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Development and Assessment of Orodispersible Tablets Utilizing Natural Superdisintegrant.

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Abstract:

The current study aimed to develop Diltiazem HCl orodispersible tablets using banana powder as a superdisintegrant by direct compression technique. The powder mixture prepared for compression was evaluated for angle of repose, bulk density, Carr's index, Hausner's ratio. Post-compression evaluation of prepared tablet includes drug content, weight variation, thickness, hardness, friability, wetting time, water absorption ratio, disintegration test and in-vitro drug release studies. All parameter produced good results. The drug and excipients were found to be compatible during IR testing. The study reveals that formulation prepared by direct compression F6 exhibits highest dissolution using banana powder at an 8% concentration and showed faster drug release 96.37% over a 25 minute period, while tablet disintegration time was 36 seconds when compared to other formulation batches of Diltiazem HCl.

Keywords: Orodispersible tablets, Diltiazem HCl, direct compression, banana powder

Introduction:

Tablets are the most widely used dosage form because of its ease of self-administration, compactness, patient compliance, quick onset of action, enhanced bioavailability, good stability, and ease of production. However, certain patient populations, such as the elderly, paediatric patients, and individuals with neurological disorders or dysphagia have trouble swallowing regular tablets, which results in poor patient compliance. Scientists have created novel drug delivery methods known as "melt in mouth" or "orodispersible tablets" (ODT) to address this issue. These unique tablets designed to dissolve in saliva. Their unique benefits, such as the ability to be administered anywhere and at any time without the need for water, make them suitable for geriatric, paediatric patients and individuals with neurological disorders or dysphagia. They are also appropriate for patients who are bedridden, suffer from mental illness, or lack easy access to water.[1, 2, 3, 4]

Candidates for this dosage form include a wide range of medications, including antibiotics, analgesics, narcotics, cardiovascular, antihistamines etc. Techniques like direct compression, tablet moulding, spray drying, lyophilization, sublimation, addition of disintegrants etc. are used to create orodispersible tablets. Zydis, OraSolv, DuraSolv, Flash Dose, Wow tab (Without Water), and Flashtab are a few of the patented methods for creating orodispersible tablets. Orodispersible tablets are also known as mouth-dispersing tablets, quickly dissolving tablets, orally dissolving tablets, rapidly dissolving tablets, porous tablets, quickly melting tablets, and rapidly melting tablets.

However, the USP approved these dosage forms as ODTs despite all the aforementioned terms. The United States Food and Drug Administration define ODTs as "a solid dosage form containing medicinal substances or active ingredients which rapidly disintegrates within a few seconds when placed up on the tongue." [5, 6, 7, 8]

Recent use of the term "Orodispersible tablet" by the European Pharmacopoeia, refers to a tablet intended to be put in the oral cavity where it rapidly disperses before being swallowed, highlights its expanding significance. Various formulation techniques are employed to achieve the desired characteristics of the orodispersible tablets, such as rapid disintegration, palatability, and mechanical strength.

Evaluation of the formulated tablets encompasses a comprehensive assessment of various parameters, including hardness, friability, weight variation, content uniformity, wetting time, water absorption ratio, disintegration test and in vitro drug release studies. Overall, ODTs represent a significant advancement in the field, providing a convenient, effective, and patient-centric approach. Their rapid disintegration, ease of administration, and versatility make them a valuable addition

offering benefits for individuals of all ages and health statuses.[9, 10, 11, 12]

Materials and Methods:

Materials Used: Diltiazem hydrochloride was purchased from Balaji Drugs, Gujarat. Banana powder was purchased from M D Enterprises, Maharashtra. Microcrystalline cellulose, mannitol, talc, magnesium stearate, sodium hydroxide, potassium dihydrogen phosphate were purchased from S. D. Fine Chemicals, Mumbai. All other chemicals and reagents used were of analytical grade.

Method:

Development of Diltiazem HCL Orodispersible tablets: Using the direct compression method, tablets were prepared with different concentrations of banana powder (Table 1), all of which kept the tablet weight constant at 200 mg. In a mortar and pestle, all the ingredients were mixed, and then talc and magnesium stearate were added. After that, the mixture was compressed using tablet punching machine.

Between batches F1 and F6, the concentration of microcrystalline cellulose decreased from 68 mg to 58 mg, while the concentration of banana powder increased from 6 mg to 16 mg (3 to 8 %). Before tablet preparation, the powder mixture has been assessed for compatibility and precompression characteristics, including angle of repose, bulk density, tapped density, Hausner's ratio, and Carr's index.

