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FORMULATION DEVELOPMENT AND EVALUATION OF CYCLIZINE HYDROCHLORIDE ORODISPERSIBLE TABLET USING NEW GENERATION EXCIPIENT

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ABSTRACT

Current study attained the successful, cost effective formulation of orodispersible tablet of Cyclizine HCl, histamine blocker used as anti-motion sickness or anti-emetic drug, which improves the patient's compliance and also provides faster and better drug release, thereby improving the bioavailability of drug as compared to the conventional formulation effecting cost. Comparison of evaluation data of tablets prepared by using new generation excipients and by using plain crospovidone revealed that use of new generation excipient gives better results with low cost. It was concluded that orodispersible tablet of Cyclizine HCl can be successfully prepared by using Ludiflash granules and plain crospovidone. New generation excipient, Ludiflash granules, was found to be superior to that of regular excipient, plain crospovidone. Cyclizine HCl was mixed with new generation excipient (50% to 65%) and regular conventional excipient crosspovidone (2% to 5%) and then compressed into tablets by direct compression method. The prepared tablets were evaluated for various pharmaceutical characteristics such as hardness, friability, weight variation, thickness, disintegration time, drug content, and *in vitro* drug release. All the formulated tablets were within the acceptable limits. Among the tablet formulations, formula P5 containing 5.5mg of crosspovidone and 90 mg of drug along with other regular excipient showed short disintegration time of almost 34 sec and about 89.41% of drug release after 20 minutes which was much higher than those tablets prepared with 120 mg ludiflash and 50 mg of drug (L5) having disintegration time of almost 24 sec and about 97.54 % of drug release after 20 minutes.

KEYWORDS: CyclizineHCl, orodispersible, crospovidone, Ludiflash, new generation excipient.

1. INTRODUCTION

Drug delivery through oral route is the most common and preferred route of drug administration for liquid and solid dosage forms. Solid dosage forms are popular because of the stability, ease of administration, accurate dosing, self-medication, pain avoidance and most importantly the patient compliance.[1,3] Although, tablets and capsules are the most popular solid dosage forms but many patients find difficulty in swallowing of these conventional tablets. The problem can be resolved by the creation of rapidly dispersing or dissolving oral dosage forms, which do not require water to aid swallowing. The dosages forms are placed in the mouth, allowed to disperse or dissolve in the saliva, and then are swallowed in the normal way. Such a tablet disintegrates into smaller granules or melts in the mouth from a hard solid to a gel-like structure, allowing easy swallowing by patients. A new term has been introduced by the European Pharmacopoeia – "Orodispersible tablets". These are uncoated tablets which, when taken into the mouth, get easily dispersed within 3 minutes before swallowing.[4] US Food and Drug Administration Centre for Drug Evaluation and Research (CDER) defines, in the 'Orange Book', an ODT as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue" Such a tablets disintegrate rapidly in saliva, usually in seconds, without the need to take water by using suitable diluents and superdisintegrants. Drug dissolution and absorption as well as the onset of clinical effect and drug bioavailability may be significantly greater for FDTs when compared to conventional dosage forms.[5]

Compared with existing excipients, the improved physical, mechanical, and/or chemical properties of such excipients have helped in solving formulation problems such as flowability, compressibility, hygroscopicity, palatability, dissolution, disintegration, sticking, and dust generation. So to fulfil this requirement and to improve product efficiency coprocessed excipients are available like Ludiflash, Pharmaburst, F-melt, Modified chitosan with silicon dioxide. In excipients mannitol are used as diluents but now a day's modified mannitol is available which give extensive flow, compression and rapid dispersibility to the tablet e.g., Orocell, Mannogem EZ, and Pearlitol 200 SD etc.[6]

2.1 Ideal Properties of Orodispersible Tablet

1. It should not require water for oral administration yet disintegrates and dissolves in oral cavity within a few seconds.
2. It should have sufficient strength to withstand the rigors of the manufacturing process and post-manufacturing handling.
3. It should allow high drug loading.
4. It should have pleasant mouth feel.
5. It should be insensitive to environmental conditions such as humidity and temperature.
6. It should be adaptable and amenable to existing processing and packaging machineries.
7. It should be Cost-effective.
8. It should be compatible with taste masking and other excipients.
9. It should leave minimal or no residue in the mouth after oral administration.[7]

1.2 Advantages of Orodispersible Tablet

1. Ease of administration to patients who cannot swallow, such as the elderly, stroke victims and bedridden patients; patients who should not swallow, such as renal failure patients; and who refuse to swallow, such as pediatrics, geriatric and psychiatric patients.
2. Patient's compliance for disabled bedridden patients and for travelling and busy people who do not have ready access to water.
3. Good mouth feel property of mouth dissolving drug delivery system helps to change the basic view of medication drugs.
4. Convenience of administration and accurate dosing as compared to liquid formulations.
5. Benefit of liquid medication in the form of solid preparation.
6. More rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and oesophagus which may produce rapid onset of action.
7. Pre-gastric absorption can result in improved bioavailability, reduced dose and improved clinical performance by reducing side effects.
8. New business opportunities: product differentiation, line extension and lifecycle management, exclusivity of product promotion and patent-life extension.
9. Conventional processing and packaging equipments allow the manufacturing of tablets at low cost.

1.3 Limitations of Orodispersible Tablet

1. Careful handling is required because tablets usually have insufficient mechanical strength.
2. If tablets are not formulated properly they may leave unpleasant taste or grittiness in the mouth.
3. Drugs difficult to formulate into ODT with relatively larger doses.
4. Drugs with short half-life and frequent dosing and those whom require controlled or sustained release are unsuitable candidates for ODTs.

1.4 Mechanism of Action of Disintegrant

The tablet breaks to primary particles by one or more of the mechanisms listed below

a) By capillary action.
b) By swelling.
c) Because of heat of wetting.
d) Due to release of gases.
e) By enzymatic action.
f) Due to disintegrating particle/particle repulsive forces.
g) Due to deformation.

1.5 TECHNOLOGY FOR ORODISPERSIBLE TABLETS

Many techniques have been reported for the formulation of fast dissolving tablets or orodispersible tablets.[8]

A. Conventional Techniques:

- Sublimation.
- Mass Extrusion.
- Spray Drying.
- Tablet Molding.
- Lyophilization or Freeze-Drying.
- Direct Compression.
- Use of Superdisintegrants.
- Sugar Based Excipients.

