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PREPARATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF NSAID AND ANTI HISTAMINE DRUG IN COMBINATION

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ABSTRACT
Tablets are the most widely used dosage form due to its advantages as ease of administration, low cost of manufacturing. Whereas conventional tablets have several disadvantages as they are difficult to swallow by geriatric and pediatric patients which result in poor patient compliance. So to provide medication with more conventional mean there is a desire to formulate Fast dissolving tablets. Also new chemical entry (NCE) discovery and development are time consuming and very much expensive. So pharmaceutical industries focusing on development of a new drug delivery system instead of developing new chemical entry which result in increased bioavailability, less side effects and more convenience for patients. Orally disintegrating tablets (ODTs) are novel technology, there tablets may rapidly undergo disintegration and dissolution into a form of solution without the need of water. Paracetamol is mostly used NSAID's drug having both analgesic and antipyretic action also have less anti inflammatory action. It is suitable for both pediatric and geriatric patients; also it is most suitable analgesic for pregnant woman. Levocetirizine Dihydrochloride is a third generation non-sedative antihistaminic which is orally active. It is used mainly for seasonal, perennial allergic rhinitis, hay fever also for chronic idiopathic urticaria. The present work revealed that mouth dissolving tablet of Levocetirizine dihydrochloride and paracetamol with smaller disintegration time, sufficient mechanical strength, were achieved by using proper concentration of superdisintegrants and other excepients. FTIR studies show no shifts in peak of drugs that reveal that there is no interaction between drugs and excepients.

KEYWORDS: ODT, Paracetamol & Levocetirizine Dihydrochloride.

INTRODUCTION
Oral route is the mostly acceptable way for the drug deliver. Many formulations as solid dosage form are available in market, among which solid dosage form as tablet most widely used because of its various benefits as ease of manufacturing, accurate in doses, relatively easy to administer, low manufacturing cost, higher bioavailability and higher patient compliance these all properties made tablet s the most preferred drug delivery system. Many conditions are there where patients having inconvenience in swallowing solid dosage form as tablet as when water is unavailable like mostly in conditions of allergic conditions, motion sickness. So there is necessary for alteration in conventional dosage forms as tablet, capsule to orally disintegrating tablets (ODTs) or fast orally dissolving tablets.[1]

Orally disintegrating tablets (ODTs) are novel technology, there tablets may rapidly undergo disintegration and dissolution into a form of solution without the need of water. According to Orange book by U.S Food and drug administration center for drug evaluation and research (CDER) ODT could be defined as "A solid dosage form which contains medicinal substances, rapidly disintegrate within a matter of seconds when put upon tongue". According to European pharmacopeia, ODTs are "Oro dispersible tablets" which are defined as "Oral dispersible tablets are uncoated tablets when put in mouth they got rapidly dispersed before swallowed".[2-3] ODTs when placed upon tongue start to disintegrate and dissolve without need of water. This help in fast and effective administration of active pharmaceutical ingredients (API). After disintegration or dissolution, tablet's active ingredients got absorbed in the gastro intestinal tract which results in desired therapeutic effects. Active ingredients of tablet remain in oral cavity until the tablet is completely swallowed. There should be minimal or no residue in mouth after swallowing. ODTs dissolve in mouth and takes about 15 second to 3 minute for complete dissolution. ODTs are designed that their absorption occurs by buccal and esophageal mucosa as when the mouth's saliva passes into stomach. ODTs having various properties like good stability ease of manufacturing and the most accurate

dosing. During preparation of ODTs mainly superdisintegrants like cross linked carboxymethyl cellulose (croscarmellose), poly vinyl pyrollidine, sodium starch glycolate etc. these superdisintegrants provide onset dissolution and disintegration of tablet when put upon tongue and then it release the drug in saliva so that it can absorb fastly. Drug candidates which are going to formulate as ODT undergoes pre gastric absorption and show better oral bioavailability. Some drugs absorption can be increase simply by increasing its absorption in oral cavity. Also, the quantity of drug that is required for first pass metabolism is comparatively reduced to standard tablet. The oro dispersible tablets are also known as fast dissolving tablets, fast disintegration tablets, melt in mouth tablets, porous tablets, rapid melt, rapidly disintegration tablets.[4]

Ideal properties of orally disintegration tablets (ODTs)[5]

- Unpleasant substances taste should be masked.
- Should be portable.
- No requirement of water for swallow it but it should be such that it dissolves in matter of second.
- There should be no effect of environmental conditions as humidity and temperature.
- After oral administration, there should be no residue in mouth.
- It should be harder and less friable also have a pleasant mouth feel.
- Could be easily manufactured through existing processing and packaging machinery.
- Tablets disintegration and dissolution should occur in few second in mouth.
- ODTs should be produced by cost effective method.
- ODTs should always have a proper taste masking properties.

