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INFLUENCE OF SUPER DISINTEGRATING AGENTS ON *IN-VITRO* RELEASE OF CHLORPHENIRAMINE MALEATE SUBLINGUAL TABLETS

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ABSTRACT

The term Sublingual referred as "under the tongue". In this route of administration the drug permeates through the tissues under tongue into the blood stream. The Sublingual route of administration play important role in avoiding first pass metabolism. The main objective is to improve bioavailability, rapid onset of action and solubility of the drug increased and protein binding is avoided. Sublingual tablets of Chlorpheniramine maleate formulated by using direct compression method. Nine formulations were formulated using Rotary compression machine to explain the effects of the sodium starch glycolate, Cross Povidone, Cross Carmellose Sodium on disintegration time, *In-vitro* release of the drug and % drug release. In addition the tablets are also evaluated for the weight variation, thickness, diameter, hardness, wetting time, water absorbivity ratio, FTIR, DSC and drug release studies. The Batch F8 is having the higher dissolution and disintegration rate for optimized sublingual Chlorpheniramine maleate tablet, for rapid onset of action for management of tussiveness. The F8 Formulation is having less wetting time and high water absorption ratio.

KEYWORDS: Chlorpheniramine maleate, Sublingual Tablets, Anti-Tussive, Anti-Histaminic.

INTRODUCTION

As now a day's most of people need effective relief in very short period of time. So most of the people belonging to age group of pediatric and geriatrics are mostly widely accepting this sublingual route of administration. Because they cannot swallow tablets and capsules and feel incontinence. Due to this the sublingual route has been developed. Sublingual route is having increased bioavailability and potential effectiveness of the drug has been increased. The patient acceptability towards the sublingual tablets has been increased. The sublingual tablets reach directly into the systemic circulation through the ventral surface of the tongue and floor of the mouth. The drug is rapidly absorbed into the floor reticulated vein that lies underneath the oral mucosa and transported through the facial veins, internal jugular vein, bracicocephalic vein and then drained into systemic circulation. Considering the oral cavity, sublingual area is the most permeable part in the buccal cavity.

CPM is most commonly used for treatment of histaminic and tussive. According to BCS, CPM belongs to the class-I drug, which means the high solubility and high permeability through the GIT. The increase in dissolution rate and disintegration rate by using super disintegrating agents like sodium starch glycolate, crosspovidone, cross carmallose sodium and MCC-102.

MECHANISM OF SUBLINGUAL ADMINISTRATION: The absorption is effected by the lipid solubility and hence the permeability of the solution commonly known as osmosis, the ionization and molecular weight of the drug. The cells of oral epithelium adsorb the drug by the process of endocytosis.

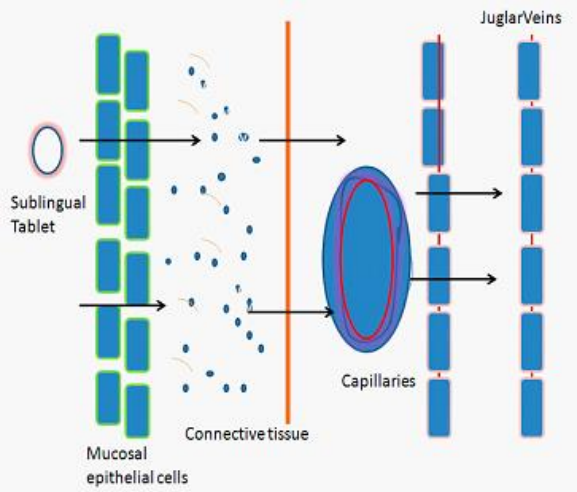

FIGURE NO. 1

However, it is believed that acidic stimulation of salivary glands, with accompanying vasodilatation, facilitates absorption and uptake into the circulatory system. The salivary glands consists lobules of cells which secret saliva through salivary ducts into the mouth. The three pairs of salivary glands are the parotid, the sub mandibular and the sublingual which lies on the floor of the mouth. The more acidic the taste, the greater the stimulation of salivary output; serving to avoid potential harm to acid-sensitive tooth enamel by bathing the mouth in copious neutralizing fluid. The main objective is to improve bioavailability, rapid onset of action and solubility of the drug increased and protein binding is avoided.

FACTORS EFFECTING THE SUBLINGUAL ABSORPTION:

LIPOPHILICITY OF DRUG: For a drug to be absorbed completely through sublingual route, the drug must have slightly higher lipid solubility than that required for GI absorption is necessary for passive permeation.

SOLUBILITY IN SALIVARY SECRETION: In addition to high lipid solubility, the drug should be soluble in aqueous buccal fluids i.e., biphasic solubility of drugs is necessary for the absorption.

pH AND pKa OF THE SALIVA: As the mean pH of the saliva is 6.0, this pH favors the absorption of drugs which remains unionized. Also, the absorption of the drugs through the oral mucosa occurs if the pKa is greater than 2 for an acid and less than 10 for a base.

BINDING TO ORAL MUCOSA: Systemic availability of drugs that bind to oral mucosa is poor.

THICKNESS OF ORAL EPITHELIUM: As the thickness of sublingual epithelium is 100 – 200 µm which is less as compare to buccal thickness. So the absorption of drugs is faster due to thinner epithelium and also the immersion of drug in smaller volume of saliva.