B. Important Patented Technologies

- Zydis Technology.

- Orasolv Technology.
- Durasolv Technology.
- Wowtab Technology.
- Flashtab Technology.
- Advatab Technology.
- Flash Dose Technology.
- Frosta Technology.
- Shearform Technology.
- J. Ceform Technology.
- Pharmaburst Technology.
- Lyoc Technology.
- Oraquick Technology.
- Quickdis Technology.
- Dispersible Tablet Technology.
- Nanocrystal Technology.

1.6 New Generation Excipient For Orodispersible Tablet

There is a strong trend in the pharmaceutical industry toward developing Orodispersible tablets. Various new generation excipients are used for developing orodispersible dosage forms. Compared with existing excipients, the improved physical, mechanical, and/or chemical properties of such excipients have helped in solving formulation problems such as flowability, compressibility, hygroscopicity, palatability, dissolution, disintegration, sticking, and dust generation. An ideal bulk excipient for orally disintegrating dosage forms should have the following properties:

1. Disperses and dissolves in the mouth within a few seconds without leaving any residue.
2. Masks the drug's offensive taste and offers a pleasant mouth feel.
3. Enables sufficient drug loading and remains relatively unaffected by changes in humidity or temperature.

Table1.1: Types Composition and characteristics new generation excipients.

Excipient	Composition and Characteristics
Ludiflash	Coprocessed blend of 90% Mannitol, 5% Kollidon ® CL-SF(Crospovidone) 5% Kollicoat SR 30 D (polyvinyl Acetate)
F-MELT	Coprocessed blend of carbohydrates, disintegrant and inorganic ingredients. F-melt are commercially available Type C &Type M
Modified chitosan	Co precipitation of chitosan and silica,It acts as superdisintegrant and

with silicon dioxide	filler
Orocell 200 & Orocell 400	Spheronised mannitol with a binder, filler and carrier property Orocell 200 with 90% mannitol (<315µm), Orocell 400 with 90% mannitol (<500µm).
Mannogem EZ	Spray dried Mannitol, Sweet taste (50%) as sweet as sucrose
Advantose	Spray dried disaccharide carbohydrate maltose powder
Glucidex IT	Agglomerated spray dried range of maltodextrins
GalenIQ	Isomalt, a disaccharide alcohol act as Fillers and binders
Polacrilin Potassium	Potassium salt of a cross linked polymer derived from methacrylic acid and divinyl benzene
Pearlitol SD	Spheronised granulated mannitol, Sweetening 40% that of sucrose. Pearlitol® 100SD, Mean diameter: 100 µm, Pearlitol® 200SD Mean diameter 180 µm

1.7 Ludiflash

Rapid dissolution, smooth mouth feeling, and excellent compressibility are three properties of fast dispersible excipients that are extremely important No single materials meet all these requirements, so Ludiflash (BASF SE, Ludwigshafen, Germany) was developed.

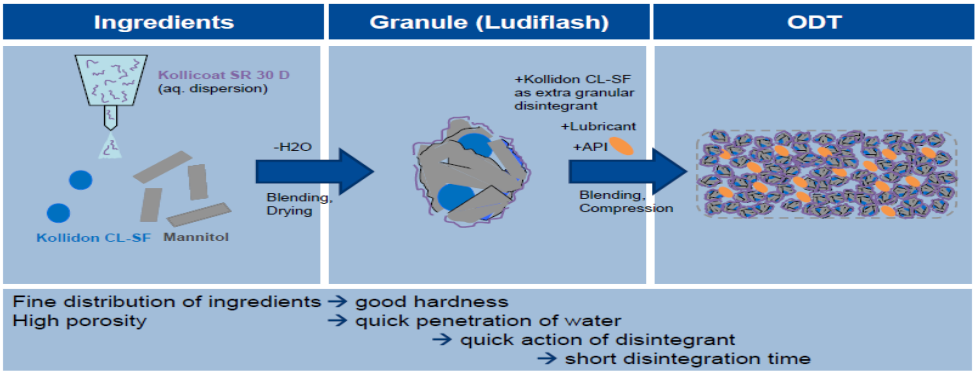

Figure 1: Ludiflash ready to use granules.

This formulated mixture of mannitol, polyvinyl acetate, and crospovidone is a highly functional material that can be compressed directly and does not need complex and time-consuming processes such as mixer granulation, fluidized bed granulation, roller compaction, or freeze drying.

Ludiflash is a formulation for fast disintegrating solid oral dosage form. It is tailored to disintegrate readily on the tongue with a pleasant creamy mouthfeel without chalky or sandy sensation. Ludiflash is suitable for direct compression manufacturing by simply blending the excipient with the active and a lubricant and is thus applicable for very cost-efficient production pathway. Ludiflash consist of D-mannitol, crosspovidone, polyvinyl acetate and some amount of povidone.

- 90% D-mannitol: Fast dissolving filler with sweet taste.
- 5% Kollidone CL-SF (crosspovidone): A superior tablet disintegrate.
- 5% Collicoat SR-30D (polyvinyl acetate): A hydrophobic binder.

1.8 General Evaluation Parameters of Orodiapersible Tablets

a) Hardness. b) Weight variation.

c) Wetting time. d) Water absorption ratio.

e) Estimation of drug content. f) Disintegration time.

g) In-vitro dispersion time. h) *In-vitro* drug release.

2. MATERIALS AND METHODS

2.1 Drug and chemicals

Cyclizine hydrochloride was obtained from Cipla, Mumbai, Ludiflash ready to use granules from BASF India Ltd, Turbhey, Mumbai. Crosspovidone, aspartame microcrystalline cellulose (MCC), mannitol Research-Lab Fine Chemical Industries, Islampur. Polo mint flavour and magnesium stearate from Research-Lab Fine Chemical Industries, Mumbai. All other materials used were of pharmaceutical grade.

2.2 Equipments

The following equipment and instruments have been used in the present studies.

Table 2.1: List of instruments/ equipments along with their models and suppliers.