Advantages of fast disintegrating tablets (FDTs)[6]

- ODTs mainly useful for those who cannot swallow, mainly for elderly persons, stroke victims and bed ridden patients also for those which are suffering from renal failure, and those which refuse to swallow such as pediatrics, psychiatric and geriatric patients.
- ODTs are easily administered when there is no water present means it can be administered any time.
- ODTs provide accurate dosing compared to liquid dosage form and have ease of administration.
- Liquid medications can be formulated in the form of solid preparation so they are more stable.
- It provides a good mouth feel property of mouth dissolving drug delivery system.
- It absorb through pre gastric area so have rapid absorption mainly from mouth, pharynx and esophagus.
- Due to pre gastric absorption it improves bioavailability so less amount of drug is required and it reduces side effects.
- With ODTs there is no risk of chocking and suffocation.
- With ODTs no need of chewing.

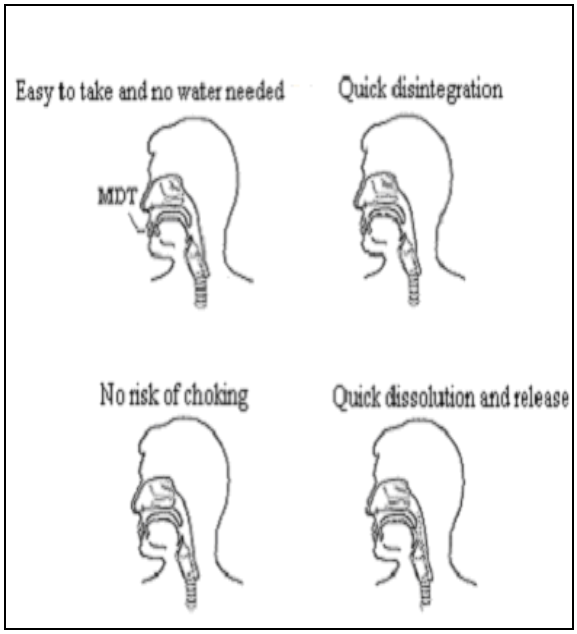

Fig No. 1: Advantages of Oro dispersible tablet (ODT).

Disadvantages of ODTs[6]

- ODTs are not suitable for those patients which are influenced with dry mouth and those patients which are on anti cholinergic medicine.
- If ODTs not formulated properly it may leave unpleasant taste and grittiness into the mouth.
- ODTs are sensitive to environmental conditions as humidity and temperature.
- Handling of ODTs should be careful because these tablets have improper mechanical strength.
- Active substances of Antibiotics are difficult to prepare as oro dispersible tablet form.

Mechanism of ODTs disintegration

The mouth dissolving tablets disintegrate into primary particles due to one or more of the mechanisms given below:

- By capillary action (Wicking)
- Because of heat of wetting
- By swelling
- By enzymatic action
- Due to release of gases
- Due to disintegrating particle, particle-particle repulsive forces.
- Due to deformation of particles.

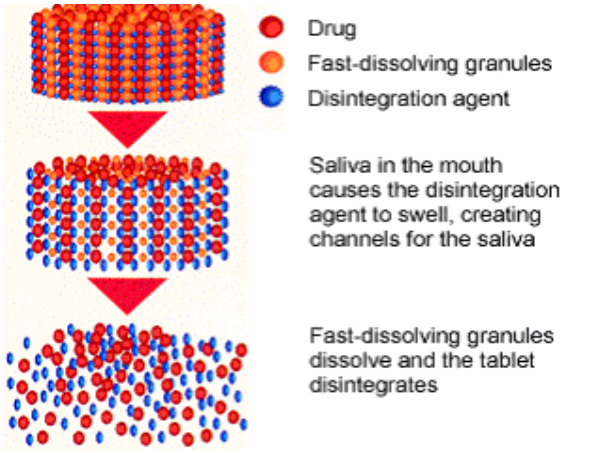

Fig. No. 2: Mechanism of action of superdisintegrants.