OIL TO WATER PARTITION COEFFICIENT: Compounds which have favorable oil to water partition coefficient are readily absorbed through the oral mucosa. Oil-water partition coefficient range of 40-2000 is considered optimal for the drugs to be absorbed sublingually.

MATERIALS AND METHODS

MATERIALS :

Chlorpheniramine maleate was received as gift sample from Natco laboratories. MCC, aerosil, magnesium stearate, menthol, cross carmellose sodium, sodium starch glycolate was received from Color Con laboratories

METHODS:

SOLUBILITY:

Take 6 clean test tubes and add water, 6.8pH Phosphate buffer, 0.1N HCl, Chloroform, Methanol and Conc. Sulphuric acid to the test tubes respectively and add a pinch of drug to all test tubes respectively and shake them vigoursly. If the drug gets soluble, then the solubility for drug with respective solvent is good. If it does not get soluble in the respective solvent it is sparingly soluble or insoluble Property.

DRUG-EXCIPIENTS COMPATABILITY STUDIES:

Drug- Excipients Compatibility Studies: Drug Interaction Study:

FTIR STUDY

Pure drug, physical mixture and prepared tablet powder (F8) were subjected to FTIR studies. Physical mixture was prepared by simple blending. The IR spectra for the test samples were obtained using potassium bromide disk method using an FTIR spectrometer (Shimadzu).

DSC STUDY

Pure drug, physical mixture and prepared tablets (F8) were studied for Differential scanning calorimetry (DSC) using METTLER instrument equipped with a thermal data system.

PREPARATION OF SUBLINGUAL TABLETS:

Chlorpheniramine maleate sublingual tablets were prepared by the direct compression method using

different excipients. The excipients used were sodium starch glycolate, cross povidone, cross carmellose sodium (super disintegrating agents), MCC (disintegrating agent), Aspartame (sweetening agent), Magnesium stearate (lubricant), Aerosil (glidant), menthol (flavouring agent), sunset yellow (coloring agent). Different concentration of excipients was used to prepare different group of sublingual tablets. All the ingredients of the sublingual tablets of Chlorpheniramine maleate were weighed and mixed in mortor with the help of pestle. The powder passed on the hoper with the help of upper and lower punches finally form a tablet by using 10 station multistationary rotary compression machine.

PROCEDURE:

All the Ingredients were weighed accurately and passed through the sieve #44. Chlorpheniramine maleate was taken and was mixed with all ingredients in geometrical ratio in polythene bag. Finally the aerosil was added and mixed thoroughly to get free flowing powder. The blend was compressed using 10.0mm standard concave punches. The following Parameters were adjusted Weight: 300±5%. Hardness: 2.5 – 3.0 kg/cm^2 Disintegration time: Not more than 1 min. The formulation as soon in Table1.

.

FORMULATION TABLE NO. -1

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
CHLORPHENIRAMINE MALEATE	5	5	5	5	5	5	5	5	5
MICROCELLUOSE CRYSTALLINE	246	237	224	246	237	224	246	237	224
SODIUM STARCH GLYCOLATE	9	18	36	----	----	---	----	----	----
CROSS PRVIDONE	----	----	----	9	18	36	----	----	----
CROSS CARMALLOSE	----	----	----	----	----	----	9	18	36
MAGNESIUM STEARATE	5	5	5	5	5	5	5	5	5
AEROSIL	5	5	5	5	5	5	5	5	5
SUNSET YELLOW	5	5	5	5	5	5	5	5	5
MENTHOL FLAVOUR	15	15	15	15	15	15	15	15	15
ASPARTAME	10	10	10	10	10	10	10	10	10
TOTAL	300	300	300	300	300	300	300	300	300

EVALUATION OF SUBLINGUAL TABLETS:

ANALYTICAL METHOD DEVELOPMENT:

DETERMINATION OF λmax FOR CHLORPHENIRAMINE MALEATE:

A 25µg/ml solution of chlorpheniramine maleate is stimulated in water was scanned in UV range between 200-400nm. Chlorpheniramine maleate showed maximum absorbance at 257nm. Thus 257nm selected as λmax for further analysis.

PREPARATION OF CALIBRATION CURVE:

Weigh quantity of chlorpheniramine maleate (100mg) place in 100 ml of volumetric flask and makeup the volume with water. The stock solution obtained is 1000µg/ml solution. Aliquots of 0.5, 1.5, 3.0, 4.5, 6.0 ml of stock solution was pipette out into 100ml standard volumetric flask and final volume adjust up to 100ml with water to give concentration

of 5, 15, 30, 45 and 60µg/ml. spectrophotometer against reagent blank with water.

PRECOMPRESSIONAL EVALUATION OF TABLETS :

The powder blends of tablets from different formulation (F1-F9) were subjected to preformulations studies (Bulk density, Tapped density, Hausner's ratio, Angle of repose and Percent compressibility).

ANGLE OF REPOSE (Ɵ):

The angle of repose was determined by using funnel method. The blend was poured through funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of heap (r) was measured and angle of repose was calculated using the formula.

$\tan Ɵ = h/r$

$Ɵ = \tan^{-1} (h/r)$

Where, 'Ɵ' is the angle of repose, 'h' is the height of pile and 'r' is radius of the pile. The results are in table no.2

Angle of repose: TABLE NO. - 2

Angle of repose	**Flow properties**
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

BULK DENSITY (Db):

Bulk density (Db) was determined by pouring the powder blend into a graduated cylinder. The bulk volume (Vo) and weight of powder (M) was determined. The bulk density was calculated by using the following formula

Db =M/Vo

Where M is the weight of powders; Vo is the Bulk volume of powders, it is expressed in gm/ml.

