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ENHANCEMENT OF DISSOLUTION RATE OF CYPROHEPTADINE HCL BY SOLID DISPERSION METHOD

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Abstract:
The present study was to investigate the technique in enhancement of dissolution rate of Cyproheptadine HCl using Solid dispersion method. Solid dispersion method of drug with carriers is a promising approach to alter the solid sate properties of drug substances like solubility and dissolution. The objective of the present work was to prepare, formulate and evaluate the Cyproheptadine HCl by screening various carriers. Cyproheptadine HCl were prepared by direct compression method. Orodispersible tablets of Cyproheptadine HCl were formulated, optimized and evaluated. The analysis of Infrared explicitly indicated the shifting of characteristic bands of Cyproheptadine HCl the orodispersible tablets of Cyproheptadine HCl were successfully prepared by direct compression method using Crospovidone, Croscarmellose sodium as Superdisintegrant with improved disintegration time (25 sec) and dissolution rate.
These results revealed that fast dissolving tablets of poorly soluble drug Cyproheptadine HCl, showing enhanced solubility and dissolution rate and hence better patient compliance.
Keywords: *Cyproheptadine HCl, Croscarmellose sodium and orodispersible tablets.*

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1. INTRODUCTION:

The oral route of administration is considered as the most widely accepted route because of its convenience of self-administration, compactness and easy manufacturing. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patients incompliance particularly in case of pediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or traveling, especially those who have no access to water [1]. Most of the pharmaceutical dosage forms are formulated for oral administration where, direct ingestion is intended. In such cases like those with conventional dosage forms, chewing imposes issue in pediatric and the geriatric patients form in. Further psychiatric patients, hospitalized or bedridden patients with chronic diseases finds difficult to swallow solid oral dosage. It is expected that Orally disintegrating tablets (ODTs) can address such critical issues. ODTs are solid dosage form that provides the rapid disintegration or dissolution of solid to present as solution or suspension form even when placed in the mouth under limited bio-fluid. These Orally disintegrating tablets have various synonyms such as or dispersible tablets, quick disintegrating tablets, and mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and rapimelts. The excipients which are used in ODT technology are usually hydrophilic in nature that could be selected on the basis of drug's physicochemical properties, especially, hydrophillicity or hydrophobicity. If the drug is hydrophobic then dosage form is termed disintegrating tablets whereas, if the drug is hydrophilic then it is called fast dissolving tablets [2-3].

IDEAL CHARACTERISTICS OF ODTS

ODTs should depict some ideal characteristics to distinguish them from traditional conventional dosage forms. Important desirable characteristics of these dosage forms include

1. It should dissolve or disintegrate in the mouth usually within fraction of seconds. There is no requirement of water for swallowing purpose.

2. It should provide pleasant feeling in the mouth.

3. It should be compatible with taste masking agents.

4. It should be portable without fragility concern.

5. ODTs leave negligible or no residue in the mouth after oral administration.

6. ODTs exhibit low sensitivity to altered environmental conditions such as humidity and temperature.

7. ODTs allow high drug loading.

8. Adaptable and amenable to conventional processing and packaging equipment at nominal expense.

ADVANTAGES OF ODTs

1. ODT can be administer to the patients who cannot swallow tablets/cap., such as the elderly, stroke victims, bedridden patients, patients with esophageal problems & patients who refuse to swallow such as pediatric, geriatric & psychiatric patients and thus improves patient compliance. 2. It contain the certain studies which concluded increased bioavailability and proved rapid absorption of drugs through pregastric

3. Absorption of drugs from mouth, pharynx & esophagus as saliva passes down.

4. ODT is most convenient for disabled, bedridden patients, travelers and busy people, who do not always have access to water.

5. Good mouth feel property of ODT helps to change the perception of medication.

6. As bitter pill particularly in pediatric patients.

7. The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.

8. ODT opened new business opportunity like product differentiation, product promotion, patent extension and life cycle management.