1) Drug-excipient compatibility studies: [13]
Excipients were a necessary component of almost every formulation. The successful formulation of a stable and effective solid dosage form is determined by the excipients used to support drug administration while protecting it from degradation.

FTIR studies:
Utilizing Fourier transform infrared **s**pectroscopy, it was possible to ascertain which excipients Diltiazem HCl was compatible with. We used FTIR to study the drug in its pure form as well as the drug in formulations with excipients. To remove any moisture, pure medications, polymers, and potassium bromide were heated to 105°C for an hour in a hot air oven. Next, potassium bromide was mixed 9:1

with the medication and/or polymer in the presence of an infrared light. Grinding in a smooth mortar can have an impact on mixing.

The prepared mixtures were then placed inside the sample holder of the instrument, and the spectra were recorded. Wave number ranges for the spectra were 400 cm^{-1} to 4000 cm^{-1}. The FTIR spectra of Diltiazem HCl and Diltiazem HCl with excipients were compared. The pure drug and the drug containing excipients were scanned separately. The disappearance or shift of Diltiazem HCl peaks in any of the spectra was examined.

2) Pre-compression evaluation: [14, 15]
The flow characteristics of the powder mixture were determined, including the bulk density, tapped density, Hausner's ratio, Carr's index, and angle of repose.

3) Post-compression evaluation: [16, 17, 18]
Hardness test:
Tablet hardness refers to the force required to break a tablet during a diametric compression test. The tablet's hardness was measured using a precision dial-type hardness tester. It is expressed in kilograms per square centimeter. Three tablets were randomly selected from each formulation batch to estimate the mean and standard deviation.

Friability test:
A Labline friability tester was used to assess the friability of tablets. It has a percentage (%) as its expression. Initially, ten tablets ($W_{initial}$) were weighed and placed inside the friabilator. The friabilator was rotated up to 100 times. Again, the tablets were weighed (W_{final}). The % friability was then calculated as follows:

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} x100$$

Less than 1% friability in tablets has been considered acceptable.

Weight variation test:
Twenty tablets were selected from each formulation batch, and their average weight was determined. Individual tablets were weighed and compared to their average weight. Because the tablet weighed over 200 mg, I.P. advises that it pass the test if no more than two individual weights differed from the average weight by more than 7.5%.

Weight variation = (Individual Wt – Average Wt) / (Average Wt) **X** 100

Drug content:
Five tablets were weighed, and then crashed with a pestle in a glass mortar. The fine powder was weighed to 200 mg (equivalent to 60 mg of Diltiazem) and transferred to a 250 ml conical flask containing 100 ml of phosphate buffer pH 6.8. The solution was agitated in an ultrasonicator for 45 minutes prior to filtering. The filtrate was analyzed using UV spectrophotometer at 237 nm to find drug content.

Wetting time:
A folded piece of tissue paper (12cm × 10.75cm) was put in a Petri dish with an internal diameter of 6.5 cm and 6 ml of phosphate buffer at pH 6.8. A tablet was carefully placed on the surface of the tissue paper and allowed to become completely wet. Wetting time was defined as the amount of time required to completely wet the tablet.

Water absorption ratio:
A folded piece of tissue paper (12cm × 10.75cm) was put in a Petri dish with an internal diameter of 6.5 cm and 6 ml of phosphate buffer at pH 6.8. A tablet was carefully placed on the surface of the tissue paper and allowed to become completely wet. Wetting time was defined as the amount of time required to completely wet the tablet. The moist tablet was weighed again. The water absorption ratio (R) was estimated using the equation below.

$$R = \frac{100\ (W_a - W_b)}{W_b}$$

Where, W_a: Weight of tablet after absorption
W_b: Weight of tablet before absorption

Disintegration test: Using a disintegration test device, the disintegration time of a tablet was determined in accordance with I.P. criteria. Fill each of the six tubes in the basket with one tablet. Put a disk into each tube and use 37±2°C phosphate buffer pH 6.8 as the immersion liquid to operate the gadget. It is recommended to raise and lower the assembly thirty times per minute in the 37±2°C phosphate buffer (pH 6.8). The time in seconds required for the tablet to totally disintegrate and leave no visible mass in the instrument has been determined.