TAPPED DENSITY (DT):

The measuring cylinder containing known mass of blend was tapped for a fixed time. The minimum volume (Vt) occupied in the cylinder and weight (M) of the blend was measured. The tapped density was calculated by using the following formula

Dt = M/Vt

Where M is the weight of powders and Vt is the tapped volume of powders.

CARR'S INDEX (COMPRESSIBILITY INDEX) (I):

The simplest way of measuring of free flow of powder is compressibility, an indication of the ease with which a material can be induced to flow is given by compressibility. The compressibility index of the powder was determined by Carr's compressibility index (I), which is calculated by using the following formula

I = (Dt-Do/Do) × 100

Where Dt is tapped density; Do is bulk density; it is expressed in terms of percentage. The results are in Table no. 3

HAUSNER'S RATIO (H):

Hauser's ratio is an indirect index of ease of powder flow. It can be calculated by using the following formula

H= Dt/Db

Where Dt is the tapped density of powders; Db is the bulk density of powders. Lower Hausner ratio (1.25). The results are in Table no. 4

Carr's index: TABLE NO. - 3

Compressibility (carr's index)	Flowability
5-12	Free flowing
12-16	Good flow
18-21	Fair
23-35	Poor
33-38	Very poor
>40	Extremely poor

Hausner's ratio TABLE NO. - 4

Hausner's ratio	**Flowability**
<1.25	Good flow
>1.25	Poor flow

POSTCOMPRESSIONAL EVALUATION OF TABLETS:

UNIFORMITY OF WEIGHT :

Weight variation test was done as per standard procedure. Twenty tablets from each formulation (F1-F9) by weighed using an electronic balance and the average weight was calculated and the average weight one tablet is determined from the collective weight and find out % variation. The results are shown in Table -.8

THICKNESS:

The thickness of three randomly selected tablets from each formulation was determined in mm using a digital verneir caliper. The average values were calculated. The average values were calculated. The results are presented in Table-8.

HARDNESS:

The test was done as per the standard methods. The hardness of three randomly selected tablets from each formulation F1-F9 was determined by placing each tablet diagonally between the two plungers of tablet hardness tester (with the nozzle) and applying

pressure until the tablet broke down into two parts completely and reading on the are present in Table 8.

DRUG CONTENT:
Ten tablets from each batch were finally powdered and the powder equivalent to 5mg of chlorpheniramine maleate was weighed and dissolved in the suitable quantity of water. The solution was filtered, suitably diluted the drug content was analyzed spectrophotometrically at 257nm. The results are in Table no.9 and Fig no.8

WETTING TIME:
The tablet was placed at the center of two layers of absorbent paper fitted into a dish. After the paper was thoroughly wetted with amaranthus water, excess amaranthus water was completely drained out of the dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet was then recorded using a stopwatch. The results are present in Table-9 and Fig No 5

WATER ABSORPTION RATIO:
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 completely wet. The wetted tablet was then weighed. Water absorption ratio, R was determined using following equation.

R = 100 × Wa – Wb/Wa

Where, Wa = Weight of tablet after water absorption; Wb = Weight of tablet before water absorption. The results are in Table no.- 9 and Fig No -6.

***IN –VITRO* DISINTEGRATION TIME:**
Disintegration times for sublingual tablets were determined using USP tablet disintegration apparatus with water as medium. Maintained the medium temperature at 37±2ºC. The time in minutes taken for complete disintegration of the tablets with no palatable mass remaining in the apparatus was measured. The results are present in Table-9 and Fig No-7.

***In-vitro* drug release study :**
In-vitro release rate of chlorpheniramine maleate sublingual tablets was carried out using USP dissolution testing apparatus (Paddle apparatus). The dissolution test was carried out using 900ml of water at 37±2º C and 50rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus at 2, 4, 6 and 8mins. The samples were replaced with fresh dissolution medium of same quantity. The samples were filtered through whattman filter paper no. 40 and analyzed by UV spectrophotometer at 257nm. The % drug release was calculated using an equation obtained from the calibration curve. The results are present in Table-10 and Fig-9.

RESULTS AND DISCUSSION

The powder blend for all the formulation containing various concentrations as superdisintigrant (sodium starch glycolate, cross povidone, crosscarmellose sodium) and direct compressible material such as microcrystalline cellulose were used. The chlorpheniramine maleate sublingual tablets were prepared by direct compression method using rotary compression tablet punching machine. The tablets were evaluated for weight variation, hardness, thickness, drug content, wetting time, *In-vitro* dissolution time, *In-vitro* disintegration time.

It was observed that all the tablets from each formulation passed the test for weight variation, as the % of weight variation was within the pharmacopeia limits. The weight variation in all formulations (F1-F9) was found to be in the range of 298mg to 301mg, which was within the acceptable limits.