9. Suitable during traveling where water may not be available.

10. No specific packaging required can be packaged in push through blisters.

11. Allow high drug loading.

12. No chewing needed.

13. Provides rapid drug delivery from dosage forms.

DISADVANTAGES OF ODTs

1. ODT is hygroscopic in nature so must be keep in dry place.

2. It is also shows the fragile, effervescence granules property.

3. ODT requires special packaging for properly stabilization & safety of stable product

4. The tablets usually have insufficient mechanical strength. Hence, careful handling is required. 5. The

tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly [4,5]

SUITABILITY OF DRUGS FOR ODTs

For developing ODT of a specific drug several factors should be kept forth while selecting drug, excipients and formulation method. These are as follows:

1. Drugs to be used for sustained action are not suitable candidate for ODT.

2. Drugs having very disagreeable taste are not suitable like clopidogrel.

3. Patients suffering from Sjogren's syndrome and those with less saliva secretion and not suitable for FDT dosage form.

4. Drugs of very short half life and requiring frequent dosing are not appropriate candidate. Patients on anticholinergic therapy are not suitable for ODT.

5. Drugs showing altered pharmacokinetic behavior if formulated in such dosage form with respect to their conventional dosage form are not suitable, like selegiline, swallowing bulky conventional dosage forms.[6]

7. METHODOLOGY:

7.1 Determination of Wavelength:

10 mg of pure drug was dissolved in 10 ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution again 1ml was taken it in to another volumetric flask and made it up to 10 ml with media (working solution - 10µg/ml). The working solution was taken for determining the wavelength.

7.2 Determination of Calibration Curve:

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution required concentrations were prepared (shown in Table) and those concentrations absorbance were found out at required wavelength.

Formulation development for solid dispersion:
Solid dispersions were prepared by solvent evaporation method. Methanol was used as solvent. Cyproheptadine HCL and Water soluble polymers such as PEG 4000 and PEG 8000 were selected as carriers. Drug and polymers were taken in 1:1 ratio stated in the formulation chart (Table 7.1). The prepared solid dispersions were passed through the sieve no 20 to get uniform sized particles. The solid dispersions were mixed with required quantities of super disintegrants, diluent, lubricant and glidant (shown in Table 7.2). The blend was evaluated for Precompression parameters.

Table 7.1: Formulation of solid dispersion showing various compositions (Ratios only)

INGREDIENTS	RATIOS					
	SD1	SD2	SD3	SD4	SD5	SD6
Drug	1	1	1	1	1	1
PEG 4000	1	3	5	-	-	-
PEG 8000	-	-	-	1	3	5

Table 7.2: Formulation of tablet by using solid dispersion

INGREDIENTS	FORMULATION CHART					
Equivalent to 25 mg	F1 (50)	F2 (100)	F3 (150)	F4 (50)	F5 (100)	F6 (150)
Crospovidone	30	60	90	-	-	-
Croscarmellose sodium	-	-	-	30	60	90
Lactose	q.s	q.s	q.s	q.s	q.s	q.s
Aerosil	5	5	5	5	5	5
SSF	15	15	15	15	15	15
Total Weight	250	250	250	250	250	250

7.7 Fourier Transform Infrared (FTIR) spectroscopy:

The formulations were subjected to FTIR studies to find out the possible interaction between the drug and the excipients during the time of preparation. FT IR analysis of the Pure drug and optimized formulation were carried out using an FT IR spectrophotometer (Bruker FT-IR - GERMANY).

8. RESULTS AND DISCUSSION

8.1 Analytical Method Development

8.1.1 Construction of calibration curve for Cyproheptadine HCl:

The λmax of phosphate buffer pH 6.8 of Cyproheptadine HCl were found to be at 227 nm. Standard graphs of Cyproheptadine HCl in phosphate buffer pH 6.8 were shown in Table 8.1. Good linearity was observed with concentration verses absorbance. Its R^2 value in phosphate buffer pH 6.8 was0.999 which were very nearer to '1' and so obeys "Beer -Lambert" law.

