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Formulation and Evaluation of Fast Dissolving Tablets of Rupatadine Fumarate

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ABSTRACT

Mouth dissolving tablet is an innovative solid unit dosage form that overcomes the problem of swallowing and provides rapid disintegration & dissolution to release the drug as soon as they come in contact with saliva, hence provide quick onset action. This study aimed to formulate & evaluate Fast Dissolving Tablets of Rupatadine Fumarate using a super disintegrating agent. Rupatadine is a second-generation, non-sedating, long-acting histamine antagonist with selective peripheral H1 receptor antagonist activity. It further blocks the receptors of the platelet-activating factor (PAF). Fast dissolving tablets were prepared by the direct compression method. Prepared tablets were evaluated for hardness, weight variation, friability, thickness, wetting time, dispersion time, water absorption ratio, disintegration & dissolution study. According to the results of optimized batches, it has been concluded that Formulation batch F3 was ideal.

INTRODUCTION:

Oral drug delivery has been known for decades as the most preferred and widely used route of administration among all the routes that have been explored for the systemic delivery of drugs. Oral drug delivery received the gold standard in the pharmaceutical industry because of the more flexibility in the designing of dosage form & it is regarded as safest, more convenient, and often painless, the medicament need not be sterile & provide highest patient compliance. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance, and most importantly the patient compliance. The most popular solid dosage forms being tablets and capsules; Drinking water plays an important role in the swallowing of oral dosage forms. Oftentimes people experience difficulty in swallowing (dysphasia) conventional dosage forms such as tablets when water is not available, in the case of motion sickness (kinetosis), and sudden episodes of coughing during the common cold, allergic condition, and bronchitis, during pregnancy. For these reasons, Fast Dissolving Tablets that can rapidly dissolve or disintegrate in the oral cavity have played a great deal of attention. [1, 2, 3]

Fast dissolving tablets (FDT) are also called mouth-dissolving tablets, melt-in-mouth tablets, Orodispersible tablets, rapid melts, porous tablets, quick-dissolving tablets, etc. Such tablets are those when put on the tongue disintegrate instantaneously releasing the drug into the saliva. The faster the drug into solution, the quicker is the absorption and onset of clinical effects. Some drugs are absorbed from the mouth, pharynx, and esophagus as the saliva passes down into the stomach. In such cases, the bioavailability of the drug is significantly greater than those observed from conventional tablet dosage forms. The basic approach in the development of FDT is the use of superdisintegrants like cross-linked carboxymethylcellulose (croscarmellose), sodium starch glycolate (primogel, explotab), polyvinyl pyrrolidone (polyplasdone), etc., which provide instantaneous disintegration of tablet after putting on the tongue and thereby release the drug in saliva [1]. The study aims to develop an evaluation of fast dissolving tablets of Rupatadine Fumarate 10 mg by direct compression method.

MATERIALS AND METHODS:

MATERIALS:

Rupatadine Fumarate was obtained as a gift sample from Jackson Laboratories Pvt. Ltd. Punjab, India. Microcrystalline cellulose was taken from Pharmaceutics Laboratory and was purchased from MolychemPvt. Ltd. Sodium saccharine was obtained from pharmaceutical chemistry laboratory and it was purchased from Loba Chemie Pvt. Ltd. India.

METHODS:

Preparation of Standard Calibration Curve in pH 6.8 Phosphate Buffer and simulated salivary fluid:

Preparation of standard stock solution (stock-1):10 mg of Rupatadine fumarate was dissolved in 100ml, pH 6.8 phosphate buffer to prepare (100 µg /ml) stock solution.

Estimation of λmax: The sample solution (100 µg /ml) was scanned at the range of 200-400 nm to access the λmax value for Rupatadine fumarate which was reported and confirmed by obtaining the overlain UV spectra of the drug with different concentrations between 2-25 µg/ml. The standard calibration curve was obtained with the samples of the same concentrations as opted in the process.

Preparation of Aliquots: From the stock solution (stock I) serial dilutions were prepared (2-25 µg/ml) and the absorbances were recorded at 242 nm. The standard curve was obtained by plotting absorbance v/s concentration (µg/ml).

Preparation of Simulated Salivary Fluid: To prepare simulated salivary fluid, a 5 % mucin solution was first prepared by adding 200 ml of deionized water to 10 gm of mucin and stirring the mixture until dissolved completely, then following ingredients were mixed, in the order listed below, in about 800 ml of deionized water in another one-liter capacity volumetric flask with slow stirring [4].

Table No. 1: Composition of simulated salivary fluid

S. No.	Ingredients	Quantity
1.	$NaNO_2$	0.01 gm
2.	$MgCl_2$	0.03 gm
3.	$CaCl_2.2H_2O$	0.21 gm
4.	NaCl	0.61 gm
5.	$KH_2 PO_4$	1.63 gm
6.	K_2HPO_4	0.50 gm
7.	KCl	1.00 gm
8.	$NaHCO_3$	0.25 gm
9.	Thimerosol	0.20 gm
10.	Amylase	0.725 gm
11.	Mucin (5%)	2.0 ml
12.	Antipain 50 µg/ml	0.05 gm

After complete dissolution, the final volume was adjusted with deionized water to 1000 ml. The solution was filtered once through 0.45 µm (commercially available micropore) and then passed through 0.2 µm micropore filters. Due to the viscous nature of the solution filters became clogged so it was necessary to change filters often. A 25 ml of sample solution was pipetted out and pH (6.5± 0.2) was determined.