In-vitro drug release studies: The in-vitro drug release of tablets was evaluated using USP type II equipment at 50 rpm and 900 cc of phosphate buffer pH 6.8 as the dissolution medium. The dissolving media was maintained at 37±0.5°C. At regular intervals, 5 ml of the sample was removed and refilled with fresh medium to maintain the sink condition, then filtered through Whatman filter paper. The sample's absorbance was measured with a UV spectrophotometric method at 237 nm, and the cumulative percent drug release was computed using an equation developed from a standard calibration curve.

Table 1: Development of Diltiazem HCL Orodispersible Tablets

Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Diltiazem HCL	60	60	60	60	60	60
Banana powder	6	8	10	12	14	16
Microcrystalline cellulose	68	66	64	62	60	58
Mannitol	58	58	58	58	58	58
Orange flavour	2	2	2	2	2	2
Talc	3	3	3	3	3	3
Magnesium stearate	3	3	3	3	3	3
Total Weight	**200**	**200**	**200**	**200**	**200**	**200**

Results:

Drug-excipients compatibility studies:

Fig.1: IR Spectra of Diltiazem HCL

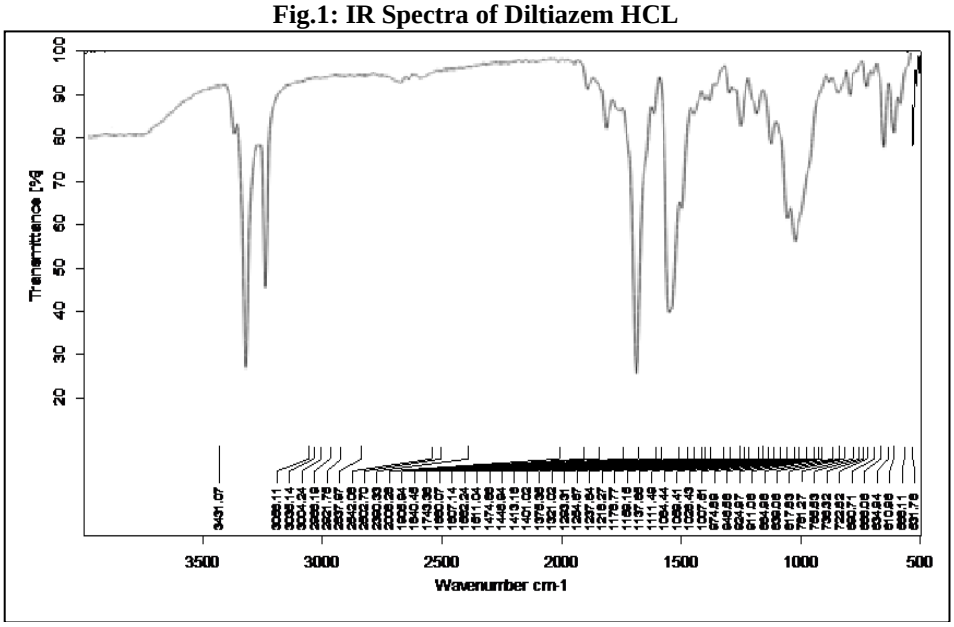


Fig.2: IR spectra of drug & excipients

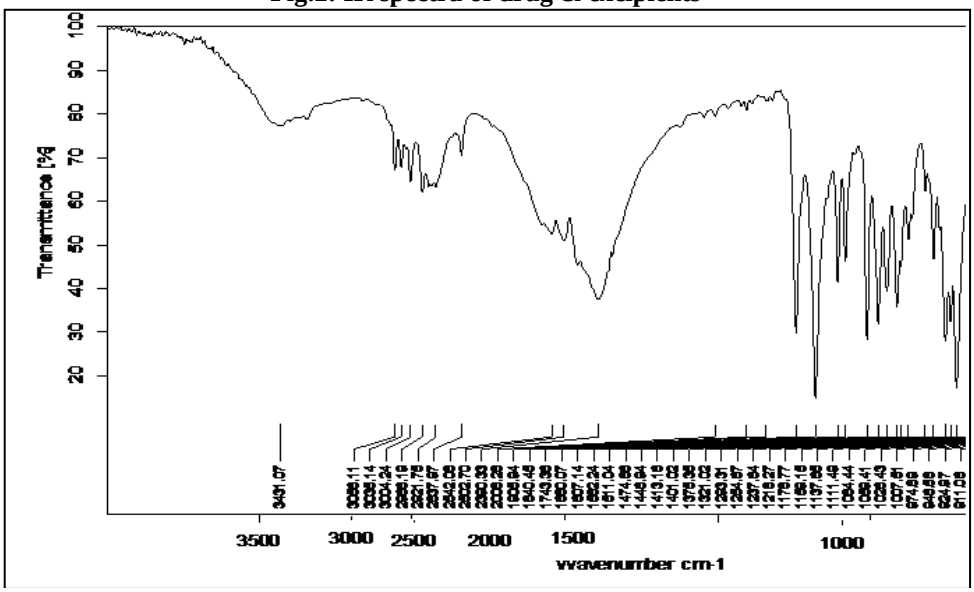


Table 2: Pre-compression evaluation of powder mixture (n=3)

Formulation batch	Angle of repose (θ°)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner's ratio	Carr's index (%)