Sr. No.	Name of Instrument	Manufacturing Company
1	Digital Balance	Wenser weighing balance Ltd, Pune
2	Tap Density Tester	Electrolab Tap Density Tester USP ETD-1020, Mumbai
3	Tablet punch machine	Lab press 12 station rotary machine, Ahamedabad
4	Tablet hardness tester	Hardness tester Veego Progressive instrument, Mumbai
5	Hot air Oven	Lab oven classic scientific, Pune
6	Friability tester	Electrolab friabilator USP EF-1W, Mumbai
7	Vernier Caliper	Mitutoyo Corporation, Pune.
8	UV vis. Double beam Spectrophotometer	Chemito spectroscan UV-2600, Mumbai
9	Tablet disso, tester	USP- Electro lab USP- TDT- 08L, Mumbai
10	pH meter	Hanna Instrument, Pune
11	FTIR Spectrophotometer	ALPHA Brucker ECO-ATR, Mumbai
12.	DSC	Toledo DSC Mettler star SW 9.20, Mumbai
13	Stability chamber	Remielectrotechnique limited, Mumbai

2.3 .Preformulation study of drug

2.3.1 Identification of drug

- Colour, odour and appearance:

  The drug sample was evaluated for its colour, odour and appearance.
- Melting point determination:
- Melting point of Cyclizine Hydrochloride was determined by capillary method. The capillary filled with drug powder was placed in Thiel's tube filled with liquid paraffin. The tube was heated and the melting point of drug was noted when last particle melted.[10]

- **Ultraviolet (UV) spectroscopy**

UV spectrum of 100 µg/ml solution of the drug powder in water and Phosphate buffer pH 6.8 was recorded in the range of wavelengths from 200 nm to 400 nm using UV-visible Double beam Spectrophotometer (UV-Chemito-2600).[11]

- **Fourier Transformation Infra-red (FTIR) analysis**

The infrared spectrum of Cyclizine Hydrochloride was recorded by using FTIR. Drug sample was placed on platform by SOP method and IR spectrum was recorded.[12]

- **Differential scanning calorimetry (DSC)**

Differential Scanning Calorimetry (DSC) is a thermoanalytical technique, used to demonstrate the energy phenomena produced during heating or cooling of a substance (or a mixture of substances) and to determine the changes in enthalpy and specific heat and the temperatures at which these occur. In this way, compatibility of drug with excipients were revealed by comparison in between DSC thermogram of drug and DSC thermograms of physical mixtures of drug with excipients.[13]

2.3.2 Compatibility study of drug with polymers

Cyclizine Hydrochloride was mixed with polymers and excipients in different ratios and were placed in amber coloured vials. Vials were sealed and kept in the stability chambers at various conditions of temperature and humidity for one month.

Table 2.2: Relationship between temperature and relative humidity.

Temperature	Humidity condition
25^0C	65% RH
40^0C	75% RH
50^0C	65% RH

Samples were analysed by FTIR Spectrophotometer for any deviation in IR spectra by comparing with standard spectra.

2.4. Formulation of Orodispersible Tablet By Using Ludiflash Granules

2.4. 1 Preparation of powder blend

Formulations were prepared by using different combinations of Ludiflash Granules. Mixing of drug, polymers and other ingredients was done by geometric mixing. Five formulations L1 -L5 employed for initial investigation containing different concentrations of Ludiflash granules, keeping the total tablet weight constant to 170 mg, Quantity of drug, Ludiflash granules, aspartame and mannitol were accurately weighed and mixed by gentle triturating with lubricant, along with adequate amount of flavour. Powder blend were prepared for the preparation of extended tablet by direct compression method. All the ingredients were mixed by passing through 60 # sieve. Mixing was again done by spatulation and tumbling in glass mortar and pestle, Formulations are enlisted in Table 2.3

Table 2.3: Formulation of Cyclizine Hydrochloride tablet using Ludiflash granules.

Ingredient	L1	L2	L3	L4	L5
	Weight in mg.				
Drug	50	50	50	50	50
Ludiflash granules	90	95	100	105	110
Magnesium tearate	2	2	2	2	2
Polomint	2	2	2	2	2
Aspartame	3	3	3	3	3
Mannitol	23	18	13	8	3
Total weight	170	170	170	170	170

2.4.2 Evaluation of powder blend

- **Angle of Repose**

Angle of repose has been defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose for the granules of each formulation was determined by the funnel method. The granules mass was allowed to flow out of the funnel orifice on a plane paper kept on the horizontal surface. This forms a pile of angle of granules on the paper. The angle of repose was calculated by substituting the values of the base radius and pile height in the following equation,[14]

$$\textbf{Tan } \theta = h/r \text{ Hence, } \theta = \tan^{-1} h/r$$

Where,

θ = Angle of repose, h = Height of the cone, r = Radius of the cone base

Table 2.4: Relationship between Angle of Repose (θ) and Flowability.

Angle of Repose (θ)	Flow ability
< 20	Excellent
20 – 30	Good
30 – 34	Passable
> 40	Very Poor

- **Carr's Compressibility Index**

An indirect method of measuring powder flow from bulk densities was developed by Carr's. The percentage compressibility of a powder was a direct measure of the potential powder arch or bridge strength and stability. Carr's index of each formulation was calculated according to equation given below.[15]

$$\% \text{ Compressibility} = \frac{Df - Do}{D_f} \times 100$$

Where,

D_F = Fluff or Poured bulk or bulk density.

D_o = Tapped or Consolidated bulk density.

Carr's Compressibility Index (%) = [(TBD-LBD) X 100] / TBD

Table 2.5: Relationships between % compressibility and flowability.

% Compressibility	Flowability
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
23 – 35	Poor
33 – 38	Very Poor
> 40	Extremely Poor

- **Bulk Density and Tapped Density**

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 20 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 100 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals. The tapping was continued until No further change in volume was noted. LBD and TBD were calculated using the following formulas.[15]

- **Hausners ratio**

Hausner"s ratio = TBD/LBD

LBD = Weight of the powder/ Volume of the packing

TBD = Weight of the powder/ Tapped volume of the packing

Table 2.6: Type of flow and Hausner ratio.

Hausner"s ratio	Type of flow
Less than 1.25	Good Flow
1.25 – 1.5	Moderate
More than 1.5	Poor Flow

2.5 Compression of Tablet

Tablets were prepared by direct compression method using rotary press using flat faced punches of 8mm diameter. Compression force for all the Tablets was adjusted to get Tablets having hardness between 4- 6 kg/cm^2.

