IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

Development and Evaluation of Fast Dissolving Tablets of Diltiazem Hydrochloride

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Abstract: This study has been carried out with a concept of formulating the fast dissolving tablets of Diltiazem Hydrochloride using various superdisintegrants. To create the dosage form, direct compression technique was used. A total for nine formulations were developed. The combination of synthetic (2-6%) and natural superdisintegrant (2-8%) was incorporated in all the formulations. All the formulations were evaluated for precompression and post compression evaluation parameters. From the observation, it was found that all the formulations were disintegrated within the time range of 27 - 64 seconds. All the prepared formulations complied with the Pharmacopoeial standard requirements of the drug contents. The optimized formulation F6 gave the best results in disintegration time and dissolution studies as compared to other created formulations. The research concluded that the nature of the superdisintegrants influenced the rate of disintegration and drug release rate. From the study, it was assumed that combination of superdisintegrants in certain amount or ratio can enhance the disintegration time for increasing patient compliance.
Keywords: Diltiazem Hydrochloride, Fast Dissolving Tablets, Superdisintegrants, Direct Compression Technique, Combination.

I. INTRODUCTION

Oral drug delivery is the most fancy and commodious route of administration of medications due to diverse merits including nondetrimental and painless issuing of dosage forms into the body. Additionally, no additional assistance is required for delivering the drug[1]. The bioavailability of the drug entered through this route is reduced as it reached the duodenum. The main cause is the pancreatic enzymes that prompt the enzymatic alteration which accompany to the first pass metabolism[2]. The duodenum and jejunum in the upper gastrointestinal system are the primary sites of drug absorption when taken orally. Because of its smaller surface area and thicker mucus layer, the stomach has a lower capacity for absorption. One of the main obstacles to drug absorption is the intestinal epithelial lining. With 3,000–7,000 microvilli in each cell of the small intestine, there is a lot of surface area available for drug absorption and interaction. Understanding obstacles and addressing issues such the food impact, gastrointestinal discomfort, sluggish action, lack of dose proportionality, and high variability are necessary for the development of oral formulations for hydrophobic medications. To increase water solubility, strategies such as salt selection, particle size reduction, and surfactant selection are employed. By opening intracellular connections, surfactants—which have a hydrophilic head and a hydrophobic tail—improve medication solubility and permeability. Greater concentrations, nevertheless, may be dangerous[3].

Most of the solid dosage forms are administered through the enteral route. The major drawback is reported by the geriatric patients as they have fear of choking, hand tremors, dysphagia and in young individuals due to underdeveloped muscular and nervous systems and in schizophrenic patients which leads to poor compliance. Difficulties in swallowing of tablet and capsule are also occur when water is not available. Approximately one – third of the population (mainly pediatric and geriatric) has swallowing difficulties. For these reason, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention[4]. Scientists have developed "melt in mouth" or "mouth dissolve (MD)" tablets, which disintegrate in saliva and are suitable for geriatric, pediatric, mentally ill, bedridden, and patients without easy access to water. These tablets offer benefits like patient compliance, rapid action, increased bioavailability, and good stability, and are used for a wide range of drugs. Patented technologies include Zydis, OraSolv, DuraSolv, Flash Dose, Wow tab, and Flashtab. Fast dissolving tablets disperse rapidly to form a suspension or solution of the drug after mixing with saliva which is easily swallowed by the patients[5, 6].

FDTs are defined by the FDA as "a solid dosage form containing the medicinal ingredient or active component that rapidly disintegrates or dissolves when placed on the tongue"[7]. Over half of patients prefer FDTs over other dosage forms, formulated using superdisintegrants and pore structure maximization through freeze drying and vacuum drying. Fast dissolving dosage forms are ideal for patients who cannot swallow traditional tablets or capsules with an 8-oz glass of water, including pediatric and geriatric patients, those with difficulty swallowing solid dosage forms, those fearing choking, elderly depression patients, allergic patients, schizophrenic patients, and those with persistent nausea or limited water access. These types of formulations claim to increase bioavailability and faster action by allowing pre-gastric absorption in saliva, avoiding first-pass metabolism, and improving safety profiles for drugs with high toxic metabolites[8-10].

