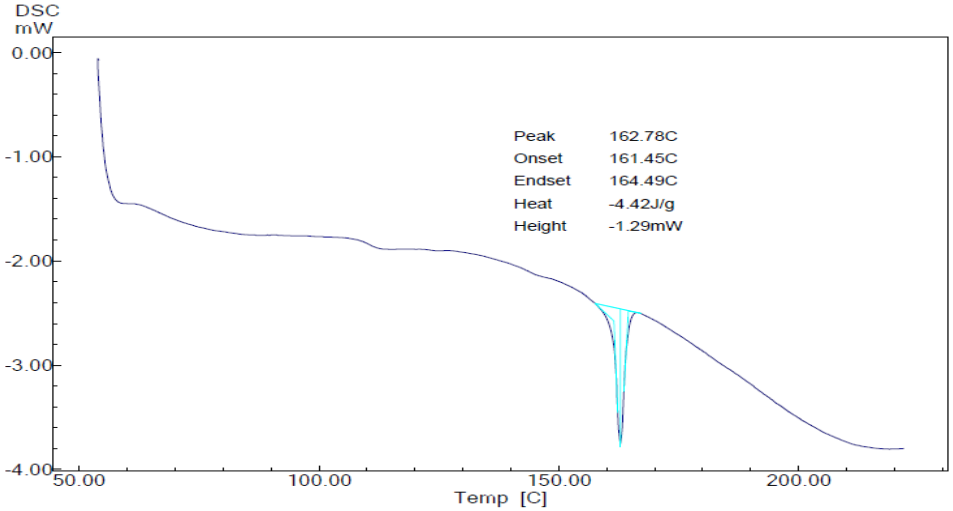

Fig 3.4: DSC of Chlorpheniramine+ Excipients.

3.2. Physical properties

3.2.1. Solubility study of Chlorpheniramine

Chlorpheniramine is soluble in water, ethanol, methanol.

3.2.2. Melting point

The melting point of Chlorpheniramine was found to be 188^0C to value as reported in literature, thus indicating purity of the drug sample. Any impurity, if present, will cause variation in the melting point of a given drug substance.

3.2.3. Compatibility studies

From the spectra of pure drug and the combination of drug with excipients, it was observed that the entire characteristic peaks of were present in the combination spectrum, thus indicating compatibility of the drug and excipients. On the basis of IR spectra and DCS study of the pure drug and in combination with the excipients are shown the compatibility.

3.2.4. Determination of maximum absorption of Chlorpheniramine

The pure drug Chlorpheniramine was scanned over a range 200-400 nm to determine its λ-max. The peak was observed at the 231 nm for Chlorpheniramine (Figure No.8.5). The obtained results conforms the identification of Chlorpheniramine in Phosphate Buffer 6.8.

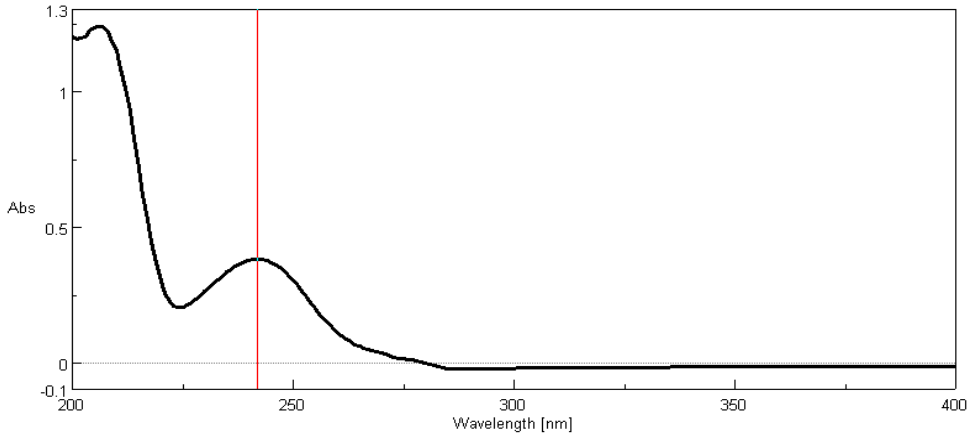

Fig 3.5: Maximum absorption of Chlorpheniramine.

3.3. Standard calibration curve of Chlorpheniramine

Table No. 3. 2: Standard calibration curve of Chlorpheniramine.