2.5.1 Evaluation of Orodispersible tablets

The tablets were evaluated for following test parameters.

a) Physical Evaluation of tablets
- Weight variation test.
- Friability.
- Hardness.
- Dimension.

b) *In-vitro* disintegration studies.

c) Uniformity of content.

d) Wetting time.

e) Water absorption ratio.

f) Dissolution Studies.

g) Study effect of temperature and humidity.

h) Taste evaluation.

a) Physical Evaluation of tablets

Weight variation: It was performed as per the method given in the Indian pharmacopoeia. Twenty tablets were selected randomly from each batch, weighed individually and the average weight and percent weight variation were calculated. The batch passes the test for

weight variation if not more than two of the individual tablet weight deviate from the average weight.[16]

Table 2.7: Weight variation test.

Sr. No	Average wt. of tablet		% of Deviation
	I.P.	U.S.P.	
1	80 mg or less	130 or less	± 10
2	> 80 to < 250 mg	> 130 to < 324 mg	±7.5
3	more than 250	more than 324	±5

- **Friability**

Friability is the measure of tablet strength. Roche Friabilator was used for testing the friability using the following procedure. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of preweighed 20 tablets was placed in Roche friabilator which was then operated for 100 revolutions i.e. 4 minutes. The tablets were then dusted and reweighed. A loss of less than 1 % in weight in generally considered acceptable. Percent friability (% F) was calculated from this following equation.[17]

$$\% \text{ Friability} = \frac{\text{Initial weight-final weight}}{\text{Initial weight}} \times 100$$

- **Hardness**

Hardness was measured using Monsanto tester or Pfizer hardness tester. Measure the pressure required to break diametrically placed matrix tablet, by a coiled spring. For each batch five Tablets were tested.[17]

- **Thickness**

The thickness of the tablets was determined using a Vernier Caliper. Twenty tablets from each batch were used and mean ± SD was calculated.[16]

- **Dimension**

The thickness and diameter of the tablets was determined using a micrometer screw gauge. Three tablets from each batch were used and average values were calculated.

b) *In-vitro* Disintegration Studies

The disintegration time for fast disintegrating tablet was measured using the conventional test for tablets as described in the Pharmacopoeia. Tablets were placed in the disintegration tubes in buffer pH 6.8 medium and time required for complete disintegration without leaving any residues on the screen was recorded as disintegration time.[18]

c) Uniformity of Content

Twenty tablets were accurately weighed and finely powdered. A quantity equivalent to 20 mg of Cyclizine HCl was transferred to a 200 ml volumetric flask. To it, 50 ml of methanol was added and shaken to dissolve drug. Resulting solution is then diluted to volume with methanol and filtered. 20 ml of filtrate diluted to 100 ml with methanol and mixed. Absorbance of the resulting solution at maximum at about 225 nm was measured UV spectroscopically.[19]

d) Wetting Time

Wetting time corresponds to the time taken for the tablet to disintegrate when placed statically on the tongue. Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. A piece of tissue paper double folded double was placed in a petridish (internal diameter is 10 cm) containing 10 ml of water. The tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds. The method was slightly modified by maintaining water at 37^0 C.[20]

e) Water Absorption Ratio[4]

A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of water. A tablet was put on the tissue paper and allowed to wet completely. The wetted tablet was then weighed. Water absorption ratio R was determined using following equation.[21]

$$\frac{Wa - Wb}{Wb} \times 100$$

Wa = Weight of the tablet after wetting.

Wb = Weight of the tablet before wetting.

f) Dissolution Studies

Dissolution studies were carried out for optimized formulation employing USP XXIII paddle method (Apparatus 2) using pH 6.8 phosphate buffer, as the dissolution medium (900 ml) at

50 rpm and 37 ± 0.5ºC. An aliquot of sample was periodically withdrawn at suitable time intervals and volume replaced with equivalent amounts of plain dissolution medium. The samples were analyzed spectrophotometrically at 225 nm. Samples of 5 ml, was withdrawn at regular intervals. The volume withdrawn was replaced by fresh volume of dissolution medium to maintain constant volume of medium. The filtered samples were analyzed spectrophotometrically at 225 nm.[22]

g) Stability study (Effect of temperature and humidity)

Effect of temperature and humidity was studied by analyzing the optimized batch kept in environmental stability chamber maintained at 40 ºC ± 2 ºC/75% ± 5%RH for 15, 30, 45 and 60 days. The tablets were found to be stable and showed no changes in appearance, hardness, disintegration time and drug content.[23]

h) Taste evaluation

The taste of tablet from optimized batch was checked by panel method. For this purpose 8 human volunteers in the age group of 20 to 25 years were selected. The study protocol was explained and written consent was obtained from volunteers. Their mouth was thoroughly rinsed with purified water then tablet was placed on tongue and taste evaluated after 30 seconds. The members of the panel were asked to gargle and wait for 20 minutes before another sample was given to them for tasting. The taste given by each volunteer was recorded against pure drug as a standard, using a numerical scale as a bitterness level (3 = very strong biter; 2 = bitter; 1 = slightly bitter; 0 = tasteless). Mean of all the scores given by volunteers for optimized batch L5 were taken into consideration for taste evaluation purpose.[24]

2.5. Formulation of Orodiapersible Tablet By Using regular excipient

2.5.1 Preparation of powder blend

Formulations were prepared by using different combinations of regular excipient.

On trial and error basis 10 to 12 batches were prepared by using regular excipient and evaluated. There was no much difference in evaluation results after batch P5, when quantity of superdisintegrant / crospovidone increased more than 5.5 mg. So, the range of superdisintegrant and excipient from batch P1 to P5 were selected. Mixing of drug, polymers and other ingredients was done by geometric mixing. Five formulations P1-P5 employed for initial investigation containing different concentrations of regular excipient, keeping the total tablet weight constant to 170 mg, Formulations are enlisted in Table2.9

Table 2.8: Formulation of Cyclizine Hydrochloride tablet using Ludiflash granules.

Ingredient	P1	P2	P3	P4	P5
	Weight in mg.				
Drug	50	50	50	50	50
Crospovidone	3.5	4	4.5	5	5.5
MCC	15	15	15	15	15
Magnesium tearate	2	2	2	2	2
Polomint	2	2	2	2	2
Aspartame	3	3	3	3	3
Mannitol	94.5	94	93.5	93	92.5
Total	170	170	170	170	170

Compression and evaluation of Tablets are done exactly same way as had been done with new generation excipients.

2.5.3 Stability studies

Stability of a pharmaceutical preparation can be defined as "the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specifications throughout its shelf life."

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted. The International Conference on Harmonization (ICH) Guidelines titled "stability testing of New Drug substance and products" (QIA) describes the stability test requirements for drug registration applications in the European Union, Japan and the United States of America. ICH specifies the length of study and storage conditions.