Paracetamol also abbreviated as Acetaminophen, it is mostly used to reduce fever and also used as the counter (OTC) pain drug. Paracetamol is also used as a main ingredient in cold medications; it is used in headache and other pain and aches. Paracetamol is also used for control of severe pain as cancer pain and post surgical pain, when it comes in combination with opoid analgesic. Paracetamol may classified as a mild analgesic. Paracetamol reduces pain by acting upon chemicals present in the body called as prostaglandins. Prostaglandins are the substance which are present in our body and released during illness and injury. Paracetamol works against prostaglandins by blocking it and makes body less known about pain or injury. Paracetamol are safe when used accordingly to prescription or taken in prescribed dose its small over dose is dangerous. When paracetamol is compared with other OTC drugs it is more dangerous or toxic in overdose.

Paracetamol act upon that area of brain which regulates temperature of body and reduces the body temperature. It is an active metabolite of phenacetin (analgesic) and acetanilide (antipyretic). But these both drugs are carcinogenic when used alone or in combination, but paracetamol is not. Paracetamol is used to regulate inflammatory pain.[7]

Levocetirizine Dihydrochloride is a non-sedative antihistaminic belong to its third generation, it is orally active. Levocetirizine Dihydrochloride is developed from second generation antihistamine cetirizine and has more affinity as compared to cetirizine. Levocetirizine Dihydrochloride works by blocking histamine receptor in mast cell. Histamine is responsible for itching, runny nose, sneezing. Levocetirizine Dihydrochloride is helpful in control of various seasonal and perennial allergic rhinitis, hay fever and for curing chronic idiopathic urticaria. When administered orally its peak plasma concentration attained in about 0.9 hour and effect going to start within 1 hour. Levocetirizine Dihydrochloride antihistaminic effect left for about 24 hours.[8-9]

MATERIAL AND METHODS

Levocetirizine dihydrochloride and Paracetamol were received as gift sample from Kaysons Pharma,Jaipur. Microcrystalline cellulose, Cross carmellose sodium, Sodium starch glycolate are obtained from Oxford Laboratory, Mumbai. Mannitol, Talcum obtained from Rankem laboratory, New Delhi, Aspartame obtained from SD fine chemical Pvt. Ltd, Mumbai.

The pure drug sample was first identified by its organoleptic properties, FTIR and UV spectroscopic method.

Drug-excepients interaction study

The FT-IR spectrum of Levocetirizine Dihydrochloride and Paracetamol are going to be compared with FTIR spectrum of drug mixture and excepients, there would be no interference between peak of drug and excepients.

FTIR of drug and excepients sample were recorded in wave number range in the 4000-600cm^2 with Alpha-ECO-ATR spectrometer (Bruker Germany) including a ATR unit. A resolution of 4 cm^2 and a number of 32 scans per sample was used.

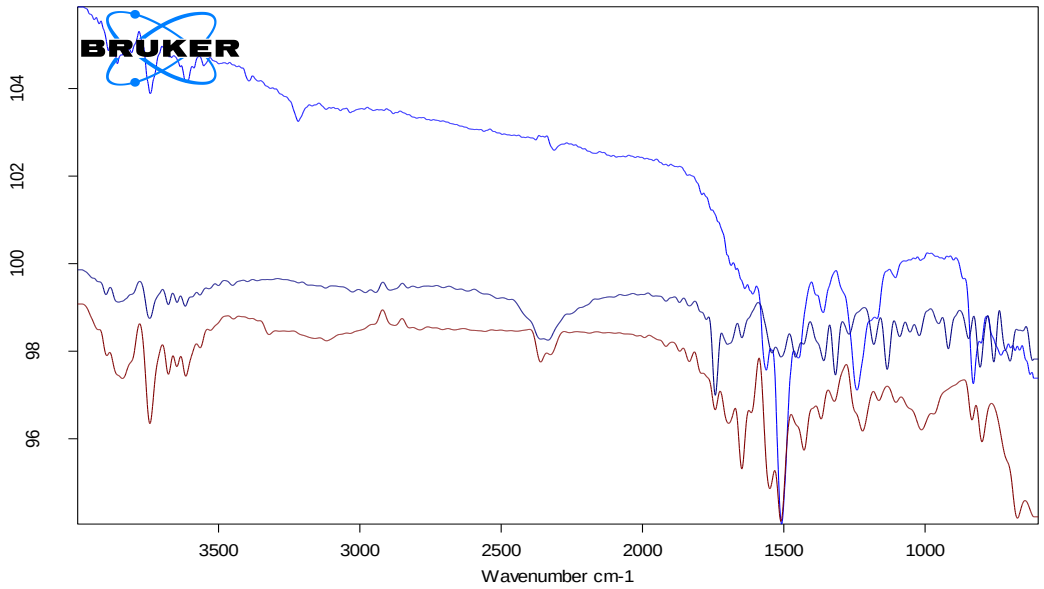

Fig. 3: FTIR spectrum of drug and sodium starch glycolate and other excepients.