F1	28.19	0.532	0.631	1.18	15.68
F2	27.96	0.567	0.664	1.17	14.60
F3	27.11	0.552	0.656	1.18	15.85
F4	28.05	0.580	0.694	1.19	16.42
F5	26.66	0.573	0.672	1.17	14.73
F6	25.79	0.537	0.628	1.16	14.49

Table 3: Post-compression evaluation

Formulation batch	Hardness* (n=3) (kg/cm^2)	Friability* % (n=10)	Weight variation* (n=20) (mg)	Drug content* (n=5) (%)
F1	3.74±0.49	0.78±0.05	200.05±2.05	95.57±0.38
F2	3.68±0.23	0.61±0.08	197.85±1.85	95.61±0.66
F3	3.46±0.36	0.69±0.04	199.45±2.10	96.52±0.72
F4	3.51±0.21	0.72±0.03	197.10±2.65	97.11±0.15
F5	3.22±0.45	0.67±0.04	198.65±1.80	98.16±0.55
F6	3.18±0.33	0.63±0.05	196.90±2.40	96.89±0.83

* Data represents mean ±SD

Table 4: Post-compression evaluation

Formulation batch	Wetting time* (n=3) (sec)	Water absorption ratio* (n=3)	Disintegration time* (sec)
F1	31.62±1.14	76.93±0.55	50±0.65
F2	28.93±0.59	69.07±0.29	51±0.17
F3	27.06±1.00	71.28±0.38	48±0.32
F4	26.95±1.06	64.35±0.16	49±0.43
F5	25.41±1.39	72.28±0.25	40±0.84
F6	23.50±1.27	74.08±0.66	36±0.56

* Data represents mean ±SD

Table 5: In-vitro drug release studies

Time (Min)	% drug release					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
0	0	0	0	0	0	0
5	34.17	36.54	38.11	37.96	39.00	41.82
10	54.98	56.01	58.27	57.86	60.48	64.29
15	74.08	75.82	77.25	79.02	81.04	83.67
20	82.99	84.09	85.47	88.99	88.69	90.86
25	92.84	93.11	93.88	95.03	95.95	96.37