Table: 8.1 calibration curve of Cyproheptadine HCl in phosphate buffer pH 6.8

Concentration(µg/mL)	Absorbance
0	0
10	0.125
20	0.255
30	0.361
40	0.477
50	0.599

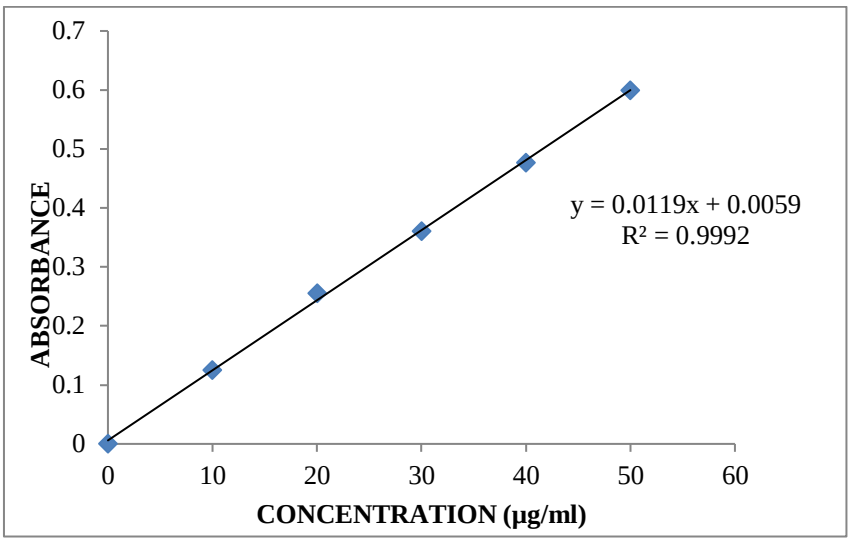

Figure: 8.1 Calibration curve of Cyproheptadine HCl in phosphate buffer pH 6.8

8.2 Micromeritic properties:

Table: 8.3 Evaluation of pre compression parameters of blend

Formulation Code	Angle of repose(θ)	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's index	Hausner ratio
F1	30°45' ± 1.118	0.373 ± 0.0077	0.406 ±0.0034	11.84±0.217	1.130±0.0027
F2	35°26'± 0.922	0.314 ± 0.0019	0.391 ±0.0082	12.41±1.392	1.145±0.0182
F3	31°17'± 1.950	0.305 ± 0.0028	0.392 ±0.0025	11.48±0.192	1.139±0.0025
F4	38°65' ± 2.506	0.347 ± 0.0022	0.380 ±0.0023	12.9 ± 0.075	1.108±0.0009
F5	24°05' ± 1.259	0.335 ± 0.0018	0.377 ±0.0031	12.01±0.262	1.113±0.0032
F6	30°19' ± 1.205	0.334 ± 0.0034	0.378 ±0.0028	14.62±0.292	1.118±0.0036

The micrometric properties of blend of Cyproheptadine HCl were characterized with respect to angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. Angle of repose was less than 38°65, Carr's index values were 9.45 ± 0.075 to 14.78±1.547 for the pre compression blend of all the batches indicating good to fair flow ability and compressibility. Hausner's ratio was less than 1.145 for all the batches indicating good flow properties.

Table: 8.2 Evaluation of pre compression parameters of blend

8.3 Post compression parameters:

The results of the weight variation, hardness, thickness, friability, and drug content of the orodispersible tablets were given in Table. All the tablets of different batches complied with the official requirement of weight variation as their weight variation passes the limits. The hardness of the tablets ranged from 5.0 to 5.9 kg/cm^2 and the friability values were less than 1% indicating that the tablets were compact and hard. The thickness of the tablets ranged between 4.89 to 5.98 mm. All the formulations satisfied the content of the drug as they contained 96.14 – 99.57 % of Cyproheptadine HCl and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found to be practically within control limits.

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%loss)	Disintegration time (sec)	Content uniformity (%)
F1	246.25	4.21	5.9	0.45	53	97.12
F2	250.01	4.61	5.6	0.58	43	99.35
F3	249.34	4.99	5.2	0.39	25	98.64
F4	248.19	4.32	5.0	0.67	61	99.14
F5	249.98	4.89	5.4	0.53	58	98.60
F6	250.15	4.98	5.9	0.41	41	99.37