Concentration (µg/ml)	Absorbance (nm)
5	0.2074
10	0.4094
15	0.6576
20	0.9018
25	1.1219

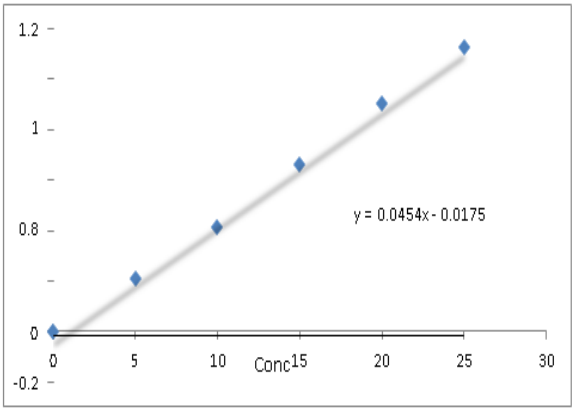

Fig 3.6: Standard calibration curve of Chlorpheniramine.

3.4. Determination of Effect of concentration of resin on drug loading

Table No 3.3: Effect of concentration of resin on drug loading.

Drug :Resin Ratio	% Drug bound
1:2	82.94
1:3	88.35
1:4	90.78

3.5. Taste Evaluation

Table No. 3.4.: Taste evaluation of DRC.

Volunteers	30sec	1min	2min
1.	1	1	1
2.	2	1	1
3.	1	1	1

0=tasteless, 1=acceptable bitterness, 2=slightly bitterness, 3=strongly bitterness.

3.6. Evaluation Parameter

Table No. 3.5: Precompression parameters of Chlorpheniramine.

Batch	Angle of repose(θ)	Bulk Density(gm/cm2)	Tapped Density(gm/cm2)	Carr's Index
F1	26.06±0.04	0.8221±0.03	0.9247±0.02	12.48
F2	24.67±0.01	0.864±0.02	0.9234±0.04	11.73
F3	28.08±0.02	0.845±0.02	0.9916±0.01	9.67
F4	25.55±0.02	0.867±0.02	0.9135±0.02	5.30
F5	23.67±0.02	0.8284±0.03	0.9286±0.04	11.96
F6	27.08±0.01	0.8321±0.02	0.9221±0.02	10.81
F7	28.08±0.01	0.8439±0.04	0.9121±0.02	8.49
F8	26.06±0.04	0.8294±0.02	0.9296±0.03	12.08
F9	24.85±0.01	0.8221±0.03	0.9247±0.02	12.48

The values of bulk density and tapped density were found in the range from 0.8221 to 0.867 g/ml and from 0.9121 to 0.9916 g/ml respectively. The Carr's Compressibility indices were in the range of 5.30 to 12.48% and angle of repose was in the range of 24.67 to 28.08 Ø. This indicates that formulations have good flow property.

3.7. Post -compression Parameter

3.7.1. Shape and color of tablets

Randomly picked tablets from each formulation batch examined under lens for shape and in presence of light for color. All tablets of all the batches showed flat, circular in shape and white in color.

3.7.2. *Uniformity of thickness*

The thickness of the tablets was measured by using vernier caliper by picking the tablets randomly. The mean values are shown in Table 9.7 The values are almost uniform in all formulations. Thickness was found in the range of 4mm to 4.2 mm respectively.

3.7.3. *Hardness test*

Table No. shows results obtained for of all the formulation of hardness. Hardness test was performed by Monsanto hardness tester. Hardness was found to be within 4 kg/cm^2, as these tablets are immediate released. The lower standard deviation values indicated that the hardness of all the formulations were almost uniform in specific method and possess good mechanical strength with sufficient hardness.

3.7.4. *Friability test*

The study results are tabulated in Table No. 9.7, was found well within the approved range (<1%) in all the formulations. Formulation F1 to F9 possesses good mechanical strength.

3.7.5. *Weight variation test*

The percentage weight variation for all the formulation is tabulated in Table No9.5.2. All the tablets passed weight variation test as the % weight variation was within the pharmacopoeias limits of not more than 5%. It was found to be from 250.16±0.28 to 252.66±0.57mg. The weight of all the tablets was found to be uniform.