Preparation of standard stock solution (stock-2): 10 mg of Rupatadine fumarate was dissolved in 100 ml (including adjustment of final volume) in simulated salivary fluid (as prepared above) to produce (100 µg /ml) stock solution.

Preparation of Aliquots: From the solution (stock -2) appropriate serial dilutions were prepared (2-25µg/ml) and the absorbance was estimated (for each dilution) at 242 nm. The standard curve was obtained by plotting the absorbance v/s concentration (in µg/ml) graph.

Compatibility study using FTIR technique: Drug-excipient interaction study was carried out using FTIR (Shimadzu, Affinity-1) spectrophotometer. The mixture of drug and KBr (potassium bromide) was ground into a fine powder using a mortar pestle and then compressed into discs in a hydraulic press at a pressure of 75 Kg/cm2. Each KBr disc was

scanned 45 times at a resolution of 2 cm–1. The characteristic peaks were recorded and compared with those obtained with individual formulations [5].

Formulation Design of Fast Dissolving Tablets: The fast dissolving tablet formulations of Rupatadine fumarate were divided into twelve batches prepared with different concentrations of four superdisintegrants as depicted in the table below:

Table No. 2: Formulation composition chart for FDTs of Rupatadine fumarate

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Rupatadine fumarate	10	10	10	10	10	10	10	10	10	10	10	10
Lactose	78.5	77	75.5	78.5	77	75.5	78.5	77	75.5	78.5	77	75.5
Microcrystalline cellulose	20	20	20	20	20	20	20	20	20	20	20	20
Crospovidone	4.5	6	7.5	-	-	-	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	4.5	6	7.5	-	-	-	-	-	-
L-HPC	-	-	-	-	-	-	4.5	6	7.5	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	-	-	-	4.5	6	7.5
Pregelatinized starch	20	20	20	20	20	20	20	20	20	20	20	20
Aspartame	20	20	20	20	20	20	20	20	20	20	20	20
Sodium bi carbonate	3	3	3	3	3	3	3	3	3	3	3	3
Magnesium stearate	1	1	1	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1	1	1	1
Total	150	150	150	150	150	150	150	150	150	150	150	150

Preparation of formulation blend: All the ingredients were shifted individually through sieve no. 40 to ensure the absence of any unwanted particulate matter and to break up the lumps, if present, for the ease of mixing and to ensure the proper flow. All the shifted ingredients were then weighed individually for each batch using an electronic weighing balance. The weighed ingredients were then transferred to a laboratory mixer sequentially. First, the drug was mixed with the bulking agent i.e. ½ portion each of lactose and MCC to ensure the uniformity of active medicament throughout the blend and then other excipients were added. Talc and magnesium stearate were added few minutes before the start of compression [6].

Angle of repose: The frictional forces in a loose powder can be measured by the angle of repose, 'θ' regarded as the maximum angle possible between the surface of a pile of powder and the horizontal plane.

$$\tan \theta = hr \; \theta = \tan^{-1} (h/r)$$

where θ is the angle of repose

h is the height in centimeters.

r is the radius.

True density: The true density of a substance is the average mass of the particles divided by the solid volume, exclusive of all the voids that are not a fundamental part of the molecular packing arrangement. The true density (ρ) was calculated using the following equation:

$$\rho = wV$$

where 'w' is the weight of the sample and 'V' is the powder volume.

Bulk density: It is the ratio of total mass to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in gm/ml given by

$$Db = MVb$$

where M is the mass of powder

Vb is the Bulk volume of the powder.

Tapped density: It is the ratio of total mass to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume and expressed in gm/ml.

$$Dt = MVt$$

where M is the mass of powder

Vt is the tapped volume of the powder.

Carr's index (compressibility index): It indicated the ease with which a material could be induced to flow and expressed in percentage as given by

$$C.I = Dt - DbDt \times 100$$

where Dt is the tapped density of the powder.

Db is the bulk density of the powder.

Hausner's ratio: Hausner's ratio is closely related to C. I and it was calculated using the following equation:

$$Hausner'sratio = DtDb$$

where Dt and Db were tapped and bulk density respectively.

Preparation (Using the Direct Compression Technique) and Evaluation of the FDT's: The fast dissolving tablets of Rupatadine fumarate were prepared by compressing the powdered formulation blend by direct compression method using a single punch hand operated tablet punching machine. The prepared tablets were then evaluated for the following post-compression parameters [7]:

Tablet weight variation: From each batch 20 tablets were randomly selected and their average weight was calculated. The individual weight of each tablet was compared with the average weight of 20 tablets. The tablets were said to pass the weight variation test if they complied with the weight variation specifications as per I.P.

Tablet thickness: The crown thickness of the individual tablet was measured with a digital vernier caliper. Tablet thickness should be controlled within a ± 5 % variation of the standard value of predetermined thickness.

Hardness: The hardness of the tablet was measured using the Monsanto hardness tester. Tablet was placed between two anvils and a force (kg/cm2) was applied. The crushing strength that just caused the tablet to break was recorded.

Friability: The friability of the tablets was measured using the laboratory friability apparatus known as Roche friabilator. A pre-weighed sample of tablets was placed in the friabilator and operated for 100 revolutions at the rate of 25 rpm. These tablets were dedusted, reweighed and the percent friability was calculated using the following formulae:

$$F = Winitial - Wfinal\ Winitalx\ 100$$

where Wfinal = final weight of tablets after 100 rotations and Winitial = initial weight of tablets

The acceptance value for the tablets to pass friability was not more than 1% [7].