Table: 8.4 Evaluation of post compression parameters of orodispersible tablets

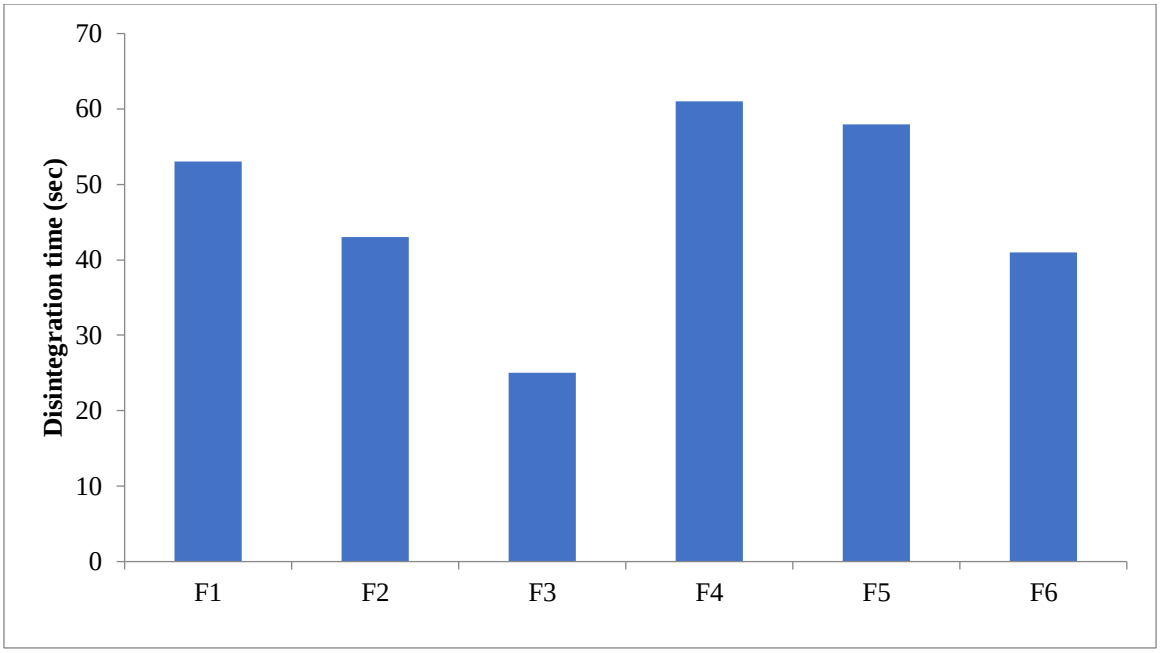

Fig: 8.3 Disintegration Time

From the above pre and post compression of orodispersible tablets of all the required evaluation tests were found to be within limit. Less disintegration time is F3 formulation i.e., 25 seconds. The disintegration time was decreased with increasing concentration of Superdisintegrant owing to sufficient swelling of tablet required for disintegration and wicking action of Superdisintegrant.

Table: 8.5 Evaluation of post compression parameters of Tablet

Formulation code	Wetting time (sec)	Water Absorption Ratio (%)
F1	21±0.59	92.12±0.19
F2	36±0.31	86.41±0.24
F3	18±0.92	96.51±0.12
F4	28±0.12	90.14±0.24
F5	43±0.26	87.62±0.36
F6	36±0.18	89.10±0.75

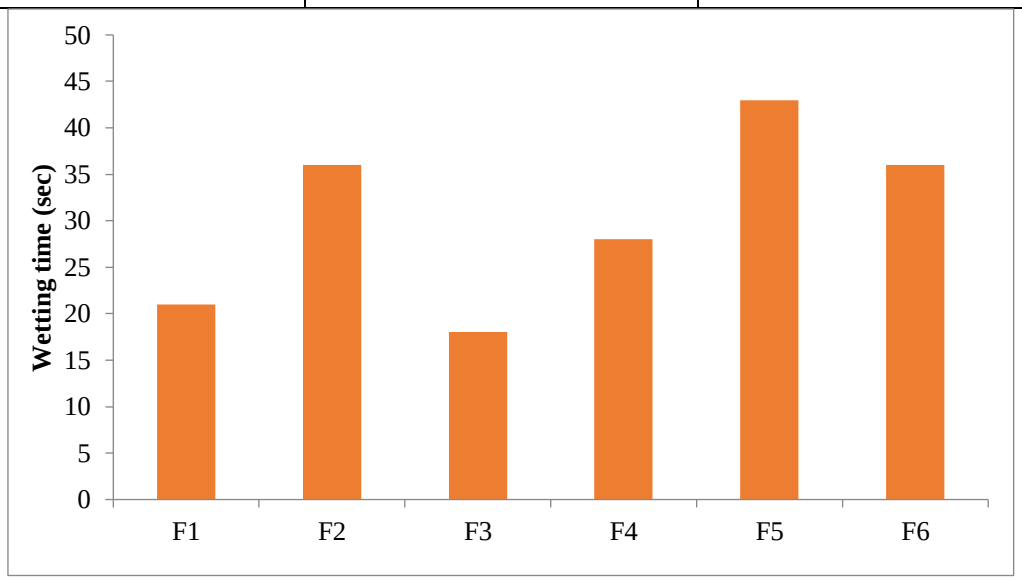

Fig 8.4: Wetting time (sec)