Diltiazem Hydrochloride tablets are indicated for the treatment of chronic stable angina and hypertension. Diltiazem is well-absorbed from the gastrointestinal tract but has a significant hepatic first-pass effect. Its bioavailability is around 40%, with only 2% to 4% appearing in urine. Its plasma elimination half-life is 3.0 - 4.5 hours and its therapeutic blood level ranges from 40 to 200 mg/ml. *In vitro* binding studies showed it is 70% to 80% bound to plasma proteins[10]. The study aims to create a fast dissolving dosage form of diltiazem hydrochloride, which offers fast relief and higher bioavailability, by masking its bitter taste using combination of natural and various synthetic superdisintegrants, thereby enhancing its palatable form.

II. MATERIALS AND METHODS

2.1 Materials Used:

Diltiazem hydrochloride was purchased from Yarrow Chem Products Pvt. Ltd. Synthetic polymers were obtained from Indian Fine Chemicals, Mumbai. Natural superdisintegrant was prepared following the procedure mentioned in the references. All other chemicals and reagents used were of high analytical grade. Distilled water was used in all the experiments.

2.2 Method Used:

2.2.1 Preformulation Studies[11-15]:

- Calibration Curve of Diltiazem Hydrochloride: 100 mg of diltiazem Hydrochloride was accurately weighed and dissolved in 100 ml of phosphate buffer pH 6.8 to get a stock solution of 1 mg/ml. Further, an aliquot was pipetted out and diluted suitably to get the concentration in the Beer's range and was scanned in the wavelength region of 200-350 nm to record the wavelength of maximum absorption (λ max). An accurately weighed quantity of Diltiazem Hydrochloride (100mg) was dissolved in small quantity of phosphate buffer pH 6.8. The volume was made up to 100 ml with phosphate buffer pH 6.8 to generate a primary stock solution of 1mg/ml. 1ml of the primary stock solution was further diluted upto 50ml to produce a secondary stock solution having concentration of 20µg/ml. Working standard solutions having concentrations 2 to 12µg/ml were prepared by appropriately diluting the stock solution. The absorbance of the working standard solution was recorded and a graph of concentration of the solution was plotted against absorbance.
- Bulk density and Tapped density: Apparent bulk density and tapped density were determined used bulk density apparatus prior to specified tapping and after tapping measurement using the following formula

$$\rho_b = M/V_b$$
$$\rho_{tap} = M/V_t$$

where, ρ_b = Bulk density
ρ_{tap} = Tapped density
M = mass of the powder blend
V_b = bulk volume i.e. volume prior to tapping
V_t = tapped volume i.e. volume after tapping.

- Compressibility Index and Hausner's Ratio: The data obtained from the bulk density and tapped density were used in the following formula to calculate Carr's index and Hausner's ratio, parameters to determine the flow ability of the powder.

$$CI = \frac{\rho_{tap} - \rho_b}{\rho_{tap}} \times 100\%$$
$$Hausner's\ Ratio = \rho_{tap}/\rho_b$$

- Angle of Repose: Angle of repose is the maximum angle possible between the base of the pile of the powder and height of the pile. It is determined by the fixed funnel method. The angle of repose (θ) is given by

$$\theta = \tan^{-1} h/r$$

Where, θ = Angle of repose in degree
h = height of pile of powder
r = radius of the base of pile

Table 1: Relationship between Flow Property, Carr's Index, Hausner's Ratio and Angle of Repose

Flow Property	Carr's Index	Hausner's Ratio	Angle of Repose
Excellent	≤ 10	1.00-1.11	25-30
Good	11-15	1.12-1.18	31-35
Fair	16-20	1.19-1.25	36-40
Passable	21-25	1.26-1.34	41-45
Poor	26-31	1.35-1.45	46-55
Very Poor	32-37	1.46-1.59	56-65
Very Very Poor	> 38	> 1.60	> 66

2.2.2 Formulation of Fast-Dissolving Tablets:

- Preparation of Dried Banana Powder: Raw banana was washed, pulp separated, mechanically chopped, and processed into a paste using a hydraulic shear and colloidal mill. The paste was dried, comminuted, and the powder was sieved and stored as dried banana powder. Banana powder, with a one-year expiration date, is a high-carbohydrate, low-protein source, and natural superdisintegrant, with its beneficial components surpassing other fruits.
- Direct Compression of Tablets:

The tablets were prepared by direct compression method. All the ingredients were accurately weighed as mentioned in table 2 and were passed through a sieve number 20 prior to mixing. The API and all the excipients except magnesium stearate were properly mixed for 30 min in a suitable container to obtain a uniform blend. The blend was further lubricated with magnesium stearate and mixed in a poly bag for 2 minutes. The blend was compressed into tablets with an average weight of 200 mg using an 8mm flat punch in a rotary tablet press.