Fig.3: In-vitro drug release studies of F1 batch

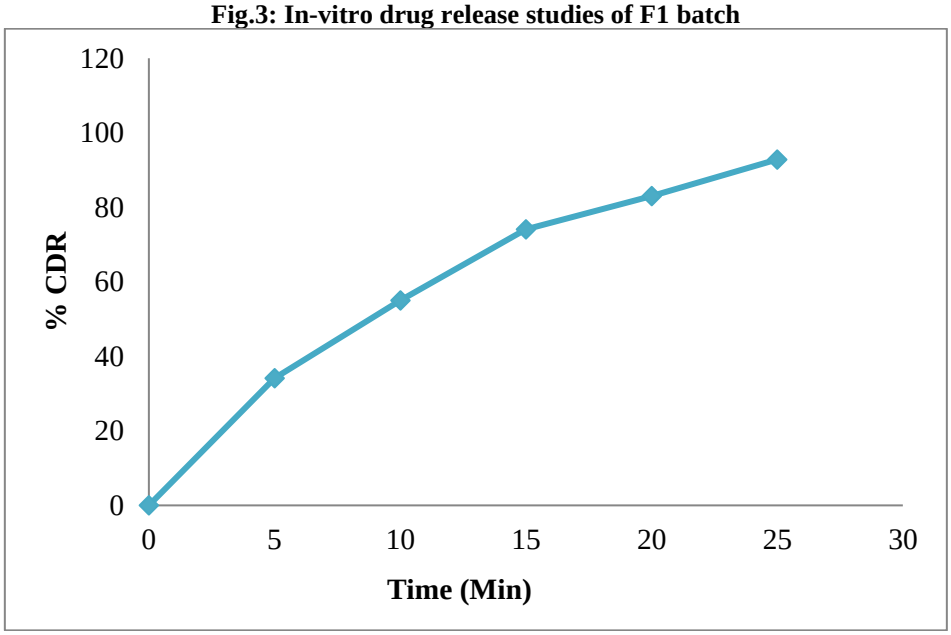


Fig.4: In-vitro drug release studies of F2 batch

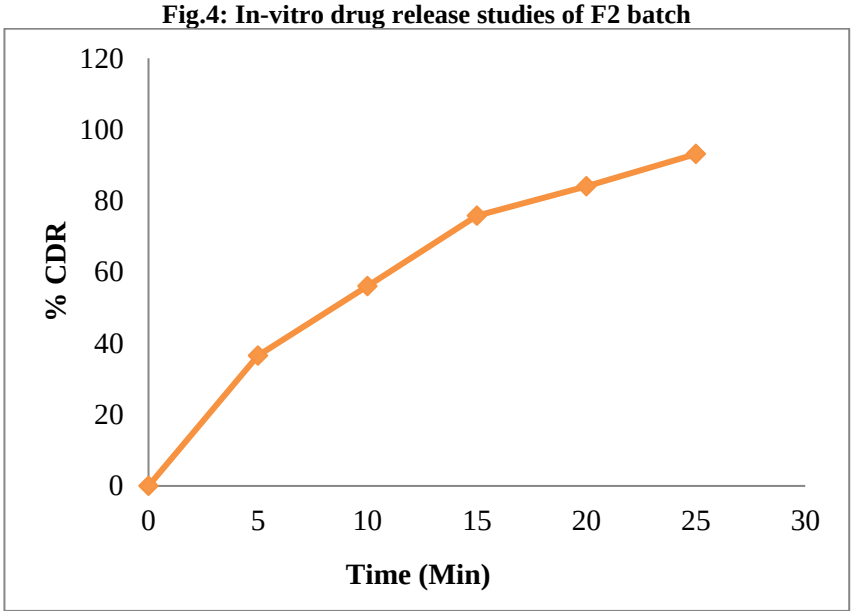


Fig.5: In-vitro drug release studies of F3 batch