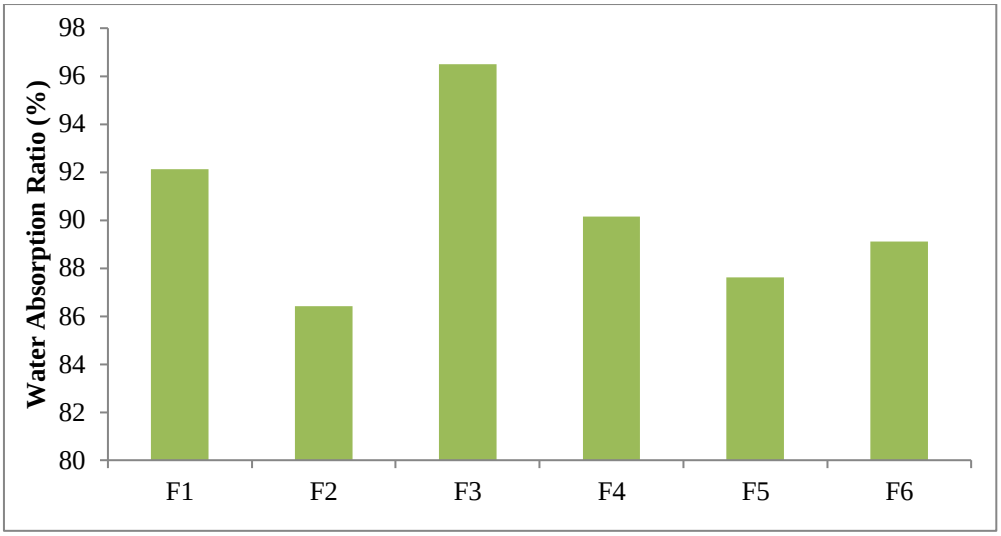

Fig 8.5: Water Absorption Ratio

8.4. *In vitro* Dissolution Studies

Table: 8.6: *In vitro* dissolution studies of formulated orodispersible tablets

Time(min)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
5	25.26	27.36	32.36	30.09	38.94	40.18
10	39.52	42.19	48.80	42.39	45.02	49.35
15	45.68	50.24	55.27	47.58	58.40	54.14
20	51.34	56.56	63.19	56.90	63.32	69.67
30	59.19	63.81	79.10	70.34	67.24	77.95
45	67.03	75.46	87.47	86.61	88.66	87.24
60	72.71	84.73	98.17	90.57	93.71	96.90