Long-Term Testing: 250 C ± 20 C / 60% RH ± 5% for 12 Months.
Accelerated Testing: 400 C ± 20 C / 75% RH ± 5% for 6 Months.

The selected formulations were packed in amber-colored bottles, which were tightly plugged with cotton and capped. They were then stored at 40^0 C / 75% RH for 3 months and evaluated for their physical appearance, drug content and drug excipients compatibility at specified intervals of time.[23]

3. RESULTS AND DISCUSSION

The aim of the present work was to formulate and evaluate orodiapersible tablets of Cyclizine Hydrochloride by direct compression for quick onset of action. Cyclizine Hydrochloride is white, odourless fine powder having bitter taste. Melting point was found in the range of 254-258oC. The calibration curve of Cyclizine HCl was prepared in Phosphate buffer (pH 6.8). Cyclizine HCl showed maximum absorption at wavelength 225.6 nm. The straight line obtained in the Phosphate buffer (pH 6.8) had a regression coefficient of 0.9996. Linearity was found in the concentration range of 5–30 µg/ml. Cyclizine HCl showed maximum absorption at wavelength 228 nm in water. The straight line obtained in the distilled water had a regression coefficient of 0.999. Linearity was found in the concentration range of 5–30 µg/ml. IR spectra of drug in combination with excipients in 1:1 ratio was studied. The IR spectrum suggest that there is no interaction between the drug and the Excipients. DSC is useful in the investigation of solid-state interactions. The DSC analysis of pure Cyclizine Hydrochloride showed a sharp endothermic peak at 258.420C corresponding to its melting point. Physical mixture of drug and Ludiflash granules showed peak at 260.00C while physical mixture of drug – crospovidone – mannitol –MCC showed peak at 255.220C. The DSC analysis of physical mixture of the drug and excipients revealed negligible change in the melting point of Cyclizine Hydrochloride. So, the drug is compatible with the excipients. The prepared powder mixtures were evaluated for the blend property like bulk density, tapped density, Carr's index, angle of repose and Hausner's ratio. Results obtained are given in Table 3.1.

Table 3.1: Physical parameters of the powder blend prepared by using New generation excipient.

Parameters Batches	Bulk density (g/ml)	Tapped density (g/ml)	Carr's Index (%)	Hausner's ratio	Angle of repose (˚)
L1	0.472±0.004	0.57±0.005	18.49±0.54	1.20±0.006	29.22±0.40
L2	0.463±0.001	0.54±0.001	15.43±2.29	1.17±0.03	31.21±0.7
L3	0.471±0.001	0.55±0.005	15.32±0.87	1.18±0.012	28.99±0.33
L4	0.460±0.008	0.54±0.017	15.41±0.56	1.17±0.01	28.21±0.42
L5	0.434±0.003	0.52±0.01	16.45±1.51	1.18±0.02	28.04±0.33

(n=6)

All these results indicated that, the powder blend showed good flow properties into the die cavity and compressibility properties and complies with the acceptable limits.

The physical evaluation parameters such as weight variation, hardness, friability and thickness were carried out for the tablets containing new generation excipient. All these results were tabulated in Table 3.2

Table 3.2: Evaluation results for Cyclizine HCl ODT's prepared by using New generation excipient.

Parameters Batches	Weight variation	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	Disintegration time (sec)	Wetting time (sec)	Water absorbance ratio (sec)	Uniformity of content
L1	170.23 ± 0.73	4.43± 0.01	3.8 ± 0.30	0.559 ± 0.09	41.22 ± 0.35	37.88 ± 0.26	32.32 ± 0.77	99.21 ± 0.56
L2	170.26 ± 0.41	4.42 ± 0.03	4.0 ± 0.23	0.383 ± 0.11	37.09 ± 0.23	34.14 ± 0.39	34.21± 0.57	100.09 ± 0.19
L3	170.50 ± 0.29	4.43 ± 0.02	4.2 ± 0.11	0.453 ± 0.06	34.15 ± 0.32	31.35 ± 0.36	35.93 ± 0.07	98.36 ± 0.29
L4	170.34 ± 0.21	4.40 ± 0.04	4.0 ± 0.2	0.633 ± 0.042	29.30 ± 0.47	25.21 ± 0.70	37.41 ± 0.51	97.52 ± 0.17
L5	170.22 ± 0.45	4.41 ± 0.02	3.9 ± 0.30	0.443 ± 0.048	24.82 ± 0.47	21.08 ± 0.30	39.75 ± 0.53	100.21 ± 0.40

(n = 6)

The results revealed that there were variations in weight, thickness, % friability and the hardness of all the tablets were found to be well within the range limit. Other parameters like disintegration time, wetting time and drug content were also determined. The results showed drug content in the range of 97.52% to 100.21% which was within the acceptable Pharmacopoeial limits. *In-vitro* drug dissolution studies were carried out in phosphate buffer pH 6.8 using USP dissolution test apparatus II. Temperature was set to 37.70C ± 0.50C and the samples were withdrawn at 0, 5, 10, 15, 20 and min.. The results are tabulated in Table 3.3.

Table 3.3: Percentage cumulative drug release of L1 to L5 batches.

Time (in min)	Batch L1*	Batch L2*	Batch L3*	Batch L4*	Batch L5*
-	00.00	00.00	00.00	00.00	00.00
5	44.48 ± 1.37	47.34 ± 1.91	51.78 ± 1.45	54.38 ± 1.59	57.54 ± 1.25
10	58.12 ± 1.92	61.82 ± 1.01	64.43 ± 1.15	67.38 ± 1.08	70.70 ± 1.49
15	72.24 ± 1.32	75.74 ± 0.97	76.56 ± 1.63	82.55 ± 1.59	82.99 ± 1.24
20	84.32 ± 1.17	87.54 ± 1.18	90.29 ± 1.21	93.25 ± 1.17	97.54 ± 1.15

(n=6)

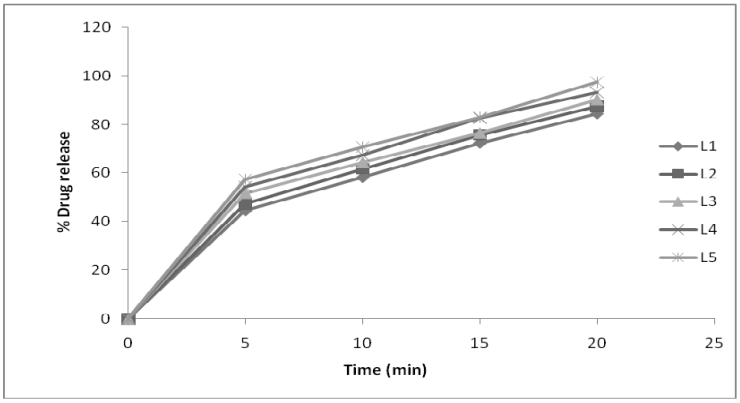

Figure 3.1: Graphical presentation of comparative dissolution profile of all formulationsbatch L1 to L5.