***In-vitro* dispersion time:** Tablet was added to 10 ml Phosphate buffer solution (pH 6.8) at 37± 2 ºC. The time required for complete dispersion of a tablet was measured [8].

Drug content uniformity: Ten tablets from each formulation of FDT's were powdered finely. An amount equivalent to 10 mg of Rupatadine fumarate was weighed and dissolved in pH 6.8 phosphate buffer in 100 ml volumetric flasks. The solution was filtered and diluted appropriately and analyzed spectrophotometrically at 242 nm using pH 6.8 buffer as blank [9].

Wetting time and water absorption ratio 56: A double folded piece of tissue paper was placed in a petri-dish (internal diameter is 6.5cm) containing 10 ml of water maintained at 37ºC. A tablet was placed on the paper and the time for complete wetting of the tablet was measured in seconds [10].

Water absorption ratio (R) was determined using the following equation: R=10×WaWb

Where Wb and Wa are the weight of tablets before & after water absorption respectively.

***In-vitro* dissolution study:** *In-vitro* dissolution study was performed using USP type II apparatus (paddle type) at 50 rpm using pH 6.8 phosphate buffer and simulated salivary fluid as dissolution media maintained at a temperature of 37 ± 0.5 ºC. Aliquots of dissolution media were withdrawn at specific time intervals replacing them with fresh media and filtered.

The amount of drug dissolved was determined by U.V spectrophotometric analysis of the withdrawn sample at 242 nm. The experiments were conducted in triplicate [11, 12].

Stability study: The optimized formulations were packed suitably and kept in a stability chamber at accelerated conditions (40 °C ± 2 °C / 75 % ± 5 % RH) for three months. The samples were analyzed at 30-, 60- and 90-days intervals for different physicochemical parameters and in-vitro drug release [13].

RESULTS AND DISCUSSION:

Spectrophotometric scan of Rupatadine fumarate: The λmax of the drug was determined by subjecting the stock solution (stock 1) to the U.V scan between 200-400 nm. The wavelength for maximum absorbance was noted from the scan at 242 nm (because of sharp and intense peak) in pH 6.8 phosphate buffer medium.

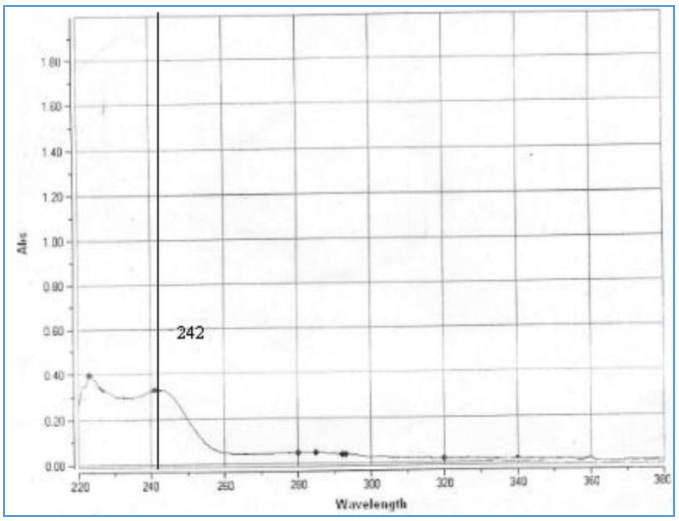

Figure No. 1: U.V Scan of Rupatadine fumarate showing characteristic wavelength

Validation of λmax: The samples containing different concentrations of the drug (2-18 µg/ml) were run and an overlain spectrum describing the reproducibility of the λmax (earlier scanned) was obtained that confirmed and validated the process.

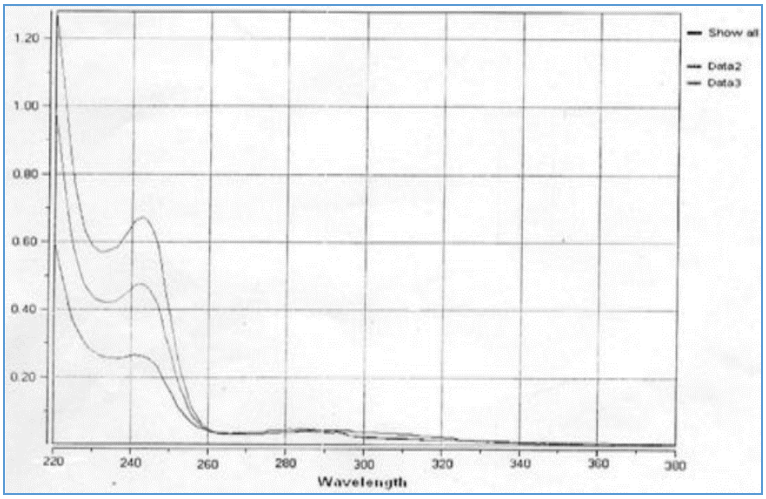

Figure No. 2: Overlain spectra of Rupatadine fumarate in pH 6.8 phosphate buffer

Preparation of standard curve using pH 6.8 phosphate buffer: A standard curve of Rupatadine fumarate was obtained by measuring the absorbance of various aliquots at 242 nm and plotting the graph [absorbance v/s concentrations (µg/ml)] which resulted in a straight line.