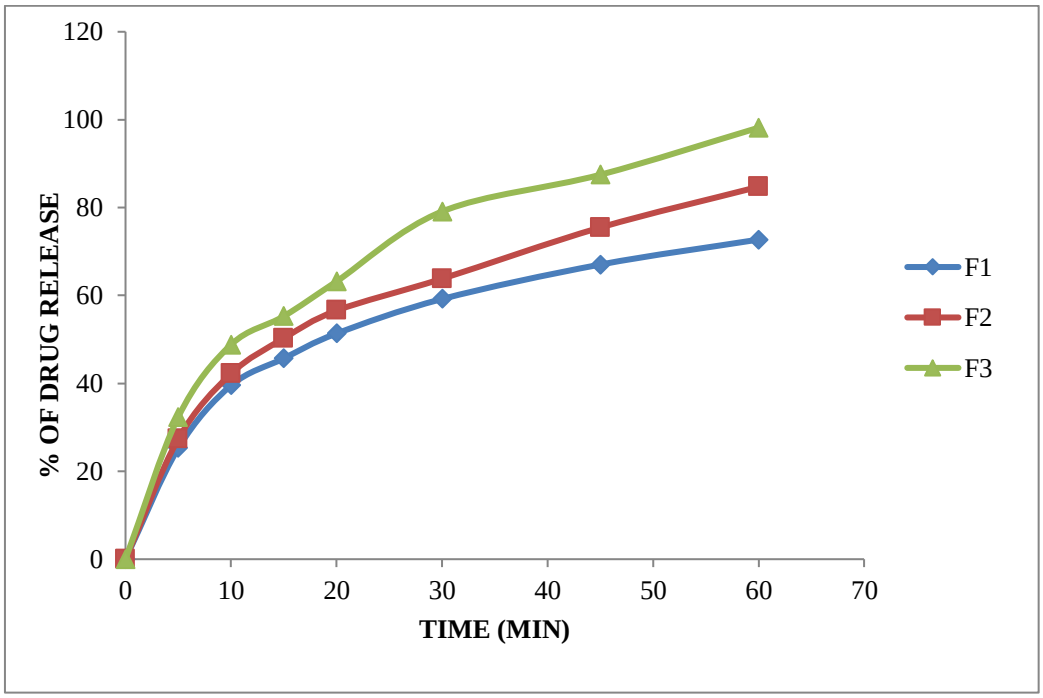

Figure: 8.6: *In vitro* dissolution studies of formulated orodispersible tablets by using Crospovidone

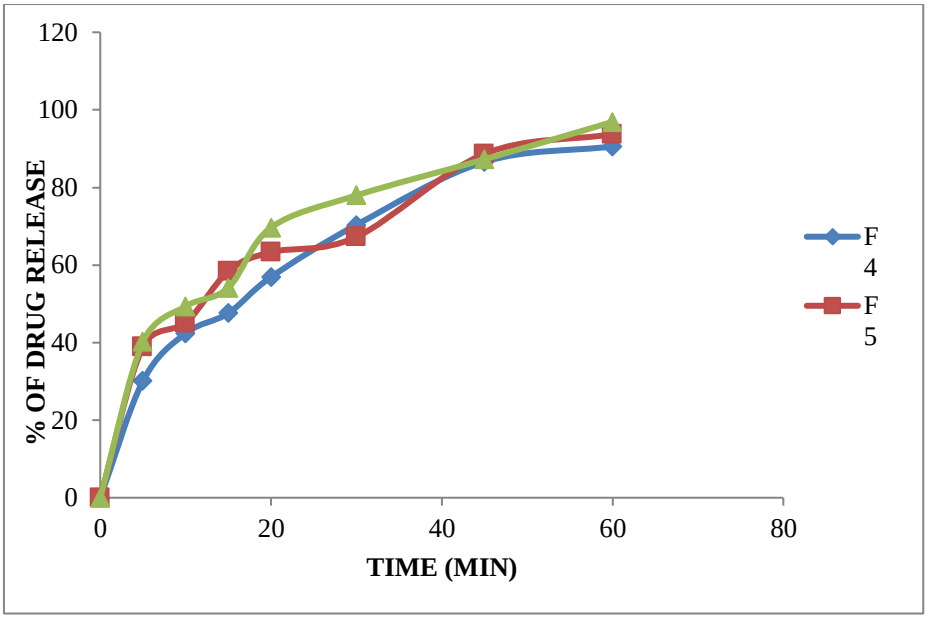

Figure 8.7: In *vitro* dissolution studies of formulated orodispersible tablets by using Croscarmellose sodium

The study was aimed to evaluate the *in vitro* dissolution behavior of developed formulations. The drug release at 60 min was considered and depicted in Figure. The F3 batch showed maximum drug release (98.17%) although F3 batch exhibited comparable drug release. This might be due to greater concentration of Superdisintegrant. Depending on the entire evaluation parameters, F3 batch was selected as optimized formulation.
From the above graphs it was revealed that F3 formulation was optimized formulation.

8.5 Drug Excipient Interactions

8.5.1 Fourier transforms infrared (FTIR) spectroscopy studies:

The pure drug and the optimised formulation (F3) were subjected to FTIR studies. The results were showed that there is no interaction between the drug and excipients.