Table 2: Formulation Table for Developing Fast Dissolving Tablets of Diltiazem Hydrochloride

Ingredients	Formulation Codes								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Diltiazem Hydrochloride	60	60	60	60	60	60	60	60	60
Sodium Starch Glycolate	3	6	9	-	-	-	-	-	-
Crospovidone	-	-	-	3	6	9	-	-	-
Croscarmellose Sodium	-	-	-	-	-	-	3	6	9
Dried Banana Powder	30	30	30	30	30	30	30	30	30
Sodium Lauryl Sulphate	4	4	4	4	4	4	4	4	4
Mannitol	50	50	50	50	50	50	50	50	50
Magnesium Stearate	10	10	10	10	10	10	10	10	10
Talc	20	20	20	20	20	20	20	20	20
Microcrystalline Cellulose	23	20	17	23	20	17	23	20	17

*** All ingredients are in mg and each formulation contain a weight of 200 mg per tablet.

2.2.3 Post compression Evaluation[16-19]:

- Thickness: Thickness and diameter of five tablets randomly selected were measured using vernier calipers. The Pharmacopoeia states that the extent of deviation in a batch of tablet should not exceed the limit of ± 5% of their determined standard values.
- Hardness: The force needed to break a tablet in a diametric compression was determined using a Monsanto hardness tester.
- Friability: Using the Roche friabilator, the percentage of tablets that were friable was calculated. Ten tablets were chosen at random, weighed initially (Winitial), and then placed in a friabilator. The friabilator was run up to 100 revolutions or for 4 minutes at 25 rpm. The tablets were weighed once more after being dedusted (Wfinal). The percentage friability was determined using the formula:

$$\% F = [\, 1 - W_{final} / W_{initial}\,] \times 100\%$$

- Weight variation: A digital weighing balance was used to weigh each of the twenty tablets that were randomly chosen from each batch in order to look for variations in weight. The average weight specified in the pharmacopeia should not be deviated from by more than two of the individual weights. The table below shows the pharmacopoeial limits.

Table 3: Limits for weight variation (USP)

Average weight of tablet	Percentage deviation (%)
130 mg or less	± 10
More than 130 mg and less than 324 mg	± 7.5
324 mg or more	±5

- Disintegration Test: The USP Disintegration Test Apparatus was used to conduct the disintegration test. Each tube of the disintegration test apparatus held six tablets individually, with discs placed on top of each tablet. The experimental conditions are used to measure the time it takes for a tablet to disintegrate in a liquid medium.
- Drug Content Uniformity: After allowing ten randomly chosen tablets to acclimate to pH 6.8 phosphate buffer overnight, the solution was filtered through Whattman filter paper the following day. With the same, appropriate dilutions were created to obtain a concentration within Beer's range. Using simulated gastric fluid as a blank, the solution's absorbance at 236 nm was recorded, allowing the drug content of each tablet to be computed.
- Dissolution Test: Type II USP apparatus was used to conduct the dissolution study. Saturated pH 6.8 phosphate buffer (900 ml) kept at 37°C was used as the dissolution medium. Throughout the study, the paddle speed remained constant at 50 rpm. Every two minutes, 5 ml of the samples were taken out and diluted to 10 ml. After that, 5 ml of fresh dissolving media kept at the same temperature was added. We used phosphate buffer pH 6.8 as a blank for spectrophotometric analysis of the samples at 237 nm. The drug release amount and cumulative drug release percentage at various time intervals were computed by analyzing the raw dissolution data.
- Release Kinetics: The in vitro release data was analyzed using a variety of kinetic models that characterize the release kinetics. The drug release profile found during the dissolution test was plotted using multiple models like Zero order rate kinetics, first order rate kinetics, Higuchi square root kinetics, Korsemeyer-Peppas model and Hixson Crowell model.

III. RESULTS

3.1 UV Spectrum Analysis:

The UV spectrum scan of Diltiazem Hydrochloride in the wavelength region of 200-350 nm showed maximum absorbance at 236 nm.