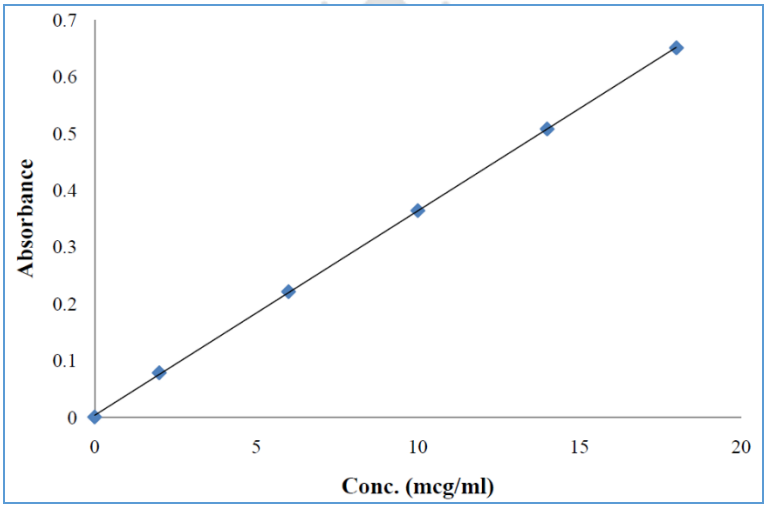

Figure No. 3: Standard curve of Rupatadine fumarate in pH 6.8 phosphate buffer

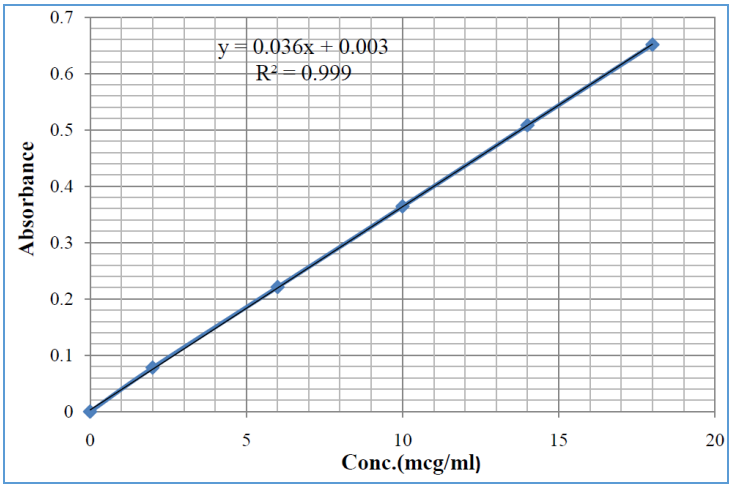

Figure No. 4: Regression curve of Rupatadine fumarate in pH 6.8 phosphate buffer.

Preparation of standard curve in simulated salivary fluid (SSF): Various samples with different concentrations were loaded on the UV spectrophotometer and respective absorbances were obtained at the λmax242 nm. A graph (concentration v/s absorbance) was plotted which resulted in a straight line concluding that the drug followed Beer- Lambert's Law at the concentration range of 2-25 µg/ml. The regression analysis was carried out on these experimental data and Y and r2 values were calculated.

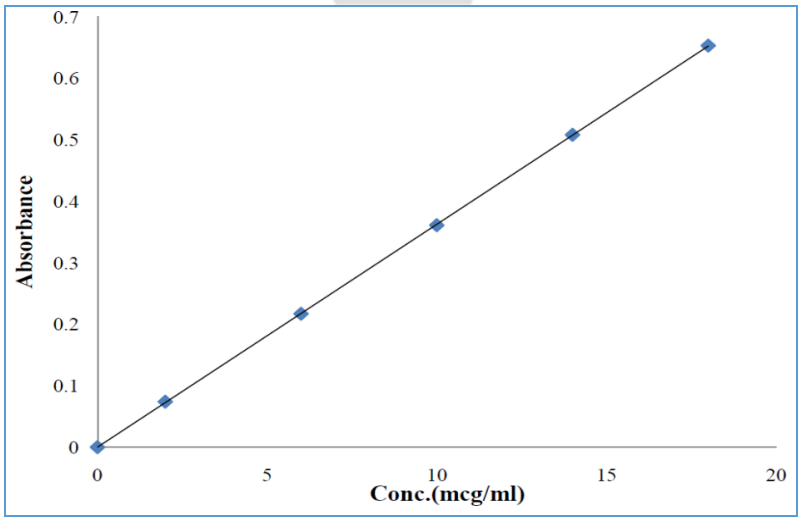

Figure No. 5: Standard calibration curve of Rupatadine fumarate in simulated salivary fluid

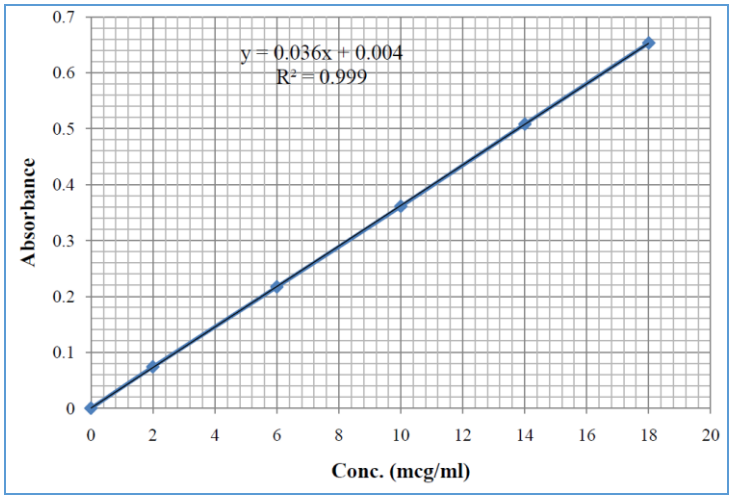

Figure No. 6: Regression curve of Rupatadine fumarate in the simulated salivary fluid.