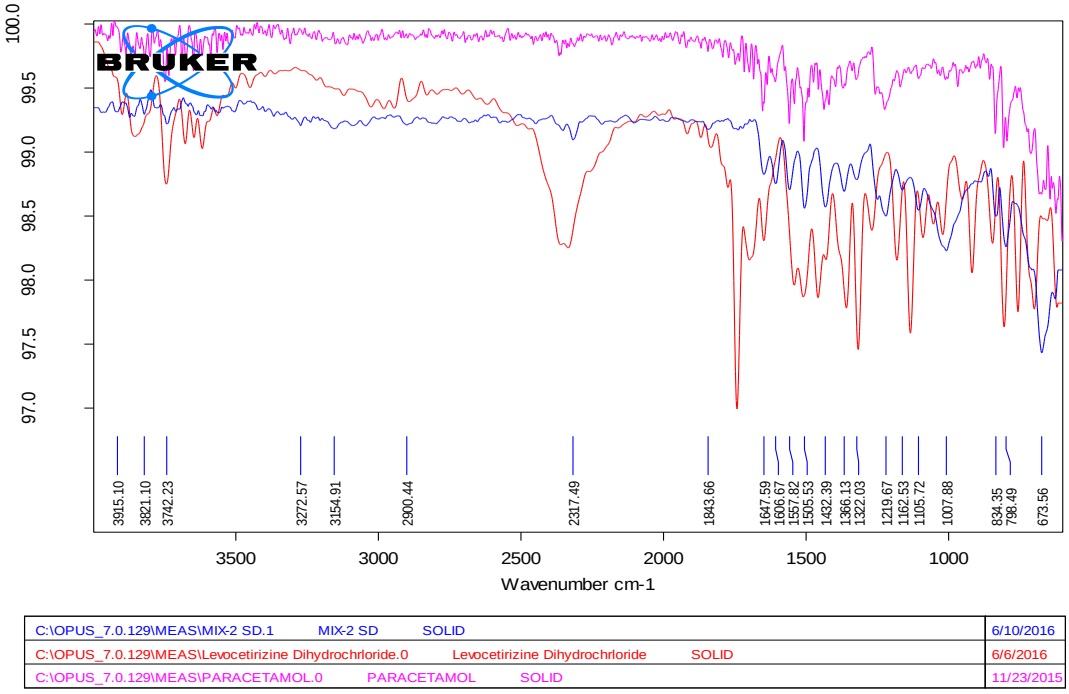

Fig 4: FTIR spectrum of drug and sodium starch glycolate, croscarmellose sodium and other excepients.

Preparation of mouth dissolving tablet using direct compression technique

Direct compression technique is the simplest and the most economical tableting process. The formulation ingredients for mouth dissolving tablets were as selected as they are supposed to be easily compressed by direct compression technique equipment. So we are using direct compression technique for formulating mouth dissolving tablet.

Levocetirizine dihydrochloride, Paracetamol and other excepients were weighed and this bulk was shifted through sieve no.80 and mixed properly for 10 min. After this separately microcrystalline cellulose and Mg. stearate were weighed and this was shifted through sieve no. 40 and both were mixed properly for 15 min. Then both the mixtures of drug and excepients were mixes properly for 5 minutes. After proper mixing powder blend was directly compressed on compression machine.

Table 1: Formula for F_1, F_2, F_3, F_4, F_5 Formulation.