The prepared tablets in all formulations possessed good mechanical strength with sufficient hardness in the range of 2.2 to 2.7 Kg/cm^2. The tablet mean thickness was almost uniform in all formulations. The thickness varies b/w 10mm. The drug content in all formulations (F1-F9) was highly uniform and in the range of 97%-99%. The wetting time was found to be in the range 2secs to 12 secs. It was observed that wetting time was increased as the concentration of cross carmellose increased. The disintegration time in all formulations was observed within fraction of minute. The disintegration time in all formulations (F1-F9) was found to be in range of 3 – 11 secs. The *In vitro* dissolution studies of all formulations (F1-F9) were conducted and results are shown in Table-10 and Fig-9

SOLUBILITY TABLE NO. -5

SOLVENT	RESULT
WATER	SOLUBLE
6.8 pH PHOSPHATE BUFFER	SOLUBLE
METHANOL	SPARINGLY SOLUBLE
CHLOROFORM	SPARINGLY SOLUBLE
0.1N HCl	INSOLUBLE

From the above solubility studies the drug is soluble in the water and phosphate buffer. It is insoluble in the 0.1N HCl and Chloroform, Methanol and Conc.Sulphuric acid.

DRUG AND EXCIPIENT COMPATABILITY:

FTIR studies:
To know the compatibility between drug and polymers used in the development of these tablets, IR spectroscopy was carried out for the pure drug and the formulation F8. Drug did not show any evidence of interaction with the Excipients used in the formulation, which was confirmed with the studies. The obtained spectra and thermo grams were shown in Figures 9.1and 9.2

Differential scanning colorimetry:
The DSC thermo gram of the physical mixture of drug and polymer (Temp at 40ºC and 75%RH) showed an endothermic peak of melting of drug was found at about 139.16 ºC and the physical mixture was at 139.6˚C indicating that there was no incompatibility between drug and polymer. The obtained spectra and thermo grams were shown in Figures 2.1and 2.2

DSC OF PURE DRUG CHLORPHENIRAMINE MALEATE:

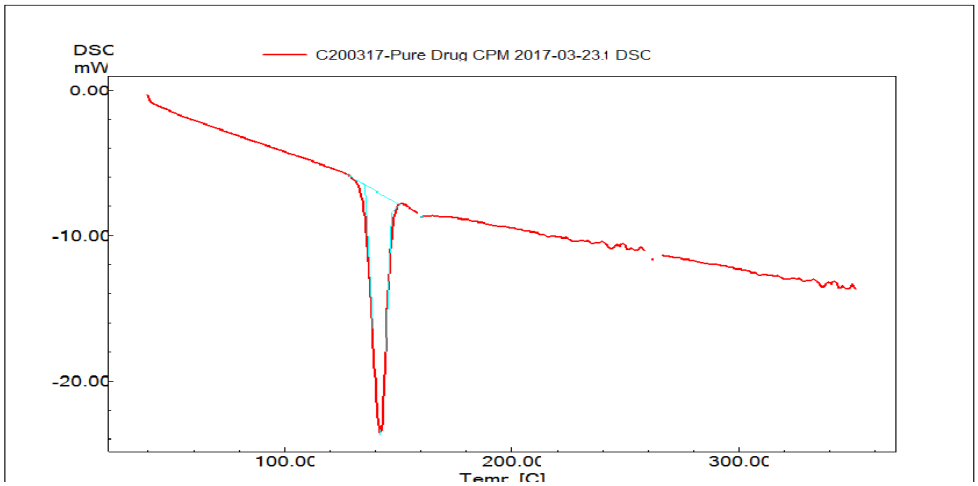

FIGURE NO. – 2.1

DSC OF F8 FORMULATION OF CHLORPHENIRAMINE MALEATE:

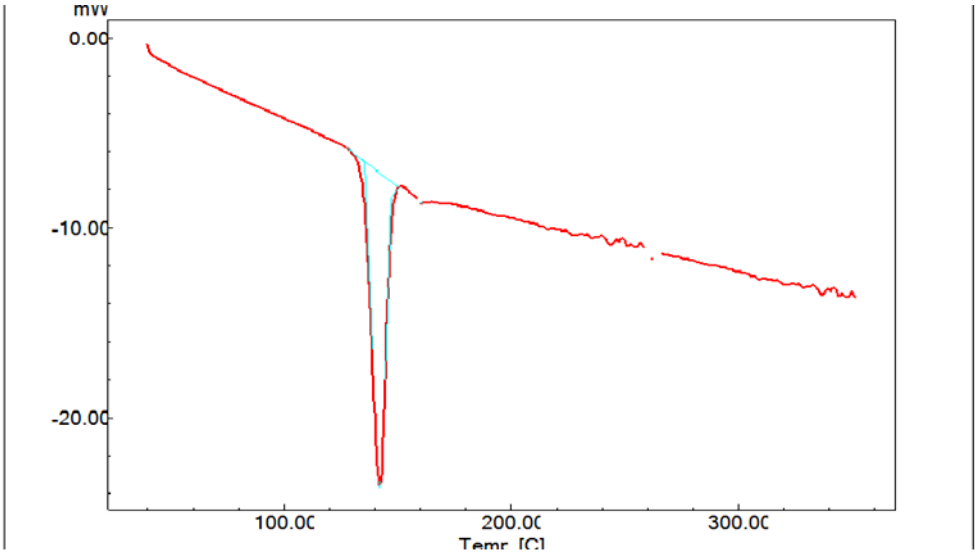

FIGURE NO. - 2.2

FTIR OF PURE DRUG OF CHLORPHENIRAMINE MALEATE:

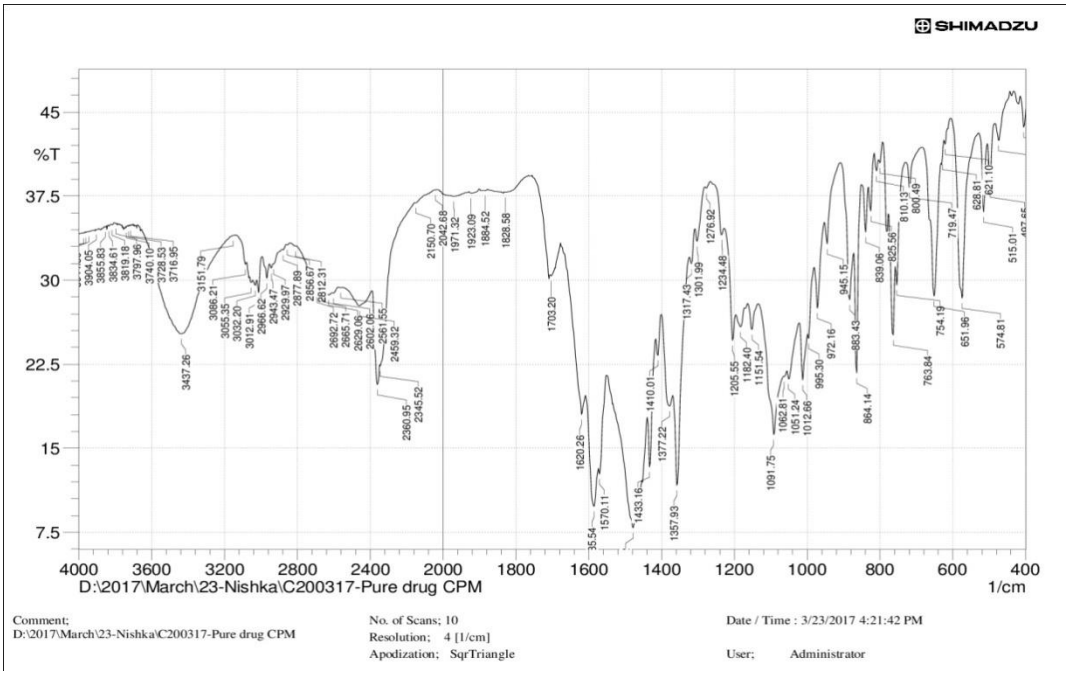

FIGURE NO. - 3.1

FTIR OF F8 FORMULATION OF CHLORPHENIRAMINE MALEATE:

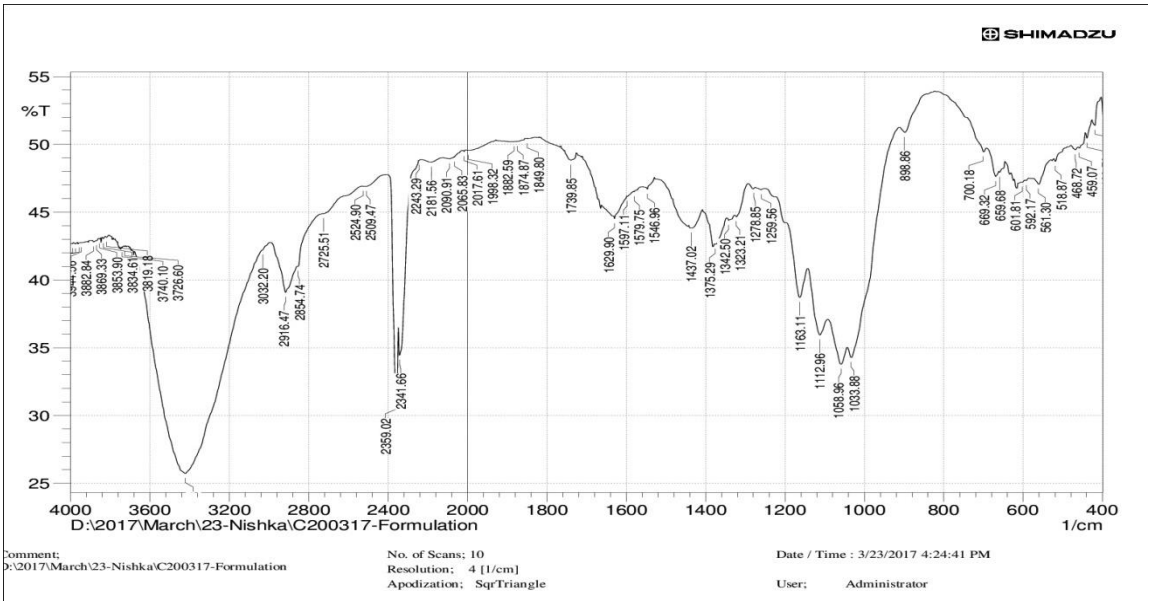

FIGURE NO. - 3.2

CALIBRATION OF CURVE:

TABLE NO. - 6

CONCENTRATION	**ABSORBANCE**
0	0
5	0.101
15	0.223
30	0.449
45	0.657
60	0.878

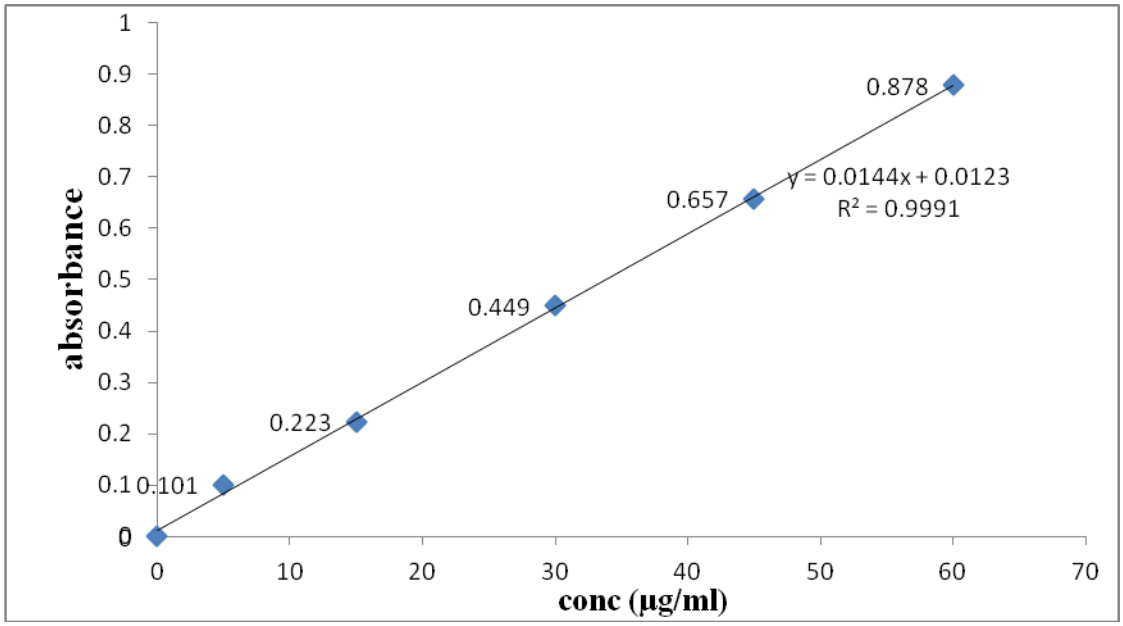

FIGURE NO. - 4

The Absorbance of the Chlorpheniramine maleate is checked at the λmax 257nm by using UV spectrophotometer. The obtained graph is linear

PRE COMPRESSION PARAMETERS: TABLE NO. -7

Formulation Code	Angle of repose (Θ)	Bulk density(gm/cm^3)	Tapped density (gm/cm^3)	Carr's Index (%)	Hausner's ratio
F1	15.10	0.52	0.60	13.33	1.15
F2	15.43	0.52	0.62	16.12	1.19
F3	16.41	0.50	0.59	15.25	1.18
F4	18.40	0.53	0.62	14.51	1.16
F5	17.12	0.56	0.64	12.50	1.14
F6	18.31	0.58	0.68	14.70	1.17
F7	16.11	0.55	0.64	14.06	1.16
F8	15.15	0.52	0.59	11.86	1.13
F9	16.10	0.53	0.62	14.51	1.16

The following Parameters averages and all the parameters, mainly the angle of repose, Carrs's index and Hausner's ratio values are within the limits of IP.
Angle of Repose values are less than 25; it indicates that the powder is having excellent flow properties

Carrs"s index values are between 12-16, it indicates that the powder is having Good Flow.
Hausner's ratio values are less than 1.25, it indicates that the powder is having Good flow.

POST COMPRESSION PARAMETERS: TABLE NO. - 8

BATCH	WEIGHT VARIATION(mg)	THICKNESS (mm)	HARDNESS (kg/cm^3)	DIAMETER (mm)
F1	298±0.35	6±0.04	2±0.2	10±0.17
F2	300±0.12	6±0.02	2±0.41	10±0.12
F3	299±0.19	6±0.04	2±0.7	10±0.21
F4	300±0.25	6±0.03	2±0.5	10±0.11
F5	300±0.32	6±0.01	2±0.7	10±0.09
F6	300±0.23	6±0.05	2±0.5	10±0.12
F7	299±0.40	6±0.03	2±0.3	10±0.15
F8	300±0.25	6±0.04	2±0.2	10±0.11
F9	299±0.53	6±0.07	2±0.4	10±0.17

TABLE NO. - 9

BATCH	WATER ABSORPTION RATIO (%)	WETTING TIME(sec)	DISINTEGRATION TIME(sec)	DRUG CONTENT (%)
F1	72%	12	10	97.34%
F2	79%	6	7	98.61%
F3	74%	10	9	97.75%
F4	77%	7	6	98.95%
F5	81%	5	5	99.46%
F6	73%	11	9	97.50%
F7	84%	3	4	99.83%
F8	89%	2	3	99.96%
F9	73%	10	8	97.65%