FTIR Analysis: The FTIR spectrum of Rupatadine fumarate was obtained using the KBr pellet technique and peaks were recorded. The retention of characteristic peaks of the pure drug in its combinations with excipient(s) confirmed the compatibility of the drug with all excipients incorporated in the formulation.

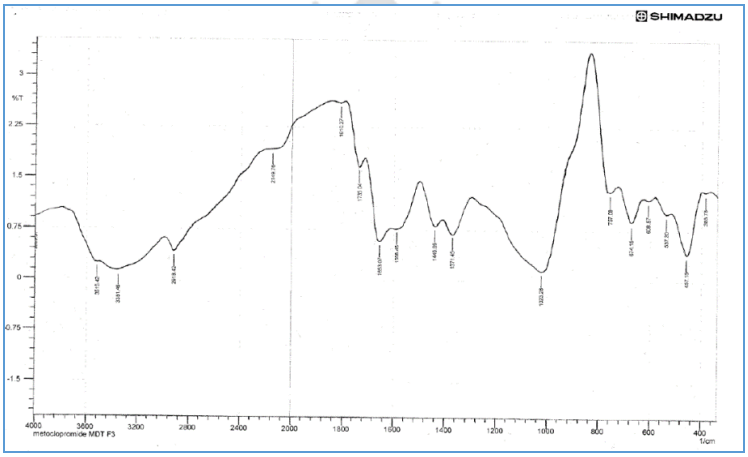

Figure No. 7: FTIR spectra of the formulation F3

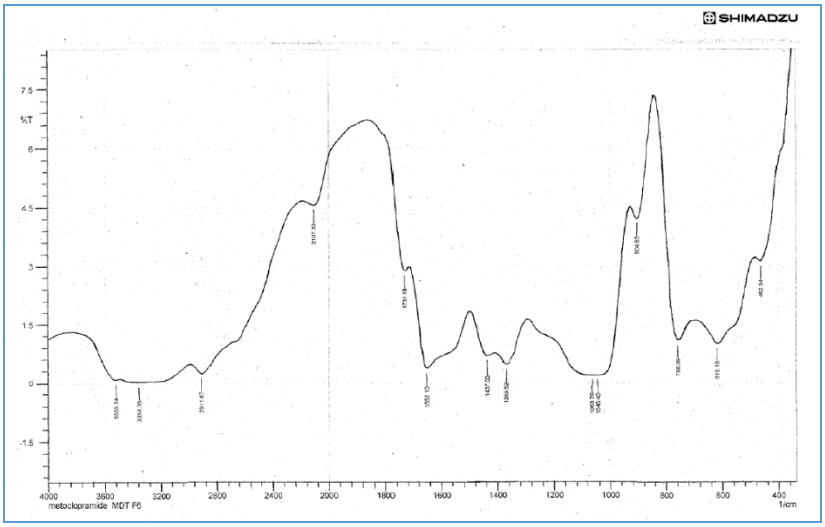

Figure No. 8: FTIR spectra of the formulation F6

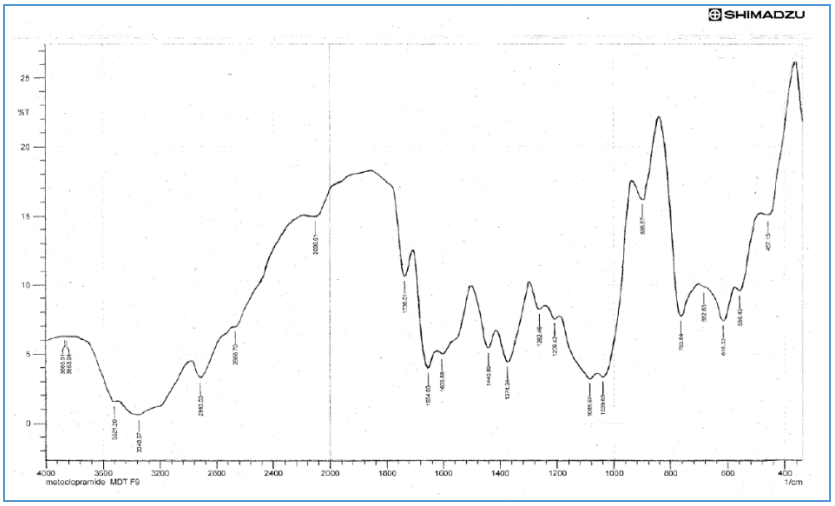

Figure No. 9: FTIR spectra of the formulation F9

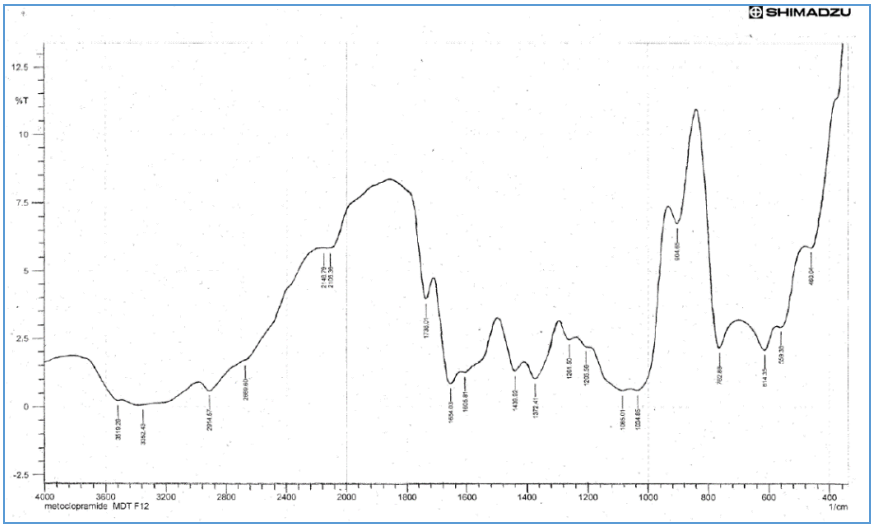

Figure No. 10: FTIR spectra of the formulation F12

Evaluation Parameters:

Pre-compression parameters: Pre-compression parameters like bulk density, tapped density, Hausner's ratio, carr's index, and angle of repose for samples of formulation blend (F1-F12) were determined and found in the range of 0.47-0.48, 0.55-0.61, 1.17-1.30, 14.54-22.95 & 28.42-39.61 respectively.

Table No. 3: Results of pre-compression parameters

S. no.	Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's ratio	Carr's index (%)	Angle of repose (θ)
1.	F1	0.48	0.6	1.25	20.0	39.40
2.	F2	0.47	0.59	1.25	20.33	37.19
3.	F3	0.47	0.55	1.17	14.54	28.42
4.	F4	0.48	0.59	1.23	18.64	33.69
5.	F5	0.48	0.6	1.25	20.0	38.16
6.	F6	0.47	0.61	1.30	22.95	38.41
7.	F7	0.47	0.6	1.28	21.67	39.61
8.	F8	0.48	0.59	1.23	18.64	37.48
9.	F9	0.48	0.59	1.23	18.64	36.25
10.	F10	0.48	0.6	1.25	20.0	39.17
11.	F11	0.47	0.59	1.25	20.33	39.40