Table 4: Data for Calibration Curve of Diltiazem Hydrochloride at 236 nm

Concentration (µg/ml)	Absorbance at 236 nm
2	0.151
4	0.247
6	0.368
8	0.474
10	0.571
12	0.702
14	0.836

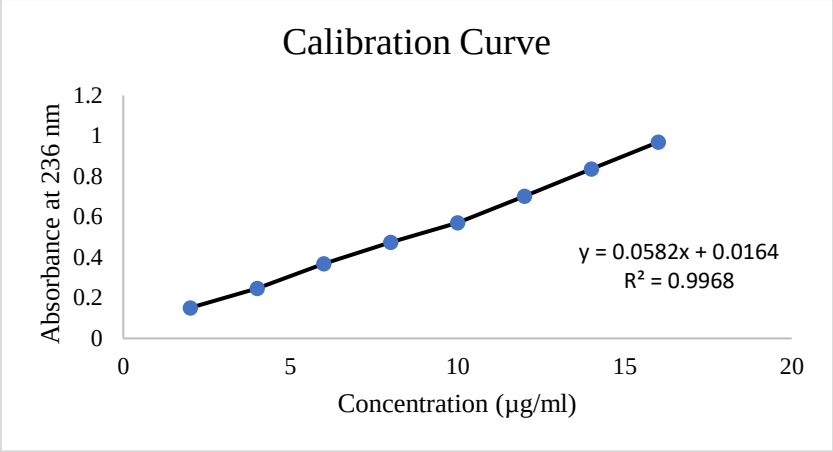

Fig 1: Calibration Curve of Diltiazem Hydrochloride at 236 nm

3.2 Pre-compression Evaluation:

The blend was evaluated for various pre-compressional parameters. The data obtained from those pre-compressional evaluation are tabulated in Table 5 as follows:

Table 5: Pre-compression Evaluation of Formulations F1-F9

Formulation Code	Bulk Density (gm/cc)	Tapped Density (gm/cc)	Compressibility Index (%)	Hausner's Ratio	Angle of Repose (°)
F1	0.538±0.002	0.658±0.001	15.96±0.05	1.22±0.01	24.16
F2	0.583±0.001	0.668±0.003	20.47±0.14	1.14±0.01	22.54
F3	0.542±0.001	0.662±0.002	18.10±0.10	1.22±0.01	24.16
F4	0.537±0.001	0.656±0.002	18.14±0.14	1.23±0.02	27.52
F5	0.539±0.002	0.645±0.003	16.43±0.23	1.19±0.02	25.78
F6	0.524±0.001	0.660±0.001	20.60±0.01	1.25±0.02	23.65
F7	0.564±0.002	0.645±0.002	13.55±0.30	1.14±0.03	24.12
F8	0.536±0.003	0.660±0.001	18.83±0.42	1.23±0.02	29.20
F9	0.546±0.002	0.662±0.001	17.52±0.27	1.21±0.01	29.22

*** The value represents Mean ± SD, n = 3

3.3 Post-compression Evaluation:

After the formulation of dosage form by direct compression technique, random samples from each batch were selected for the post compression studies. The result of the post compression studies are sorted as below:

Table 6: Post-compression Evaluation of Formulations F1-F9

Formulation Code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Weight Variation (%)	Disintegration Time (sec)	Drug Content Uniformity (%)
F1	3.12±0.02	3.53±0.03	0.51±0.02	200.70±1.45	64±0.469	97.69±0.86
F2	3.16±0.02	3.14±0.03	0.64±0.01	201.25±1.92	55±0.368	97.58±0.015
F3	3.14±0.01	3.53±0.06	0.68±0.03	201.65±1.71	46±0.356	98.90±0.042
F4	3.15±0.01	3.20±0.02	0.36±0.02	200.30±1.87	40±0.236	96.92±0.007
F5	2.98±0.09	3.26±0.02	0.78±0.02	200.35±2.03	32±0.462	98.75±0.008
F6	3.13±0.02	3.41±0.02	0.67±0.01	200.12±1.32	27±0.623	99.08±0.014
F7	2.89±0.03	3.23±0.09	0.54±0.02	200.12±1.32	40±0.782	95.27±0.020
F8	3.08±0.03	3.36±0.02	0.34±0.02	200.48±1.94	34±0.125	96.77±0.006
F9	2.97±0.09	3.23±0.007	0.56±0.02	201.54±1.28	32±0.0145	97.18±0.015