S. No.	INGREDIENTS	F1 (%)	F_2 (%)	F_3 (%)	F_4 (%)	F_5 (%)
1.	Levocetirizine dihydrochloride	1	1	1	1	1
2.	Paracetamol	65	65	65	65	65
3.	Cross Carmellose sodium	2	-	4	-	2
4.	Sodium starch glycolate	-	4	-	2	3
5.	Microcrystalline cellulose	24	22	22	24	21
6.	Mannitol	4.5	4.5	4.5	4.5	4.5
7.	Aspartame	2	2	2	2	2
8.	Magnesium stearate	0.5	0.5	0.5	0.5	0.5
9.	Talc	1	1	1	1	1
	Total (%)	100	100	100	100	100

Evaluation of Levocetirizine dihydrochloride and paracetamol mouth dissolving tablets

Pre compression parameters: The powder bed was evaluated for blend properties such as Bulk density, Tapped density, Carr's index or Carr's compressibility index., Angle of repose and Hausner ratio.[10-11]

Table. 2: Result of pre compression parameters of powder blends.

Formulation	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Carr's index (%)	Hausner Ratio	Angle of repose
F_1	0.427	0.507	15.77	1.18	29.68
F_2	0.470	0.571	17.68	1.21	27.02
F_3	0.313	0.387	19.12	1.23	30.11
F_4	0.325	0.396	17.92	1.21	29.24
F_5	0.410	0.478	14.22	1.16	26.56

Post Compression parameters[11]

Description: Take 10 tablets randomly from each formulation and these were observed for uniformity of colour, shape, cracks and edges of tablet.

Thickness: Vernier caliper was used for determining thickness of tablet.

Diameter: Vernier caliper was used for determining diameter of tablet; Record the value of vernier caliper, approximate 5-6 tablets were taken and the average value was calculated.

Hardness

The Tablets strength is depending on its hardness because it shows its tensile strength (Kg/cm^2). The hardness tester used for checking hardness was Monsanto hardness tester.

Friability: Friability of tablets was determined by using Roche friabilator.

Weight variation test: For weight variation test 20 tablets from each formulation was taken, individual weight of tablets were taken by weighing balance. Then average weight was calculated and compared with individual tablet weight.

Table 3: Results of post compression parameter of formulation.

Formulation	Diameter (m.m)	Thickness (m.m)	Hardness ($kg/cm^{3)}$	Friability (%)
F_1	13.1	5.1	3.1	0.71
F_2	12.8	5.3	3.2	0.63
F_3	12.7	5.2	2.6	0.95
F_4	12.8	5.2	2.9	0.86
F_5	12.9	5.3	3.0	0.59

***In- Vitro* Disintegration time**[12]

Disintegration time is the most important evaluation for mouth dissolving tablet. Disintegration time of mouth dissolving tablet is measured by disintegration test used for conventional tablets.

Water absorption ratio

A piece of tissue paper fold twice was placed in a 10 cm diameter petri dish which was filled with 6 ml of water. Tablet was weighed and put upon tissue paper and kept it until it become completely wet. The wetted tablet was weighted again. Water absorption ratio was calculated by using following formula:

$$R = \frac{(Wa - Wb)}{W_b}$$

Where, W_a = Weight of powder after water absorption. W_b = Weight of powder before water absorption.

Before Absorption **After Absorption**

Fig. 5: Water absorption ratio by Petri dish method.

Determination of uniformity of weight[12]

Ten tablet were selected randomly are powdered and from this drugs equivalent powder was taken dispersed it in Phosphate buffer pH 6.8 and volume of solution was made up to 10 ml using PBS (ph 6.8). The mixture was filtered and from this filtered solution takes 1 ml of filtrate and it was diluted up to 10 ml with Phosphate buffer pH 6.8. Now the samples absorbance was measured at 224.5nm for Levocetirizine Dihydrochloride and 242.5 nm for Paracetamol.

Wetting time

Wetting time of tablet was measured using petri dish method. In this a piece of tissue paper folded twice was placed in a 10 cm diameter Petri dish containing 0.2% solution of water soluble dye amaranth (10 ml). One tablet was placed on the surface of tissue paper. The time required for dye to reach top surface of tablet is noted as wetting time of tablet.

Before wetting **After wetting**

Fig. 6: Petri dish method for evaluating wetting time.

Table 4: Results of post compression parameters.