3.7.6. *% Drug content uniformity*

The content uniformity was performed for all the fore formulations and results are shown in Table No 9.7. Three trials from each formulation were analyzed spectrophotometrically. The mean value and standard deviation of all the formulations were calculated. The drug content of the tablets was found between 88 to 97.47% of Chlorpheniramine. The results indicated that in all the formulations the drug content was small changes in between fore formulations. The cumulative percentage drug released by each tablet in the in vitro release studies were based on the mean content of the drug present in the respective tablet.

Table No. 3. 6: Post compression parameters of Chlorpheniramine.

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Dispersion time(Sec)	80	62	84	55	52	61	64	52	58
Wetting time(Sec)	85	82	58	48	43	45	58	54	52

Table No 3. 7: Post compression parameters of Chlorpheniramine.

Batch	Weight Variation(%) ±SD,n=20	Friability (%) ±SD,n=20	Hardness (Kg/cm^2) n=3	Thickness (mm) n=3	Drug content (%)
F1	253.33±0.28	0.88±.001	3.5	4	88
F2	247.33±0.57	0.66±0.03	3.5	4.2	93
F3	248.66±0.57	0.48±0.03	3	4	95.30

F4	251.16±0.28	0.41±0.01	3.5	4.1	97.47
F5	247.33±0.57	0.54±0.01	3	4	94
F6	243.33±0.28	0.66±0.03	4	4	95.3
F7	249.66±0.57	0.8±0.04	3.5	4.1	89
F8	250.33±0.28	0.60±0.02	4	4.1	88.5
F9	251.66±0.57	0.54±0.01	4	4	90

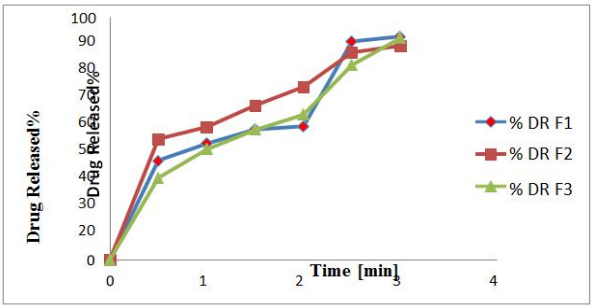

Fig 3.8: Dissolution profiles of Chlorpheniramine-Resin based comple.

Table 3.8: %DR of Chlorpheniramine-Resin based complex formulations using Superdisintegrants.

Time (min)	% Drug Released		
	F_1	F_2	F_3
0	0	0	0
0.5	40.85	49.9	33.82
1	47.81	54.2	45.64
1.5	53.69	63.3	53.63
2	54.8	71.5	59.91
2.5	89.7	85.3	80.16
3	91.96	88.4	91.47

Table 3.9: %DR of Chlorpheniramine-Resin based complex formulations using another Superdisintegrants.

Time (min)	% Drug Released		
	F_4	F_5	F_6
0	0	0	0
0.5	32.94	34.80	28.25
1.0	57.52	43.73	43.34
1.5	63.62	49.89	53.03
2.0	74.32	56.26	65.20
2.5	81.61	79.82	83.83
3.0	92.62	88.22	90.45

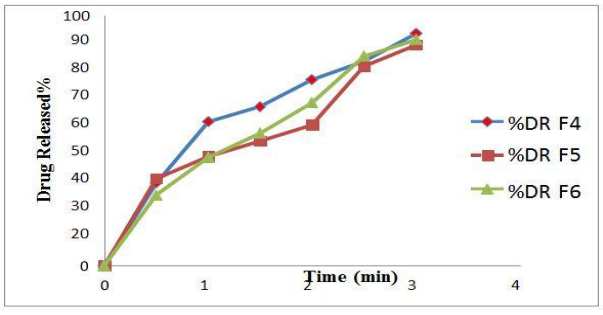

Fig 3.9: Dissolution profiles of Chlorpheniramine-Resin based complex formulations using as Superdisintegrants.

Table 3.10:%DR of Chlorpheniramine-Resin based complex formulations using Crosscarmellose as Superdisintegrants.