*** The value represents Mean ± SD, n = 3

Table 7: Drug Release and Kinetic Models Study

Formulation Code	Drug Release* (%)	Zero Order	First Order	Higuchi Model	Peppas Model		Best Fit Model
		R^2	R^2	R^2	R^2	n	
F1	97.05±0.39	0.890±0.004	0.949±0.001	0.890±0.003	0.955±0.004	0.597±0.003	Peppas Kinetic
F2	95.05±0.01	0.994±0.001	0.869±0.004	0.8696±0.001	0.869±0.003	0.985±0.003	Zero Order
F3	94.81±0.01	0.991±0.006	0.869±0.006	0.991±0.001	0.999±0.006	0.579±0.006	Peppas Kinetic
F4	93.19±0.39	0.993±0.004	0.846±0.001	0.988±0.006	0.994±0.006	1.082±0.007	Peppas Kinetic
F5	97.98±0.63	0.989±0.002	0.953±0.003	0.995±0.004	0.992±0.001	1.166±0.007	Higuchi Kinetic
F6	99.87±0.04	0.964±0.001	0.847±0.004	0.992±0.006	0.973±0.005	0.390±0.001	Higuchi Kinetic
F7	97.18±0.54	0.966±0.001	0.961±0.006	0.996±0.002	0.989±0.006	0.752±0.004	Higuchi Kinetic
F8	99.34±0.11	0.966±0.003	0.715±0.006	0.920±0.001	0.972±0.005	0.754±0.006	Peppas Kinetic
F9	99.50±0.26	0.9919±0.005	0.778±0.001	0.9517±0.003	0.962±0.002	2.108±0.002	Zero Order

* The drug release is the percentage cumulative drug release at the end of 16 minutes and all the value are Mean ± SD, n = 3