12.	F12	0.48	0.58	1.21	17.24	39.61

Post-compression parameters: The samples from each batch of tablet formulation were evaluated for post-compression parameters such as weight variation, thickness, hardness, friability, wetting time, In-vitro disintegration time & percent drug content. The results inferred weight variation, hardness, friability, and disintegration time in the range of 140-160 mg, 2.0-3.50 kg/cm2, 0.63-0.66%, and 28-71 seconds respectively.

Table No. 4: Results of post-compression parameters for batches F1-F6

S. No.	Post-compression parameters	F1	F2	F3	F4	F5	F6
1.	Weight variation (mg)	140mg to 160mg {IP limit (±7.5%):- 139.75mg to 161.25mg}					
2.	Thickness (mm)	2.28	2.34	2.30	2.29	2.28	2.30
3.	Hardness (kg/cm2)	2.75	2.75	2.00	3.00	3.00	2.77
4.	Friability (%)	0.65	0.66	0.66	0.64	0.64	0.64
5.	Wetting time (seconds)	35	30	20	55	50	30
6.	In-vitro disintegration time (seconds)	50	40	28	64	60	45
7.	Percent drug content (%)	102.00	101.33	100.67	104.67	104.00	104.00

Table No. 5: Results of post-compression parameters for batches F7-F12

S. No.	Post-compression parameters	F7	F8	F9	F10	F11	F12
1.	Weight variation (mg)	140mg to 160mg {IP limit (±7.5%):- 139.75mg to 161.25mg}					
2.	Thickness (mm)	2.27	2.31	2.36	2.26	2.29	2.34
3.	Hardness (kg/cm2)	3.00	3.00	3.50	2.75	3.50	3.50
4.	Friability (%)	0.64	0.65	0.63	0.65	0.66	0.65
5.	Wetting time (seconds)	60	45	40	50	35	30
6.	In-vitro disintegration time (seconds)	71	57	55	60	55	54
7.	Percent drug content (%)	103.33	103.33	104.67	103.33	100.67	102.00