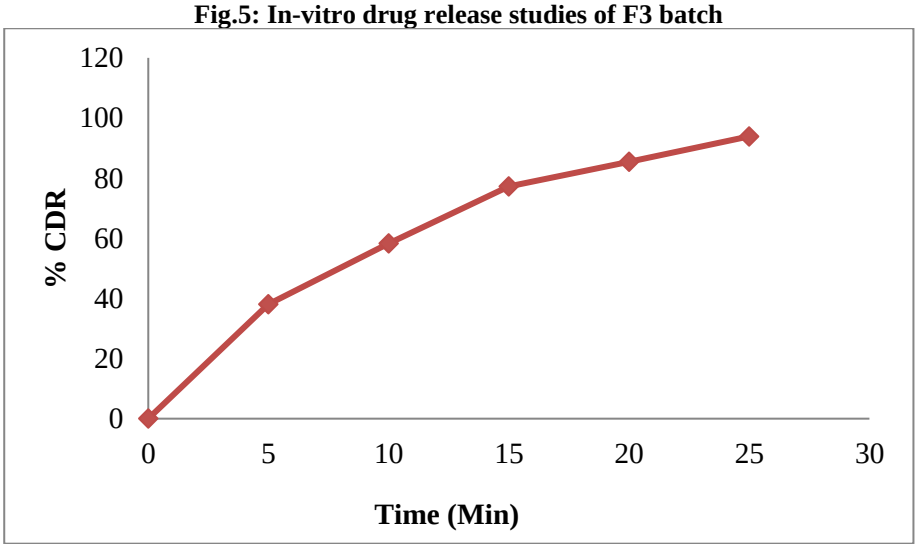


Fig.6: In-vitro drug release studies of F4 batch

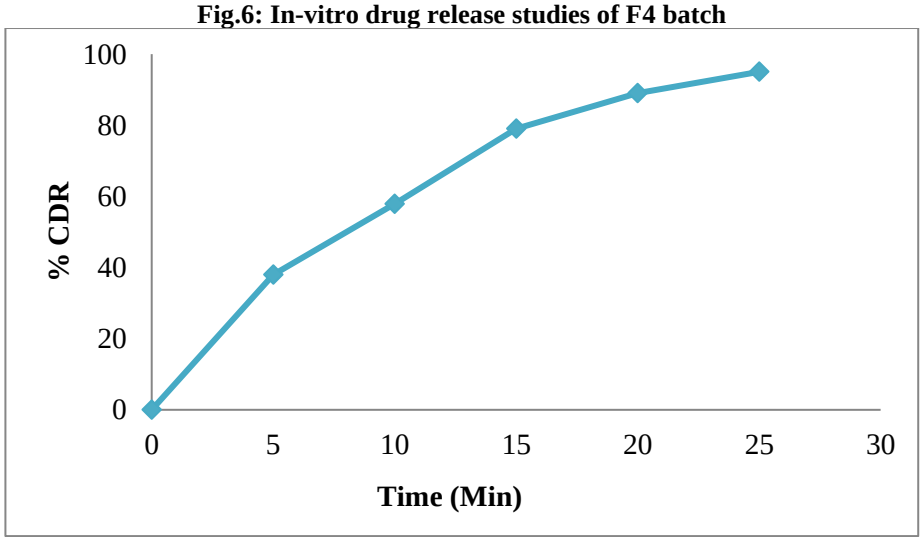


Fig.7: In-vitro drug release studies of F5 batch

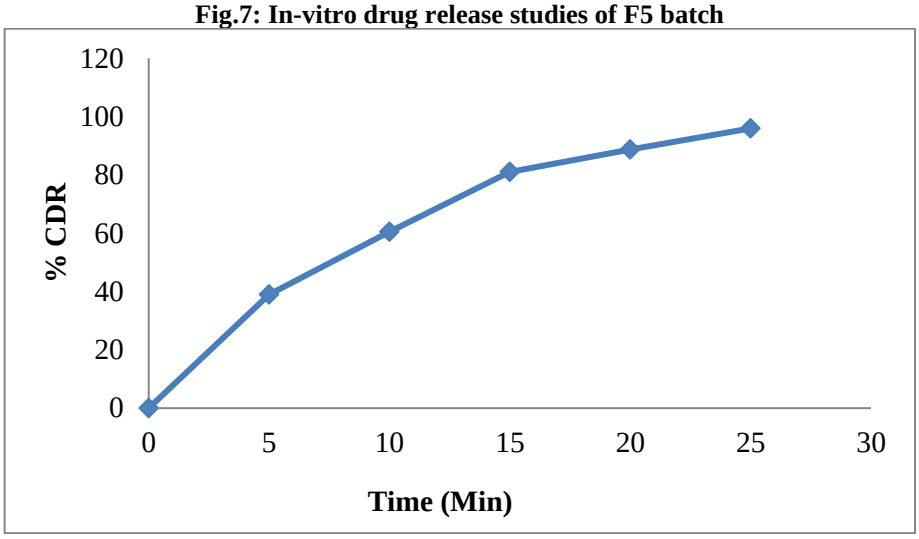