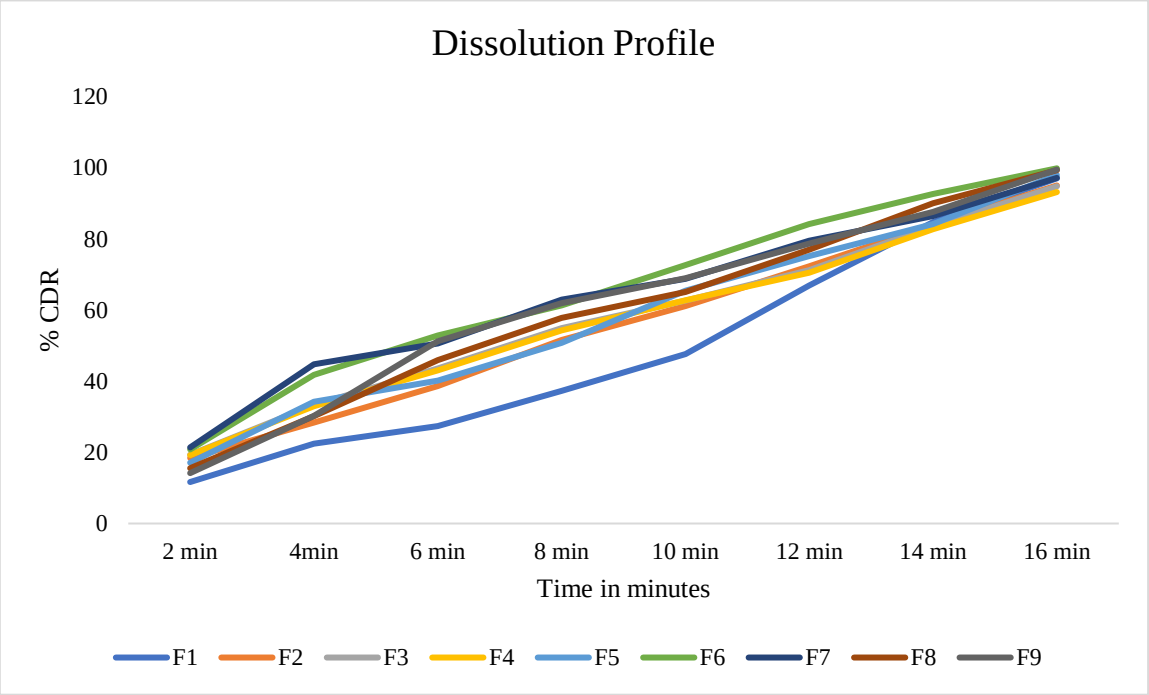

Figure 2: Dissolution Profile of Formulations F1-F9 at different time intervals

IV. DISCUSSION

A variety of artificial and natural superdisintegrants were tried to create Diltiazem Hydrochloride fast-dissolving tablets. It was looked at how varioussuperdisintegrants, at varying percentage concentrations, affected the drug release from the formulations. Numerous physicochemical parameters were used to describe the formulated tablets. The study evaluated pre-compression parameters, including angle of repose, bulk density, Carr's index, and Hausner's ratio, to improve the flow properties of pharmaceuticals, particularly in tablet formulation. All formulations were evaluated and the observed value were within the prescribed IP limits.

All of the formulations' angles of repose were found to range from 22 to 29 degrees, which is a good result. The formulations (F1 to F9) were determined to have a bulk density ranging from 0.524±0.001 to 0.583±0.001.The overall formulation's Carr's index was found to be 13.55±0.30 to 20.47±0.14, which is a good result. The compressibility of the tablet granules is good, as indicated by the Hausner's ratio of 1.14±0.01 to 1.25±0.02 for all formulations.

Observation of the post compression parameters showed that a range of 2.89 ± 0.02 to 3.16 ± 0.01 mm was found for the thickness of formulas (F1 to F9). Hardness ranged from 3.14 ± 0.12 to 3.53 ± 0.01 kg/cm2 for formulas (F1 to F9). The friability range for formulas (F1 to F9) was found to be 0.34 to 0.78 percent. 200.12 ± 1.32 to 201.65 ± 1.71 is the weight variation found for formulas (F1 to F9). A range of 93.19±0.020 to 100.09±0.014% was found to be the drug content of formulations (F1 to F9). Every result above, as displayed in Table 6, complied with the guidelines provided by the literature. The disintegration time of the tablets is shortened by an increase in superdisintegrant concentration. Of the four superdisintegrants that were employed, F6, which contained dried banana powder and crosspovidone, showed the fastest rate of disintegration. It was discovered that the disintegration times of formulations (F1 to F9) ranged from 27±0.623 to 64±0.469 seconds.

Furthermore, following the achievement of satisfactory physical parameters, tests were conducted on the dissolution of each batch. The methodology chapter's procedure was followed in conducting the dissolution study. Out of all the formulations, the batch with dried banana powder and crospovidone as superdisintegrants, F6, demonstrated a 99.87±0.04 percent release. In vitro dissolution studies yielded data kinetics that were fitted using the first-order Korsemeyer-Peppas equation. Additionally, it was noted that the Peppas model had the highest correlation (R^2>0.9945), suggesting that the drug would release through a diffusion process.

V. CONCLUSION

This study aimed to develop rapidly dissolving tablets of Diltiazem Hydrochloride for enhanced effectiveness and rapid therapeutic action. The tablets were prepared using direct compression methods and various combinations of superdisintegrants, which influenced the rate of disintegration. The dissolution profiles were fitted to First order and Korsemeyer-Peppas to establish a kinetic model of the drug. *In vitro* drug release studies showed maximum drug release within 16 minutes, suggesting that the fast dissolving tablet with crospovidone and dried banana powder as superdisintegrants could provide a convenient dosage form for optimal performance in *in-vitro* drug release, rate of disintegration, thickness, hardness, friability, and drug content.

Further research is needed to assess long-term stability and establish *in-vitro in-vivo* co-relations.

VI. REFERENCES

[1] Talevi, A. (2021). Oral Drug Delivery. In: The ADME Encyclopedia. Springer, Cham. https://doi.org/10.1007/978-3-030-51519-5_11-1.

[2] Oral Route of Drug Delivery. In: Pather I. eds. Pharmaceutics for Pharmacy Students. McGraw Hill; 2024. Accessed March 09, 2024. https://accesspharmacy.mhmedical.com/content.aspx?bookid=3459&sectionid=285254164.

[3] Alqahtani Mohammed S., Kazi Mohsin, Alsenaidy Mohammad A., Ahmad Muhammad Z. Advances in Oral Drug Delivery. Frontiers in Pharmacology (2021), Vol. 12 https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2021.618411 DOI. 10.3389/fphar.2021.618411.