The physical evaluation parameters such as weight variation, hardness, friability and thickness were carried out for the tablets containing regular excipient. The prepared powder mixtures were evaluated for the blend property like bulk density, tapped density, Carr's index, angle of repose and Hausner's ratio. All these results obtained were tabulated in table 3.4.

Table 3.4: Physical parameters of the powder blend prepared by using conventional excipient.

Parameters Batches	Bulk density (g/ml)	Tapped density (g/ml)	Carr's Index (%)	Hausner's ratio	Angle of repose (˚)
P1	0.445±0.003	0.545±0.004	18.38±0.79	1..22±0.01	32.77±0.26
P2	0.436±0.003	0.531±0.002	17.92±0.65	1.21±0.05	33.01±0.13
P3	0.421±0.006	0.529±0.001	20.38±1.36	1.25±0.02	31.69±0.21
P4	0.432±0.004	0.531±0.002	18.67±1.07	1.23±0.01	31.48±0.24
P5	0.417±0.002	0.499±0.004	16.48±0.40	1.19±0.005	29.69±0.18

(n = 6)

The powder mixtures for all five formulations were evaluated for all parameters. All these results indicated that, the powder blend showed good flow properties, compressibility properties and complies with the acceptable limits. The physical evaluation parameters such as weight variation, hardness, friability and thickness were carried out for the tablets containing conventional excipient. All these results were tabulated in table 3.5

Table 3.5: Evaluation results for Cyclizine HCl ODT's prepared by using Plain crospovidone.

Parameters Batches	Weight variation	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	Disintegration time (sec)	Wetting time (sec)	Water absorbance ratio (sec)	Uniformity of content
P1	170.35 ± 0.35	4.43 ± 0.02	3.96 ± 0.20	0.543 ± 0.09	52.82 ± 0.66	48.74 ± 0.54	29.48 ± 0.14	97.53 ± 0.36
P2	170.43 ± 0.79	4.4 ± 0.02	4.0 ± 0.15	0.466 ± 0.11	47.45 ± 0.36	41.99 ± 0.72	31.56 ± 0.09	96.36 ± 0.11
P3	170.22 ± 0.53	4.43 ± 0.01	3.7 ± 0.11	0.61 ± 0.04	42.85 ± 0.24	38.88 ± 0.28	33.41 ± 0.25	99.42 ± 0.25
P4	170.25 ± 0.69	4.39 ± 0.01	4.0 ± 0.20	0.313 ± 0.04	38.04 ± 0.16	34.84 ± 0.11	35.27 ± 0.21	98.27 ± 0.17
P5	170.53 ± 0.42	4.42 ± 0.03	3.8 ± 0.25	0.583 ± 0.17	34.23 ± 0.45	30.75 ± 0.79	37.13 ± 0.08	99.61 ± 0.25

(n=6)

Other parameters like disintegration time, wetting time and drug content were also determined. The results showed they were well within the acceptable Pharmacopoeial limits. *In-vitro* drug dissolution studies were carried out in phosphate buffer pH 6.8 using USP dissolution test apparatus II. Temperature was set to 37.70C ± 0.50C and the samples were withdrawn at 0, 5, 10, 15, 20 and min. The results are tabulated in Table 3.6.

Table 3.6: Percentage cumulative drug release of P1 to P5 batches.

Time (in min)	Batch P1*	Batch P2*	Batch P3*	Batch P4*	Batch P5*
-	00.00	00.00	00.00	00.00	00.00
5	38.67 ± 1.39	43.01 ± 1.54	46.98 ± 0.95	46.68 ± 1.32	50.81 ± 1.32
10	58.43 ± 1.08	56.17 ± 0.88	58.99± 1.18	60.59 ± 1.28	63.72± 1.41
15	65.80 ± 1.29	68.21± 1.54	69.57± 1.27	73.02 ± 1.15	75.81± 0.85
20	77.86 ± 1.24	80.71 ± 1.05	83.42± 1.23	86.84± 0.87	89.41 ± 1.89

(n=3)

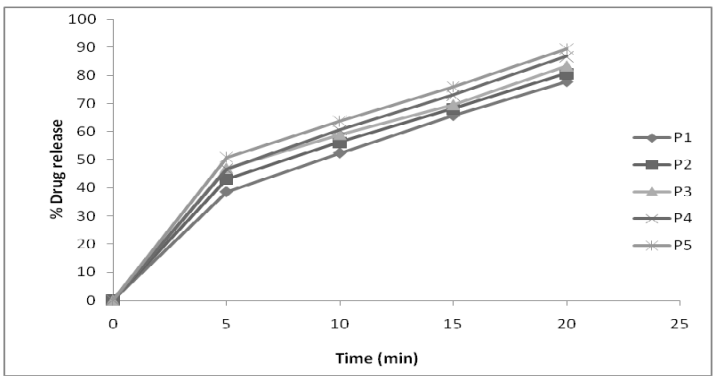

Figure 3.2: Graphical presentation of comparative dissolution profile of all formulations batch P1 to P5.

The dissolution kinetics of optimized batch was applied to various dissolution models such as Zero order, First order, Higuchi and peppas. The cumulative drug release values of optimized batch gives the highest R2 value and least slope value in Higuchi model. Thus, Higuchi model fits best for the dissolution data of the optimized batch as it showed the highest value for R2. Higuchi derived the drug release is proportional to the square root of time. Swelling or dissolution of the polymer carrier is negligible and the diffusivity of the drug is constant. Higuchi equation:

$$f_t = Q = A\sqrt{D(2C - C_s)\,C_s\,t}$$

where Q = the amount of drug released in time t per unit area A,

C = drug initial concentration,

Cs = drug solubility in the matrix media,

D = diffusivity of the drug molecules (diffusion) in the matrix substance.

Table 3.7: R2 values and for applied values of optimized batch L5 & P5.