Fig.8: In-vitro drug release studies of F6 batch

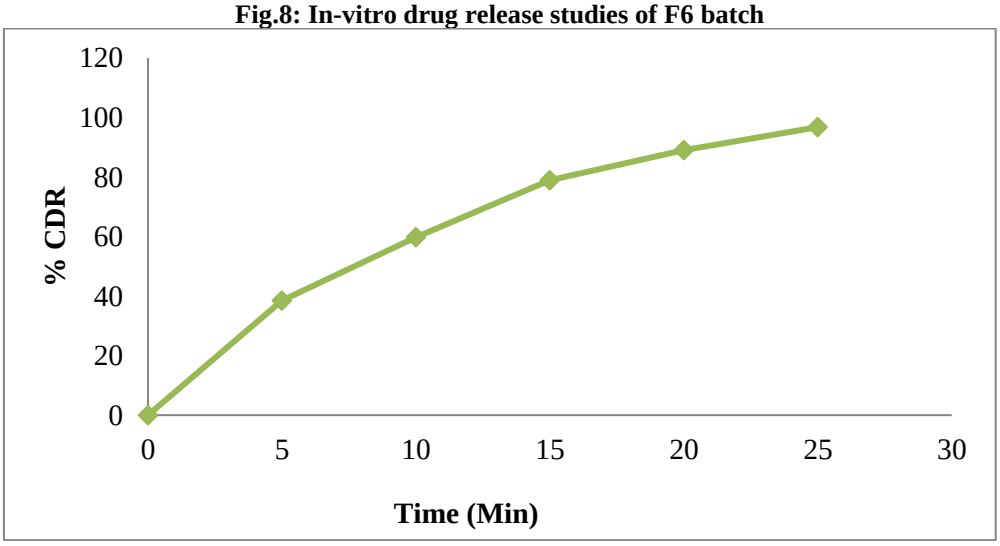


Fig.9: Comparative in-vitro drug release studies of F1, F2 & F3 batch

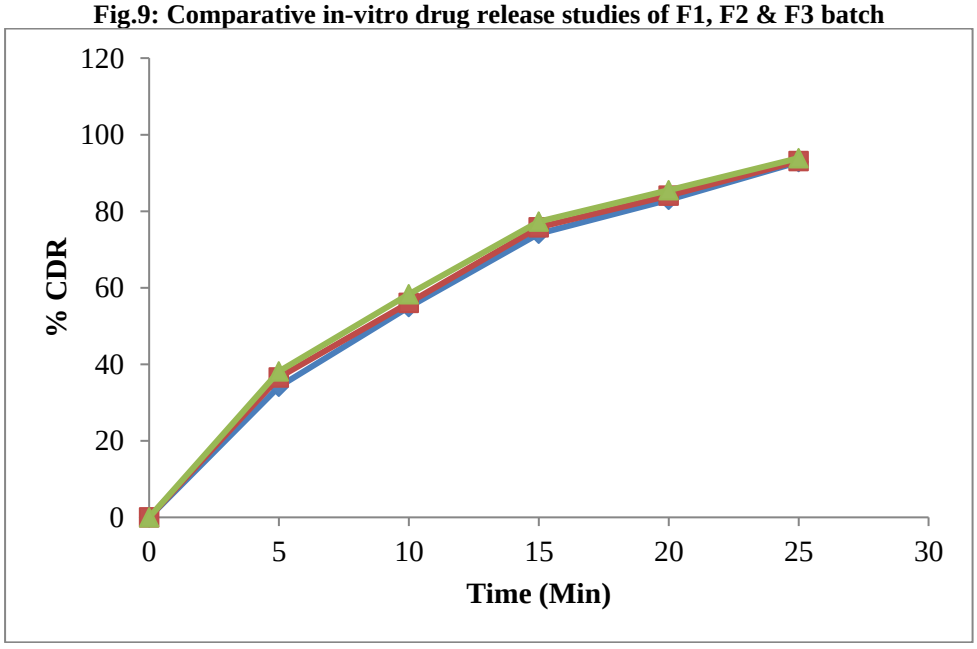
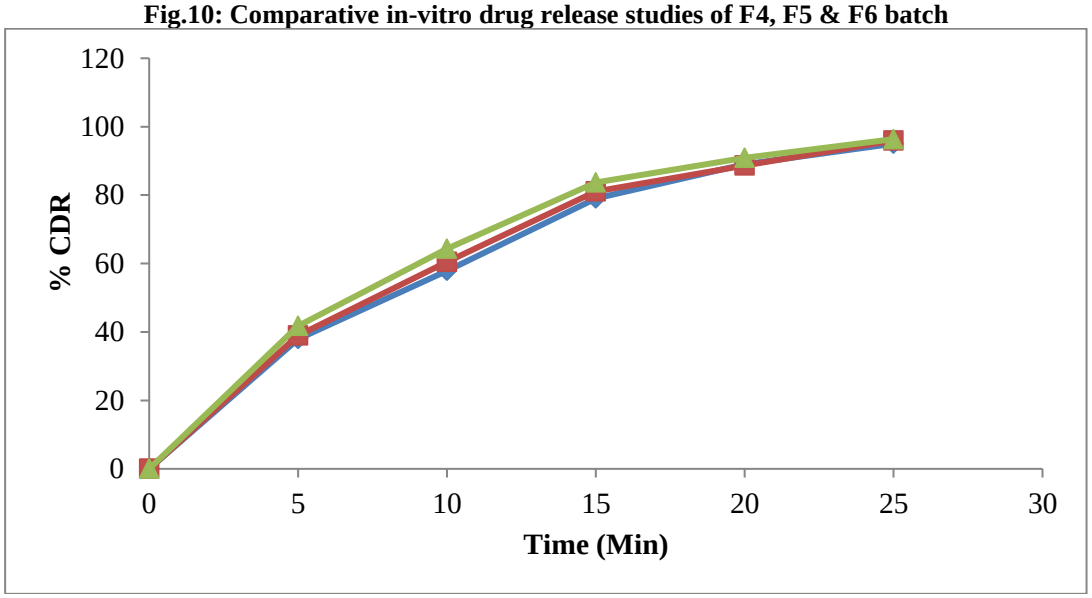