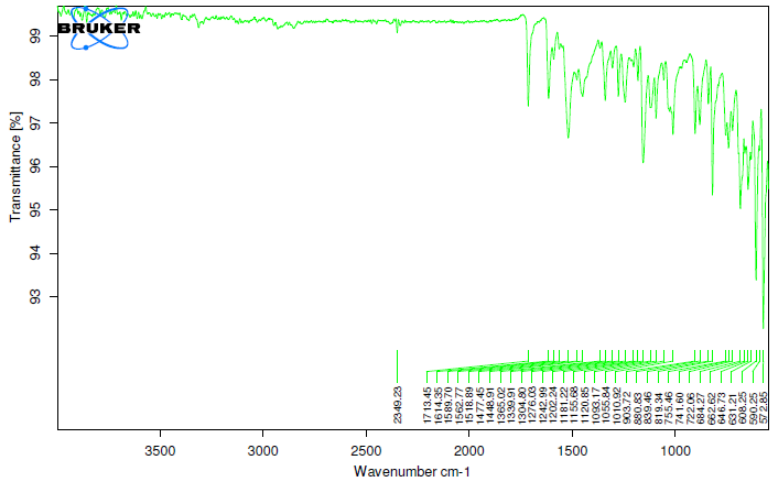

FIG 8.9: FT-IR Spectrum of Cyproheptadine HCl pure drug

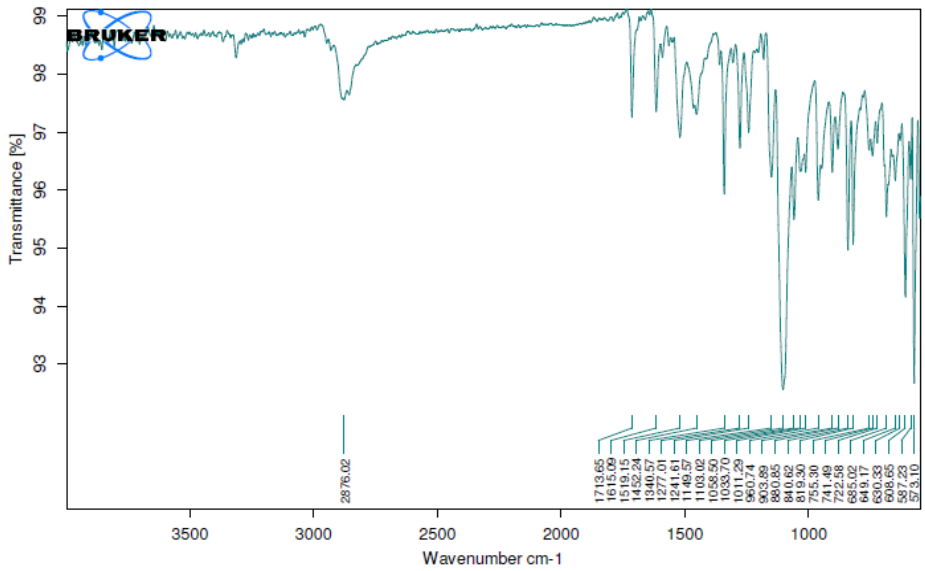

Fig: 8.10 FT-IR Spectrum of Optimised Formulation

There was no disappearance of any characteristics peak in the FTIR spectrum of drug and the polymers used. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions.

Cyproheptadine HCl is also present in the physical mixture, which indicates that there is no interaction between drug and the polymers, which confirms the stability of the drug.

9. CONCLUSION:

Cyproheptadine, sold under the brand name Periactin among others, is a first-generation antihistamine with additional anticholinergic, antiserotonergic, and local anesthetic properties.
The approach of the present study was to formulate orodispersible tablets of Cyproheptadine HCL and hence for the evaluate the release profiles of these formulations. From the results obtained in the present study, the following conclusions are drawn:

- ✓ The standard curve of Cyproheptadine HCl was obtained and good correlation was obtained with R^2 value 0f 0.999 the medium selected was pH 6.8 phosphate buffer.
- ✓ The Cyproheptadine HCl was successfully prepared using PEG 4000 and PEG 8000 were selected as carriers as guest molecule to improve the solubility and dissolution.
- ✓ The directly compressible orodispersible tablets of Cyproheptadine HCl with shorter disintegration time, low friability, and greater drug release were developed.
- ✓ F3 formulation was found promising based on the evaluation parameters. The result indicated that, selected variables showed significant effect on the responses.
- ✓ Thus Cyproheptadine HCl possessing modified physicochemical properties were obtained and successfully formulated as orodispersible tablets.

The tablets were passed all the tests. Among all the formulations F3 formulation containing, Drug and Crospovidone in the ratio of 1:3 showed good result that is 98.17 % in 60 minutes. As the concentration of superdisintegrants high the drug release was increased. Hence from the dissolution data it was evident that F3 formulation is the better formulation.

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