[4] Seager H. (1998). Drug-delivery products and the Zydis fast-dissolving dosage form. The Journal of pharmacy and pharmacology, 50(4), 375–382. https://doi.org/10.1111/j.2042-7158.1998.tb06876.x.

[5] Basu, B., Bagadiya, A., Makwana, S., Vipul, V., Batt, D., & Dharamsi, A. (2011). Formulation and evaluation of fast dissolving tablets of cinnarizine using superdisintegrant blends and subliming material. Journal of advanced pharmaceutical technology & research, 2(4), 266–273. https://doi.org/10.4103/2231-4040.90885.

[6] Baokar, Shrikrishna & Regupathi, T. & Surfraj, Shaikh. (2011). Development and Evaluation of Fast Dissolving Tablet Loperamide HCl. Journal of Phaarmacy research (JPR). Journal of Pharmacy research. 135.

[7] Kumar, R. S., & Devi, M. G. (2022). A review article on fast dissolving tablets. International Journal of Health Sciences, 6(S2), 13684–13698. https://doi.org/10.53730/ijhs.v6nS2.8960.

[8] Hannan PA, Khan JA, Khan A, Safiullah S. Oral dispersible system: a new approach in drug delivery syste. Indian J Pharm Sci 2016; 78:2-7.

[9] Siddiqui N, Garg G, Sharma PK. Fast dissolving tablets: preparation, characterization and evaluation: an overview. Int J Pharm Sci Rev Res 2010; 2:87-96.

[10] Wisher D. (2012). Martindale: The Complete Drug Reference. 37th ed. Journal of the Medical Library Association: JMLA, 100(1), 75–76. https://doi.org/10.3163/1536-5050.100.1.018.

[11] Article, Research & Kumar, Tapan & Tandan, Hitendra & Choudhary, Chhatrapal & Alexander, Amit & Badwaik, Hemant & Dulal, And & Tripathi, Krishna. (2012). IN-VITRO EVALUTION OF COMMERCIALLY AVAILABLE SUSTAINED RELEASE CAPSULE CONTAINING DILTIAZEM HYDROCHLORIDE. International Journal of Pharmacy and Pharmaceutical Sciences. 4. 523-526.

[12] Clarke's Analysis of Drugs and Poisons 3rd ed. London. Pharmaceutical Press. [Book on CD-ROM] 2005.

[13] BADWAR, MEGHAWATI & Borse, Sandhya & JUNAGADE, MANISH & JADHAV, ANIL. (2019). FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLET OF AMLODIPINE BESYLATE. International Journal of Applied Pharmaceutics. 132-139. 10.22159/ijap.2019v11i4.31288.

[14] Vemula1 SK, Neduri K. 2015. Lovastatin Fast Dissolving Tablets: Formulation and In Vitro Evaluation. Applied Science Reports, 11 (2), 76-82. Retrieved from www.pscipub.com. (DOI:10.15192/PSCP.ASR.2015.11.2.7682).

[15] Simek, Michal & Grünwaldová, Veronika & Kratochvíl, Bohumil. (2016). Comparison of Compression and Material Properties of Differently Shaped and Sized Paracetamols. Powder and particle. 2017. 10.14356/kona.2017003.

[16] Lachman L. Lieberman H. A. & Kanig J. L. (1991). The theory and practice of industrial pharmacy (3rd ed. Indian). Varghese Pub. House. pp: 296-303.

[17] Chaturvedi, Hitesh & Garg, Mr & Rathore, Udaibhan. (2022). POST-COMPRESSION EVALUATION PARAMETERS FOR TABLETS-AN OVERVIEW. EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH. 4. 526-530.

[18] Qazi, F., Shoaib, M. H., Yousuf, R. I., Qazi, T. M., Mehmood, Z. A., & Hasan, S. M. (2013). Formulation development and evaluation of Diltiazem HCl sustained release matrix tablets using HPMC K4M and K100M. Pakistan journal of pharmaceutical sciences, 26(4), 653–663.

[19] Ahmed V., Sharma S. & Bhatt P. (2020). Formulation and Evaluation of Sustained Release Tablets of Diltiazem Hydrochloride. International Journal of Pharmaceutical Sciences and Research, doi 10.13040/IJPSR.0975-8232.11 (5).2193-98.