Fig.10: Comparative in-vitro drug release studies of F4, F5 & F6 batch



Discussion:

FT-IR spectroscopy was used to investigate drug-excipient compatibility, which confirmed Diltiazem's undisturbed structure and revealed no interaction. All of the formulations were created under consistent circumstances to avoid process variation. The powder mixture has an angle of repose of less than 29, indicating good flow properties. The bulk density and tapped density of the powder mixture ranged from 0.532 gm/cm^3 to 0.580 gm/cm^3 and 0.628 gm/cm^3 to 0.694 gm/cm^3, respectively. The Hausner's ratio for all formulations ranges from 1.16 to 1.19. Carr's index (%) for the powder mixture was in between 14.49 and 16.42, showing good flowability. (Table 2)
Six formulation batches of Diltiazem hydrochloride orodispersible tablets were developed using different concentrations of natural superdisintegrant: Banana powder. For each formulation batch, blend of drug and excipients were prepared and evaluated for various parameters as previously mentioned. The powder mixture was compressed using direct compression technique.

Table 3 and 4 shows data on post-compression evaluation parameters, including hardness, friability, weight variation, drug content, wetting time, water absorption ratio and disintegration time. The hardness of all formulations ranged from 3.18 to 3.74 kg/cm^2, suggesting good mechanical strength and resistance to physical and mechanical stress during handling. The results of friability test were within the acceptable range (<1%) across all formulations. Friability was between 0.61 % and 0.78 %. The results showed that the tablets have good mechanical strength. All tablets passed the weight variation test with a percentage variation within the pharmacopoeia norm of ±7.5 %. The weight of all tablets was uniform. The percentage drug contents of all formulations were found between 95.57 % to 98.16 % of Diltiazem HCl, which was within the acceptable limits.

The wetting time of the tablets was found in between 23.50 to 31.62 sec. The wetting time in all formulations was extremely quick. Water absorption ratio for formulation batches F1 to F6 ranged from 64.35 to 76.93. Water absorption increased due to swelling properties. It has been found that when banana powder is used as superdisintegrant, the tablets disintegrate rapidly within less time due to easy swelling ability of banana powder. When compared to other formulations, batch F6 were found to have the best hardness, shortest wetting time (23.50±1.27 sec.) and disintegration time (36±0.56 sec.), all of which are ideal qualities for a dispersible type tablet.

All formulations were subjected to in-vitro drug release tests utilizing a tablet dissolution tester. Cumulative drug release (mg) and cumulative % drug release were determined using the mean amount of Diltiazem HCl present in each tablet. Formulations F1, F2, F3, F4, F5 & F6 demonstrated fast dissolution, releasing 92.84 %, 93.11 %, 93.88 %, 95.03 %, 95.95 % & 96.37 % of the drug after 25 minutes, respectively. This quick dissolution could be attributed to the rapid disintegration of particles and the absorption of drugs. At the end of 25 minutes, almost total amount of the drug (96.37 %) is released from formulation batch F6, which was made using the direct compression technique with 8% banana powder. As the concentration of superdisintegrants increased, so did the rate of drug release. According to the

concentration of superdisintegrants utilized in each batch, the release rate was found to be in the following order: F6 > F5 > F4 > F3 > F2 > F1 (Fig.6). The results of in-vitro drug release studies were given in table 5.

Conclusion:

The study discovered that orodispersible Diltiazem HCl tablets can be successfully manufactured with a natural superdisintegrant, resulting in faster absorption, higher bioavailability, more effective therapy, and patient compliance. Studies on drug-excipient compatibility discovered that the superdisintegrant and excipients were compatible with Diltiazem hydrochloride. All formulation batches met the specified requirements for orodispersible tablets. The study discovered that banana powder, used as a superdisintegrant, was effective. Tablets containing banana powder in batch F6 (8% concentration) demonstrated better micromeritic properties, disintegration time, and drug release than other formulations examined.

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