Formulation	Average weight (mg)	Uniformity of weight (%)	Wetting time (sec)	Water absorption ratio (%)
F_1	488.59	+2.65, -3.09	22	69.96
F_2	486.94	+ 2.22, -2.60	23	79.60
F_3	487.68	+2.90, -3.94	19	68.34
F_4	485.81	+3.01, -2.85	21	76.38
F_5	488.18	+2.45, -3.12	18	81.62

Table 5: Results of Disintegration time

Formulation	Disintegration time by disintegration method (sec)	Disintegration time by Petri dish method (sec)
F_1	22	30
F_2	21	29
F_3	19	32
F_4	15	30
F_5	17	26

***In- vitro* Dissolution studies**

Dissolution rate of the mouth dissolving tablets were measured by using USP type-II apparatus. Dissolution medium was phosphate buffer pH 6.8 maintained at 37 ± 0.5°C and the stirring speed was maintained at 50 rpm. Aliquots were withdrawn at every 5 minute interval and filtered, sink condition was maintained all time. Now dilute these aliquots using suitable quantity of PBS. Absorbance of filtered solutions were taken for both drug as Levocetirizine Dihydrochloride analyzed at 224.5 nm and Paracetamol was analyzed at 242.5 nm.

Table 6: Result of % Cumulative drug release of mouth dissolving tablets.

Time (min)	% Drug Cumulative release				
	F_1	F_2	F_3	F_4	F_5
0	0	0	0	0	0
5	70.92	71.36	70.62	71.23	72.95
10	77.73	81.77	78.73	79.95	88.11
15	88.42	85.09	86.76	80.63	95.23
20	92.26	88.52	88.92	89.76	98.67
25	94.07	92.16	95.63	90.05	99.29
30	96.54	98.75	97.86	97.68	99.99

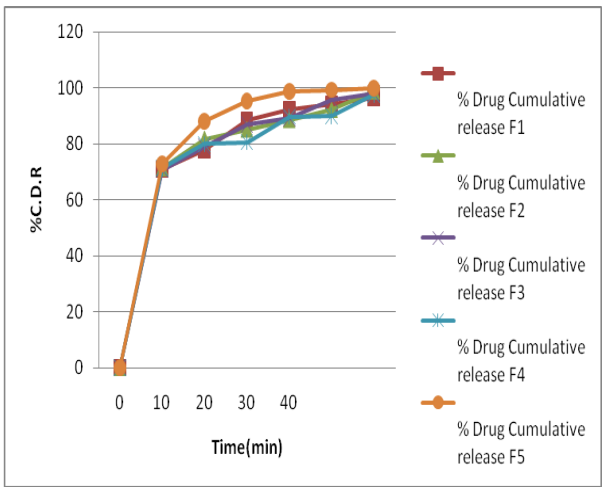

Fig 7: Comparative study of %drug release of ODT of drug.

RESULTS AND DISCUSSION

The pure drug sample was first identified by its organoleptic properties, result show drug sample purity and authenticity. The drug samples (Levocetirizine Dihydrochloride and Paracetamol) were identified spectrophotometrically by using Bruker IR and the result show drug sample purity and authenticity. Drug-excepients compatibility studied by using Bruker IR it was found that there is no deflection in peaks of drugs that means there is no influence of excepients on the peak. So by this we can assume that there is no interaction between drug and the excepients, so these excepients can be used in the formulation.The results of bulk density, tapped density, Hausner ratio, % compressibility study and angle of repose from different blend of formulations was tabulated in table 2. Pre-compression parameters result showed that Carr's index varies from 15.77 to 19.12% and angle of repose varies from 26.56 to 30.11. Thus from this result it can be said that all formulations blend have fairly good flow. The Post compression evaluation of compressed mouth dissolving tablet of Levocetirizine Dihydrochloride and Paracetamol was tabulated in table 3. The physical appearance showed that uncoated tablets are round, flat and plain in appearance. Post compression parameter result of evaluation of tablet formulation show diameter and thickness. Hardness of tablets were found to be between 2.6 to 3.2 kg/cm^3 Friability of tablets were found below 1 which shows good mechanical strength. The result of evaluation of Disintegration, wetting, water absorption, weight variation, average weight were tabulated in table 4 & 5. The disintegration of tablet was significantly better with proper concentration of disintegrants, which ultimately decides its dissolution. *In- vitro* Dissolution studies were measured by using USP type-II apparatus. The results was tabulated in table 6 & Fig 7. Formulation F_2, F_4 shows better dissolution as comparison to disintegration time of other tablet.

CONCLUSION

The mouth dissolving tablet of Levocetirizine dihydrochloride and paracetamol with smaller disintegration time, sufficient mechanical strength, were achieved by using proper concentration of superdisintegrants and other excepients. FTIR studies show no shifts in peak of drugs that reveal that there is no interaction between drugs and excepients. Among all formulation F_5 was found to be better as it has better disintegration time, fast wetting time as compared to other formulation.

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