Sr. No.	Models	R2 values for batch L5	R2 values for batch P5
1	Zero order	0.861	0.878
2	First order	0.599	0.609
3	Peppas model	0.861	0.878
4	Higuchi	0.991	0.988

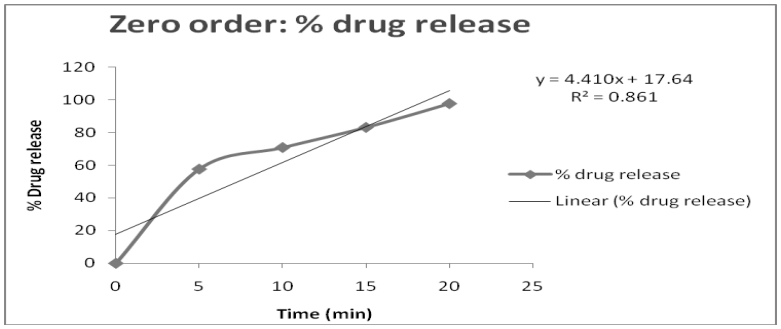

Figure 3.3: Zero order kinetics of L5 batch.

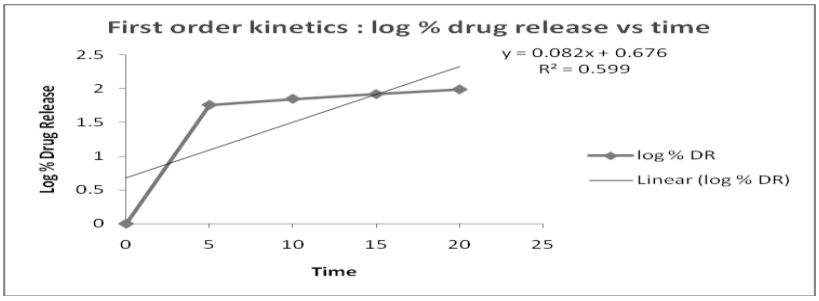

Figure 3.4: First order kinetics for optimized batch L5.

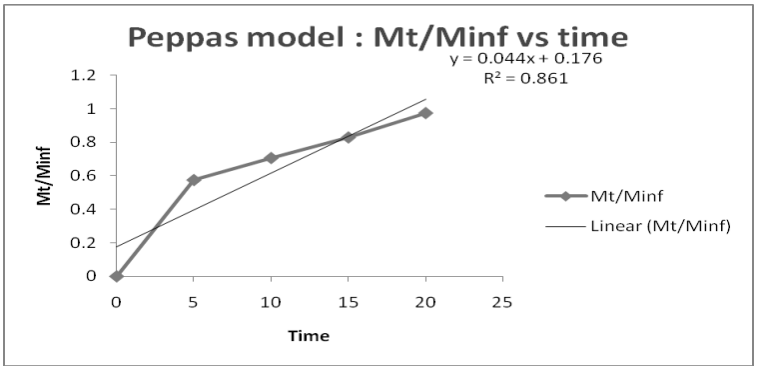

Figure 3.5: Peppas model for optimized batch L5.

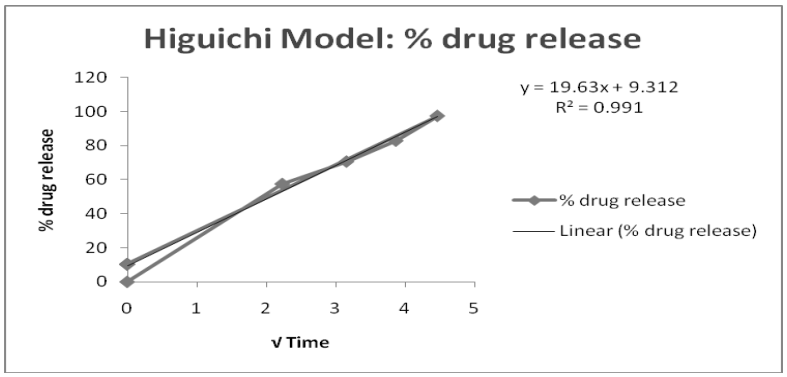

Figure 3.6: Higuchi model for optimized batch L5.

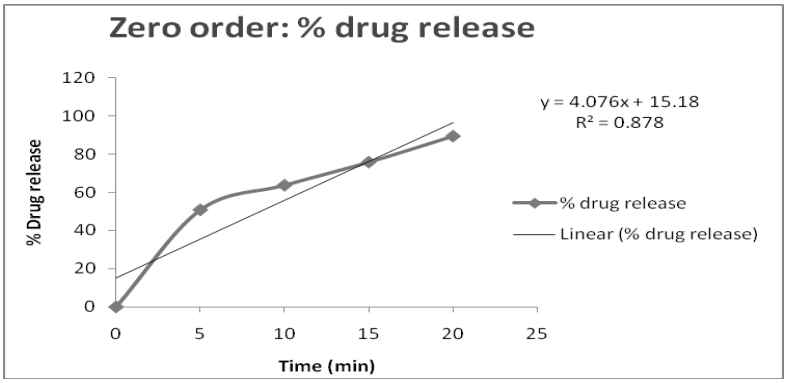

Figure 3.7: Zero order kinetics of P5 batch.

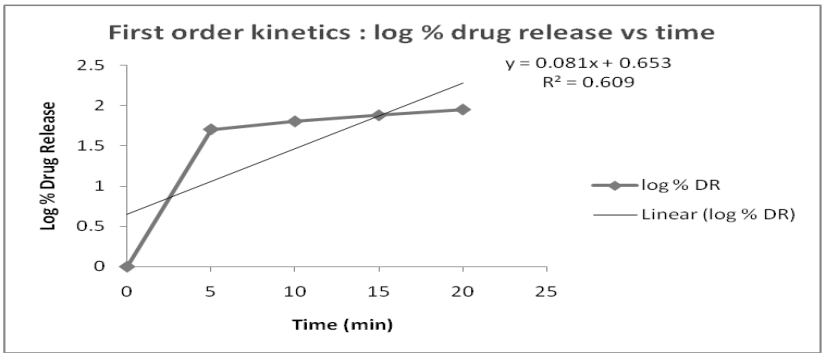

Figure 3.8: First kinetics of P2 batch.