***In-vitro* Dissolution Studies:**

***The in-vitro* dissolution profile of formulation F1 in pH 6.8 phosphate buffer:**

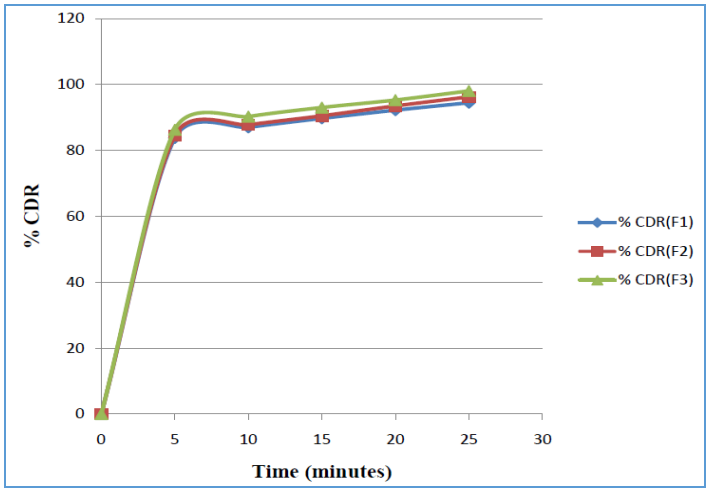

Figure No. 11: Comparative release profile of batches F1, F2, and F3

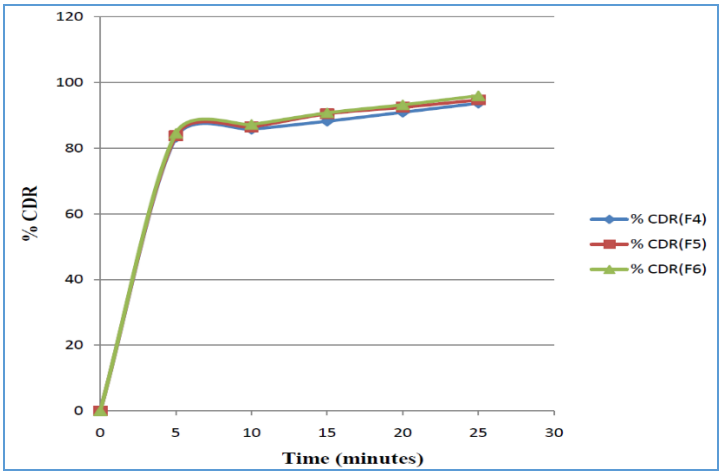

Figure No. 12: Comparative release profile of batches F4, F5 and F6

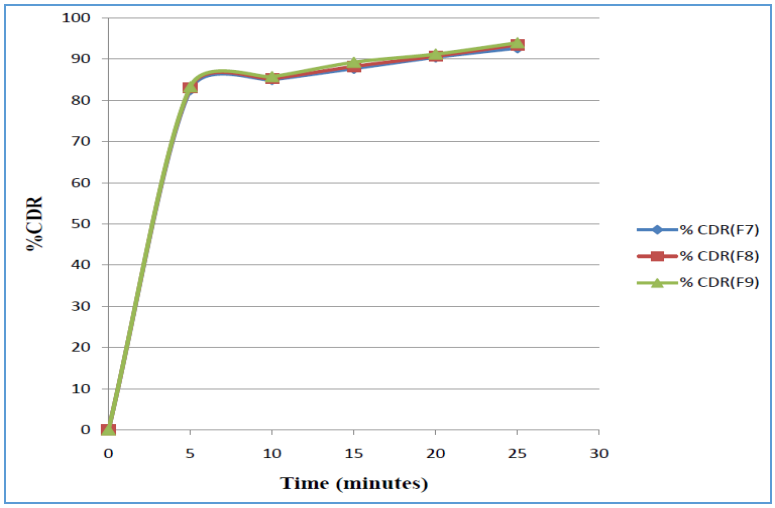

Figure No. 13: Comparative release profile of batches F7, F8 and F9

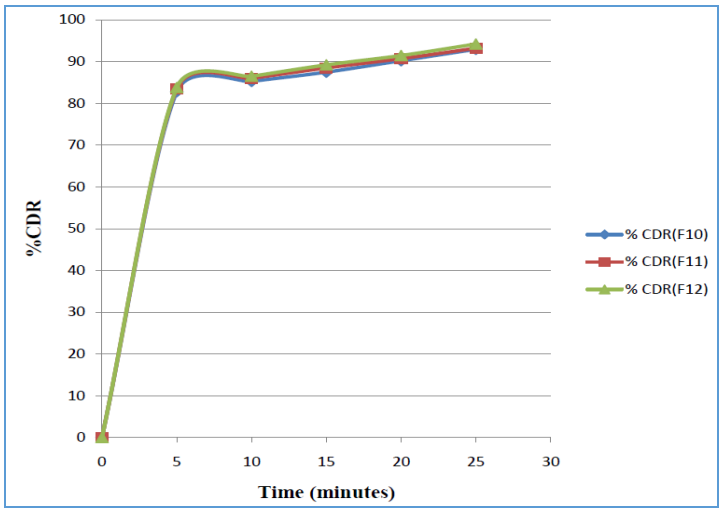

Figure No. 14: Comparative release profile of batches F10, F11 and F12

***The in-vitro* dissolution profile of formulation F1 in simulated salivary fluid:**

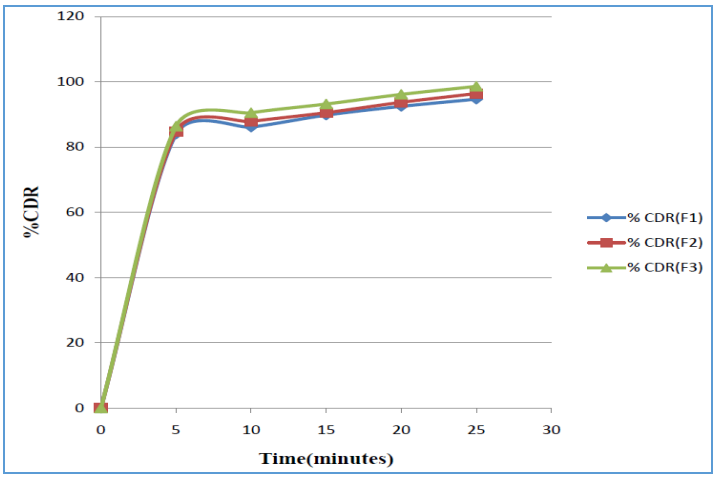

Figure No. 15: Comparative release profile of batches F1, F2 and F3.