Time (min)	%Drug Released		
	F_7	F_8	F_9
0	0	0	0
0.5	30.25	32.85	34.23
1.0	38.74	53.18	48.54
1.5	47.02	58.64	53.75
2.0	57.75	61.78	56.82
2.5	73.41	78.92	75.83
3.0	88.41	87.72	89.17

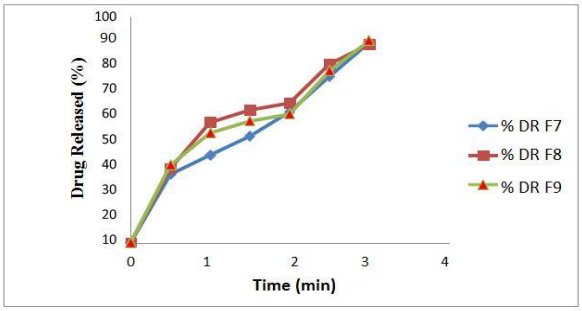

Fig 3.10: Dissolution profiles of Chlorpheniramine-Resin based complex formulations using Crosscarmellose as Superdisintegrants.

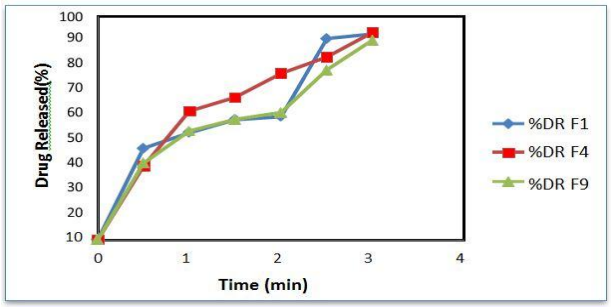

Fig 3.11: Comparison of Dissolution profiles of Chlorpheniramine-Resin based complex formulations using different superdisintegrants.

3.8. Best Formulation Model Fitting Graph

Table 3.11: In-vitro Drug Release Kinetics of F4 formulation.

Models	R^2 value	K value
Zero order	0.9071	3.5
1st order	0.9768	-0.07
Matrix	**0.9961**	**16.6**
Korsmeyer- Peppas	0.9860	14.5
Hixon- Crowel	0.9854	-0.01

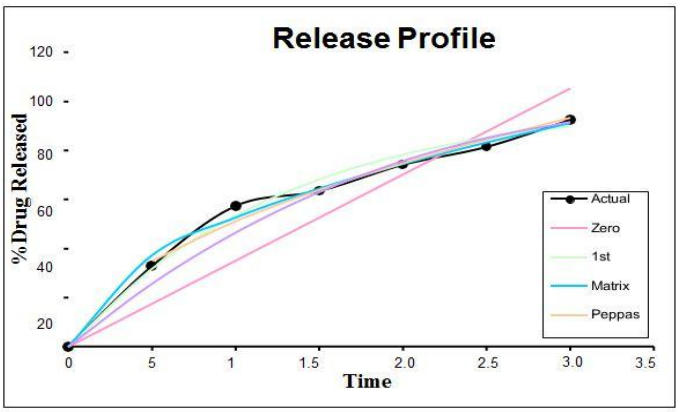

Fig 3.12: In-vitro drug released from F_4 formulation.

Table 3.12:-Stability study data of optimized batch.

Physical Parameter		Observations			
		0 day	15th day	30th day	45th day
% Drug content	Chlorpheniramine	97.49	97.35	97.33	97.32

4. CONCLUSION

The oral disintegrating tablets of Chlorpheniramine with sufficient mechanical strength, acceptable taste and smaller disintegration time were achieved employ-ing suitable superdisintegrants and other excipients at optimum concentration. Stability studies revealed that there was no significant change in drug content and dissolution profile of oral disintegrating tablets. FTIR studies revealed that there was no shift in peaks, indicating there is no interaction between Chlorpheniramine and other ingredients used. Among three superdisintegrants used, Crosspovidone showed better performance in disintegration time when compared to sodium starch glycolate and Crosscarmellose sodium. So the formulation of F4 was found to be best among all other formulations, because it has exhibited faster wetting time, good taste and faster disintegration time when compared to all other formulations. Use of cation exchange resin offers good method for preparing taste-masked substrate of Chlorpheniramine. The study was concluded that completely taste masking of Chlorpheniramine after the addition of sodium saccharin. Thus, complexation of Chlorpheniramine with Indion 204 increases acceptability and palatability of formulated rapid disintegrating tablets. Taste masking with resin and rapid disintegration of tablets formulated in this study was novel formulation. Thus, patient friendly dosage form of bitter drug Chlorpheniramine can be successfully formulated.

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