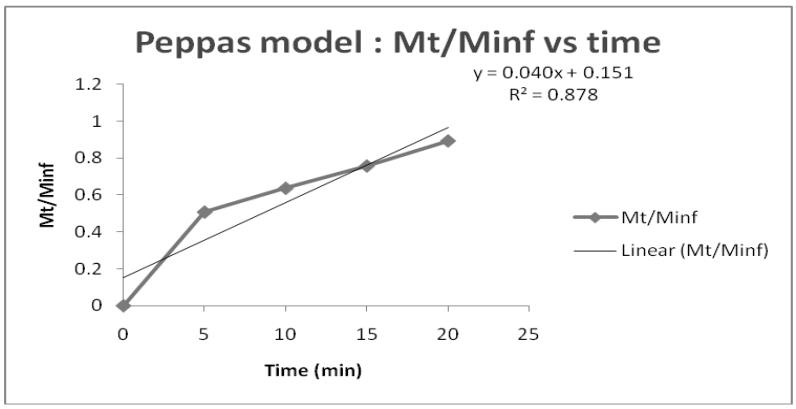

Figure 3.9: Peppas model kinetics of P5 batch.

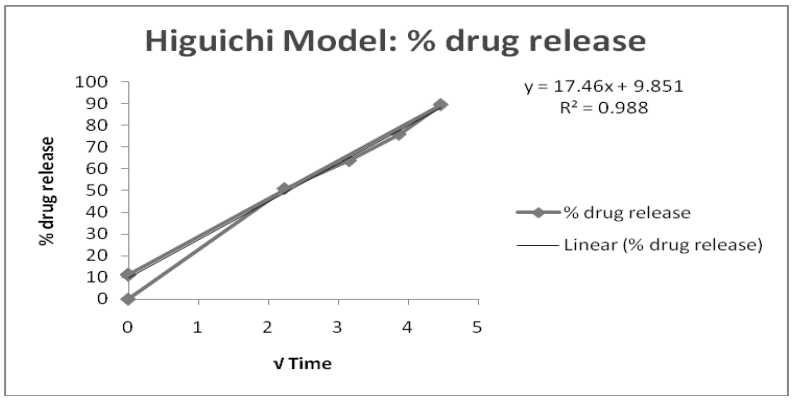

Figure 3.10: Higuchi model of P5 batch.

The effect of temperature and humidity was determined at 40ºC ± 2ºC / 75% ± 5% RH maintained in environmental 1 stability chamber for two month. Evaluation was done after 15, 30, 45 and 60 days. From the results it was concluded that there was no significant physical and chemical changes in both the optimized batch after two months.

The results of taste evaluation done by panel method are given in Table 3.8 and taste evaluation scale is given below Table 3.8. Taste evaluation study of optimized batches by panel method revealed that the bitter taste of drug was masked well by using the aspartame as sweetener and polomint as flavour. Data for batch L5, 62% volunteers were given response as the taste of tablet was tasteless and 25% volunteers were given response as slightly bitter or acceptable. While for batch, P5 50% volunteers were given response as the taste of tablet was tasteless and 37.5% volunteers were given response as slightly bitter or non-acceptable.

Table 3.8 Taste evaluation of optimized batch L5 and P5.

Volunteers	Response for Batch L5	Response for Batch P5
V1	1	2
V2	0	1
V3	2	0
V4	0	0
V5	0	1
V6	0	0
V7	1	0
V8	0	1

Scale for taste evaluation:

0 = tasteless, 1 = slightly bitter, 2 = bitter, 3 = very strong biter.

3 DISCUSSION

In the present study total ten formulations were prepared using direct compression technique, each containing 50 mg of Cyclizine HCl. All the batches L1-L5 were prepared by using 90 to 120 mg of Ludiflash granules and P1-P5 were prepared by using 4.5 to 5.5 mg of crospovidone. Other than superdisintegrant and quantity sufficient dilunt mannitol, remaining excipients are similar in both type of tablets 2 mg of magnesium stearate, 2 mg of polomint and 3 mg of aspartame. The total weight of tablet was kept constant that is 170 mg. Aspartame and polomint was added to impart sweetness and flavour to the tablet.

Physical mixtures of Cyclizine HCl and exipients were examined for drug polymer interaction by FTIR spectroscopy and DSC thermal study. The IR spectrum did not show presence of any additional peaks for new functional groups indicating no chemical interaction between drug and the used disintegrants. While thermogram of physical mixture (drug and excipient) show similar peak as thermograms of plain drug so it indicates that no interactions in excipients and drug. Formulations were evaluated for their physicochemical properties. Powder blend were evaluated for various parameters like angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. The results indicated that the powder blend had good flow properties. Directly compressed tablets were analyzed for the uniformity of drug content, thickness, hardness, weight variation, friability, wetting time, *in-vitro* disintegration time and *in-vitro* dissolution testing. From these evaluations, it was observed that the tablets complies with the Pharmacopoeial acceptable limits.

By comparing evaluation data obtained from all the optimized formulations, it was found that the ODT prepared using Ludiflash granules (batch L5) gives better results than ODT

prepared by using regular excipient (batch P5). Drug release of batch L5 is 97.54 % better than batch P5 which is 89.45 within 20 minutes. Disintegration time of tablet from batch L5 is 24.82 seconds which is better than the D.T. of P5 that is 34.23 seconds.

The studies for the effect of temperature and humidity of the optimized batch at 40ºC ± 2ºC / 75% ± 5% RH was carried out for two month which revealed that there was no significant change in the physical parameters such as appearance, hardness and disintegration time nor in the drug content for both batches.

5 CONCLUSION

The main aim of present work was to develop formulation of orodispersible, the orally disintegrating tablet of Cyclizine HCl with low cost as well as with better results by using new generation excipient. Cyclizine HCl is histamine blocker used as anti-motion sickness or anti-emetic drug. It is white crystalline powder, bitter in taste and practically soluble in water. Orodispersible tablet of Cyclizine HCl was prepared by using superdisintegrants due its low oral bioavailability. Thus, ODT's were prepared by two ways one was by using new generation excipients and another was by using regular excipient. Total ten formulations were prepared each containing 50 mg of Cyclizine HCl. All the batches L1-L5 were prepared by using 90 to 120 mg of Ludiflash granules and P1-P5 were prepared by using 4.5 to 5.5 mg of crospovidone. From the post-compression parameters, L5 was found to be the best formulation with a drug release of 97.54 % within 20 minutes. Thus, in nutshell the ODTs are found to be have a promising tool in effective drug delivery with greater bioavailability, patient compliance, cost effective and improved stability.

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