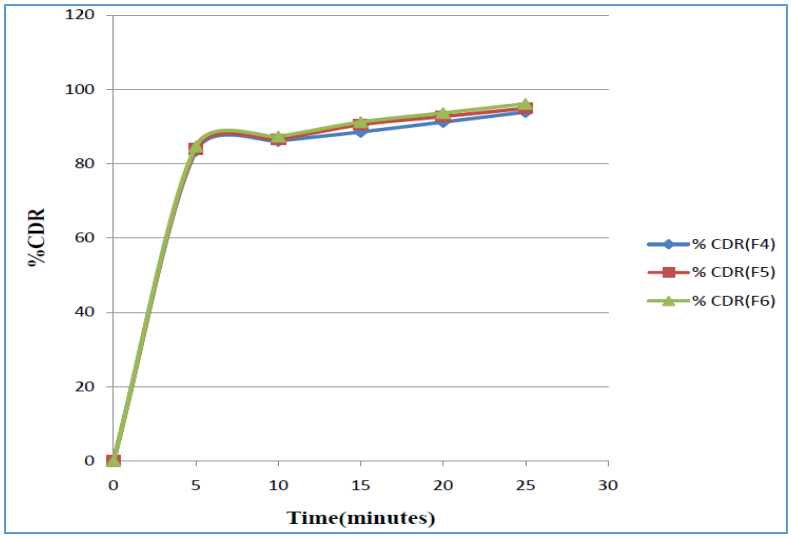

Figure No. 16: Comparative release profile of batches F4, F5 and F6

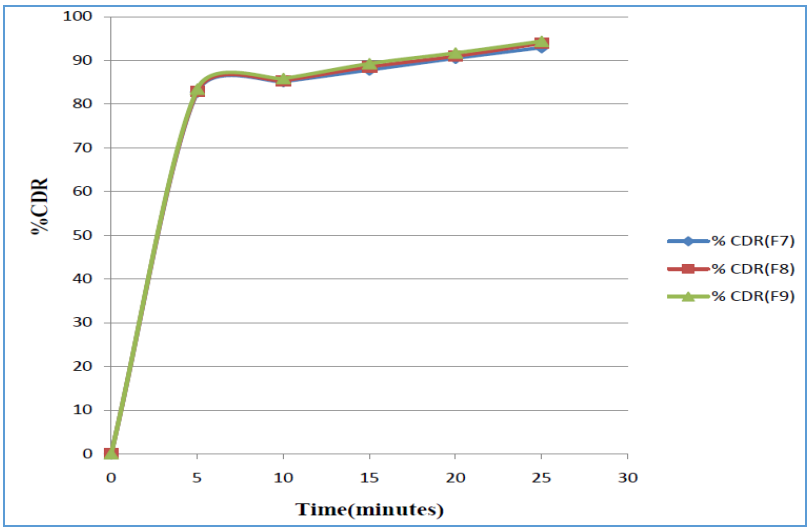

Figure No. 17: Comparative release profile of batches F7, F8 and F9

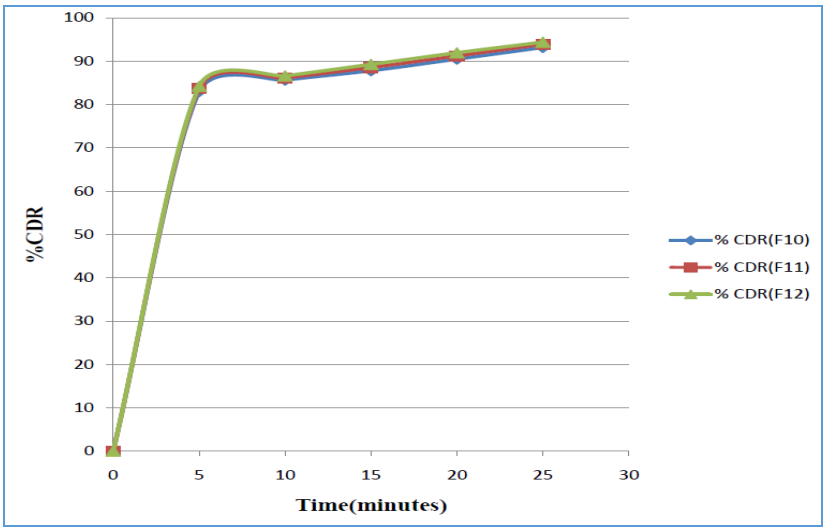

Figure No. 18: Comparative release profile of batches F10, F11 and F12

Stability Study of Optimized Formulation F3: The stability studies were performed on the prepared best-optimized formulation (F3) as per ICH guidelines at accelerated conditions (40°C ± 2 °C/ 75%±5% RH) which showed that the formulation suffered no physicochemical changes also there was no significant reduction in drug content.

Table No. 6: Observations of parameters for stability studies at accelerated conditions (40°C ± 2 °C/ 75%±5% RH).

Parameters	Time			
	0 Days	30 Days	60 Days	90 Days
Appearance	No change	No change	No change	No change
Average weight (mg)	150	150 150 151 11	151	150 150 11 151
Hardness (Kg/cm^2)	2	2	2	2
Disintegration time (seconds)	28	28	27	27
Percent friability	0.66	0.66	0.67	0.67

CONCLUSION:

The present worker tended to provide impetus for future researchers to design such novel drug delivery systems which can supersede conventional dosage forms with significant pharmacokinetic and pharmacodynamic properties.

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