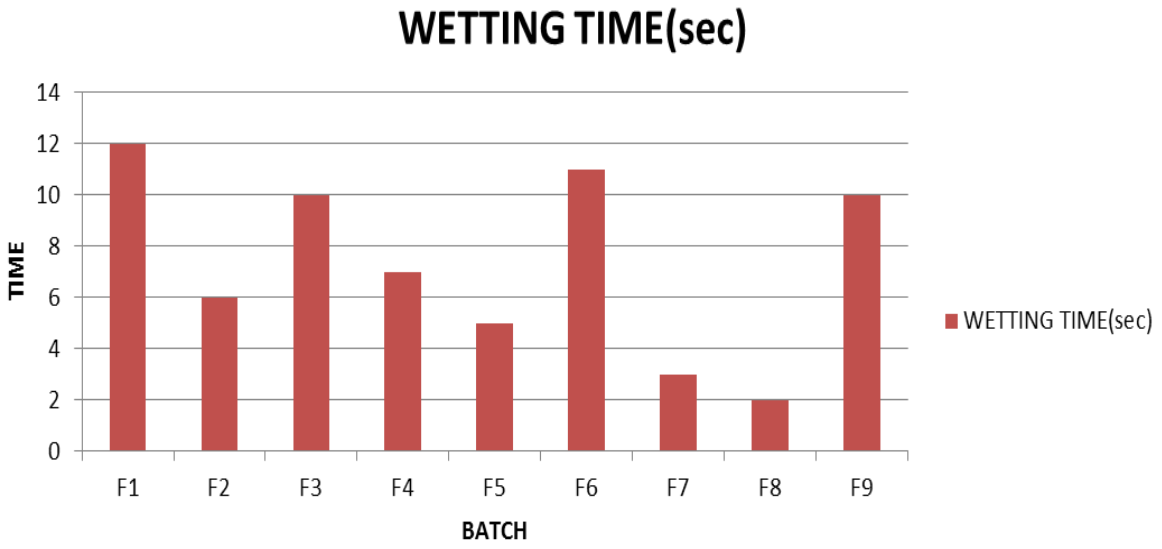

FIGURE NO. - 5

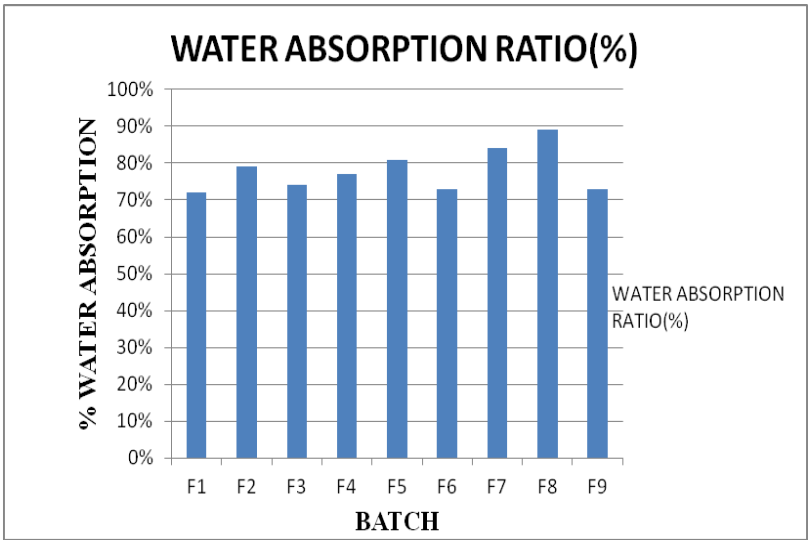

FIGURE NO. - 6

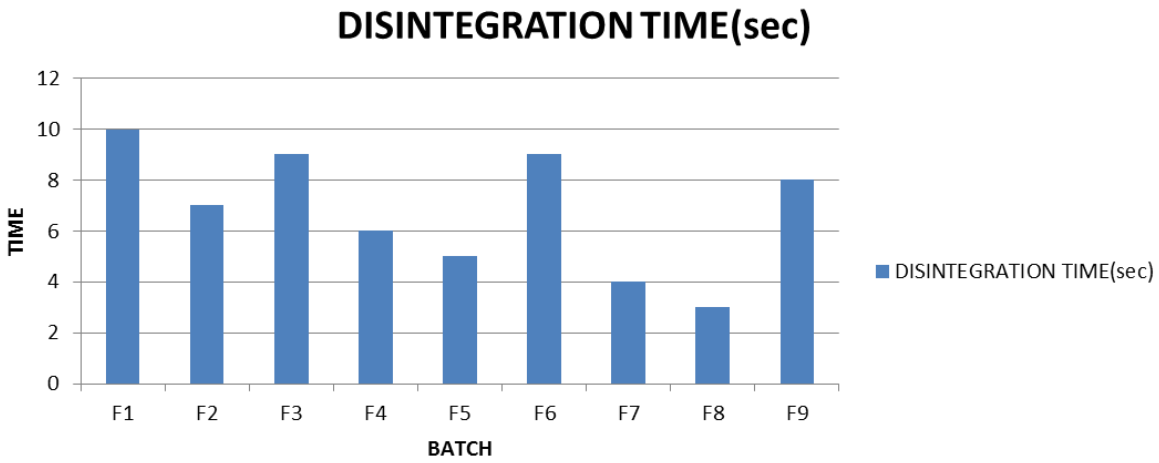

FIGURE NO. - 7

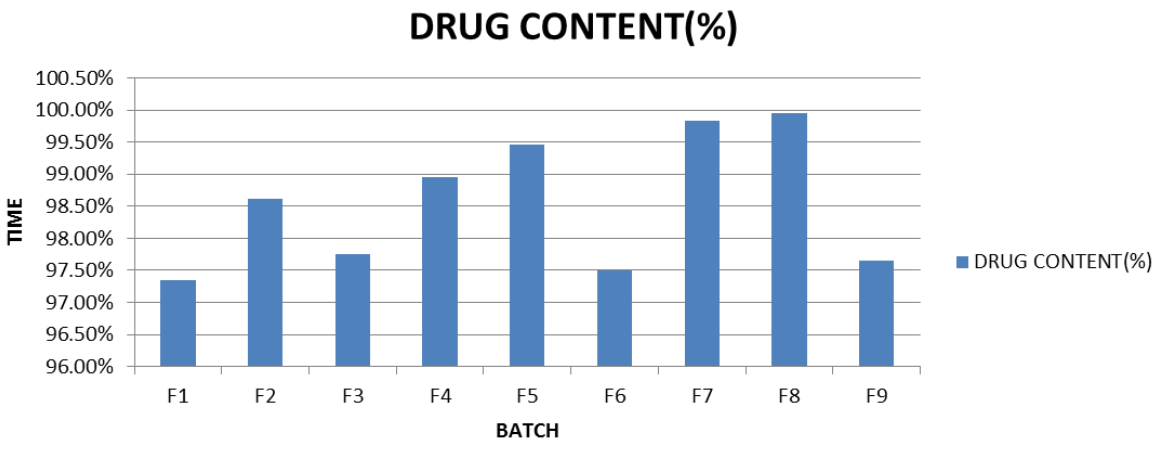

FIGURE NO. - 8

The following Parameters averages are:
Weight variation 300±5%, Hardness: 2.5 – 3.0 kg/cm^3, Disintegration time: Not more than 1 min, Wetting time: not more than 12secs, Water absorption Ratio: 72%-89%, %Drug content: not less than 97% and not more than 99%.

***INVITRO* DISSOLUTION RATE: TABLE NO. -10**

TIME	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2	62.1	77.1	60.7	54.3	77.1	67.1	96.4	98.6	63.6
4	70.0	97.2	70.0	61.4	98.6	84.3	100.9	112.9	72.9
6	91.4	98.3	84.3	80.7	100.0	100.2	100.2	100.3	88.6

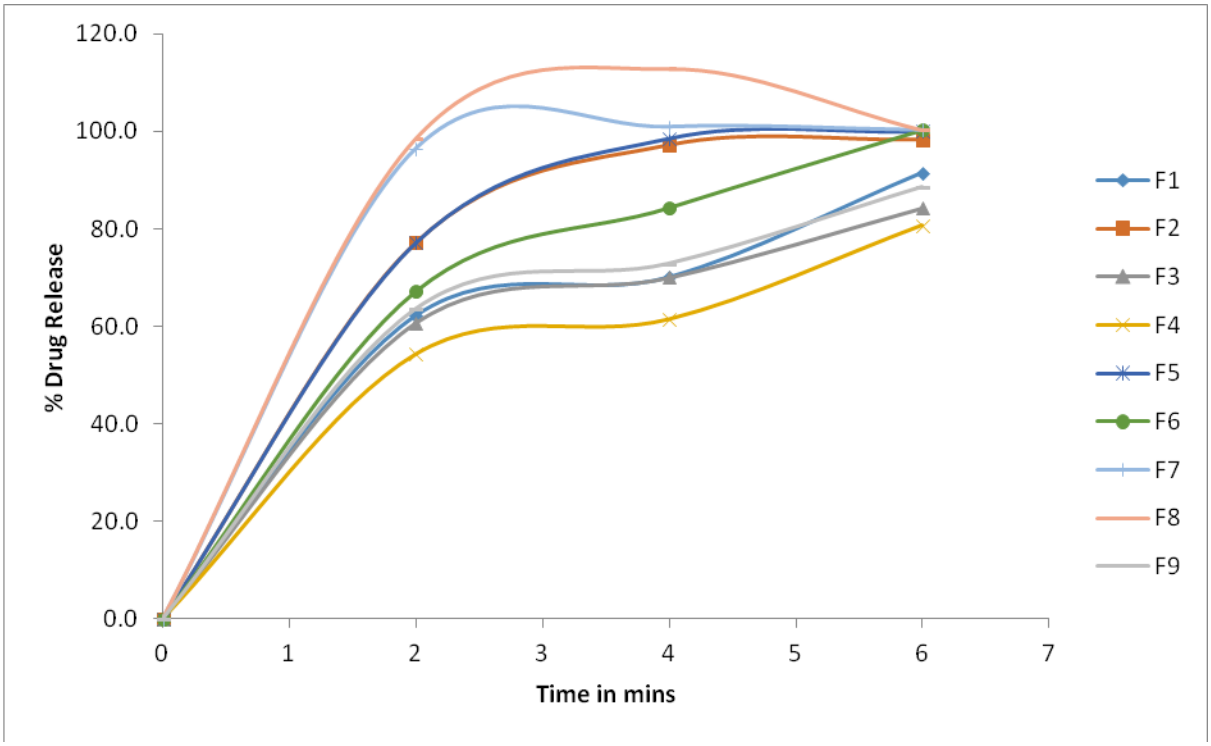

FIGURE NO.- 9
Invitro dissolution rate: F8 formulation achieved the highest dissolution rate i.e., 100.3%

CONCLUSION

• The Wetting time and Water Absorption Ratio is relatively compared. The wetting time of F8 is 2sec and its Water absorption ratio is 89%.
• The Disintegration time of the F8 formulation is 3sec
• The %Drug content of F8 is 99.96%
• The *Invitro* drug dissolution rate for F8 is 100.3%
• By using the superdisintegrating agents like SSG, Cross povidone, Cross Carmellose sodium the disintegration and dissolution time is decreased.
• For the F8 Formulation having 18% Cross Carmellose sodium achieved the highest dissolution rate 100.3% at 4mins.
• As it is anti histaminic drug, for the fast relief of allergies and flu can be achieved by Chlorpheniramine Maleate Sublingual tablets.
• The First Pass metabolism can be avoided and bioavailability is increased

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