Indian Journal of Research in Pharmacy and Biotechnology
Volume 6, Issue 2, 2018
Journal homepage: http://www.ijrpb.com

ISSN:
2321-5674 (Print)
2320-3471 (Online)

Research article

Indexed in CAS and CABI
Impact factor:0.64

Formulation and Evaluation of mouth dissolving tablets of Diltiazem HCl

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Keywords:
Diltiazem hydrochloride, Moth dissolving tablets

Article Info:
Received: 25-02-2018
Revised: 10-03-2018
Accepted: 04-04-2018

ABSTRACT

The objective of the present investigation was to formulate and evaluate mouth dissolving tablets of Diltiazem hydrochloride (DTZ HCL). Diltiazem Hcl is a calcium channel blocker used in the management of hypertension. Mouth dissolving tablets of diltiazem hydrochloride will dissolve rapidly in the patient mouth without need of water or chewing and release its drug contents instantaneously. So this dosage form is more comfortable for Paediatric, Geriatric patients. Tablets were prepared by direct compression method using sodium starch glycolate and croscarmellose sodium and crospovidone as superdisintegrants. Mannitol, Maltitol and Erytritol were used as sweetening agents. The tablets were evaluated for weight variation, hardness, friability, content uniformity, in-vitro disintegration time, in-vitro dissolution rate studies. Hardness and friability data indicated good mechanical strength of tablets. The results of in-vitro disintegration time indicated that the tablets were dispersed rapidly in the mouth within 30 seconds. It was concluded that mouth dissolving tablets of DTZ HCL were prepared to enhance patient compliance.

1. INTRODUCTION

Despite of tremendous innovations in drug delivery, the oral route remains the preferred route for administration of therapeutic agents because of accurate dosage, low cost therapy, self-medication, non-invasive method and ease of administration leading to high level of patient compliance [1]. The most popular dosage forms are conventional tablets and hard gelatin capsules. One important drawback of such dosage forms is "dysphagia" or difficulty in swallowing for many patients, almost 50% of the population is affected by such problem. Hence, patients do not comply with prescription, which results in high incidence of noncompliance and ineffective therapy[2]. Recently, fast disintegrating drug delivery systems have started gaining popularity and acceptance as new drug delivery systems, because they are easy to administer and lead to better patient compliance[3].

In some cases such as motion sickness, sudden episodes of *allergic attacks or coughing*, and unavailability of water, swallowing conventional tablets may be difficult. Particularly the difficulty is experienced by pediatric and geriatric patients. To overcome such problems, fast disintegrating tablets or mouth dissolving tablets have emerged as an alternative dosage form[4]. Recent advances in novel drug delivery systems (NDDS) aim for enhancing the safety of a drug molecule while maintaining its therapeutic efficacy so as to achieve better patient compliance[5].

US Food and Drug Administration, Centre for Drug Evaluation and Research (CDER) defines, an ODT as "a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue." European Pharmacopoeia described ODTs as "uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed" and as tablets which should disintegrate within 3 minutes[6]. Fast disintegrating tablets (FDTs) are also known as "fast dissolving," "mouth dissolving," "rapid dissolve," "quick disintegrating," "orally disintegrating," "rapimelt," "fast melts," "orodispersible," "melt in mouth," "quick dissolving," "porous tablets," "EFVDAS," or "effervescent drug absorption system" [7].

The bioavailability of drugs may be increased due to absorption of drug in oral cavity and also due to pregastric absorption of saliva containing dispersed drugs that pass down into the stomach. Moreover, the amount of drug that is subjected to first-pass metabolism is reduced as compared to standard tablet[8].

2. MATERIALS AND METHODS

Materials: Diltiazem hydrochloride (DTZ HCL) was a gift from Piramal health care Ltd., Mumbai. Mannitol was obtained from Roquette India Pvt Ltd., Mumbai. Maltitol, Erytritol were obtained from Cargill India Pvt Ltd. Crospovidone, Sodium starch glycolate were obtained from Yarrow chem products, Mumbai. Croscarmellose Sodium from Ozone international,

Mumbai. Magnesium stearate from Rasayan Laboratories, Gujarat. Microcrystalline cellulose from Indian Research Products, Chennai and talc from Otto Chemie Pvt Ltd., Mumbai.

Method of preparation: 60mg of DTZ HCL was accurately weighed and other diluents were added and mixed thoroughly and finally talc, magnesium stearate was added and blended for 5 min. These blends were compressed with 8mm punch to a hardness of 3kg/cm² by using a single stage compression machine. Various batches of tablet formulations prepared were shown in Table-1. Optimum combination was taken based on powder blend properties and disintegration time of the tablets.

Analytical method for the estimation of DTZ HCL:

Preparation of stock solution: 10 mg of DTZ HCL was dissolved in 5 mL of methanol in a 10 mL volumetric flask and the volume was made up with methanol. For the estimation of DTZ HCL the stock solution was subsequently diluted to get a series of dilutions 2, 4, 6, 8 and 10 µg/mL of solution and the absorbance values were measured at 237 nm (UV-VIS spectrophotometer, SL-150, Elico) against pH 6.8 phosphate buffer as blank.

Evaluation of micromeritic properties of blends:

Bulk density: Apparent bulk density (g/ml) was determined by placing pre-sieved bulk powder blend into a graduated cylinder via a large cylinder and measuring the volume and its weight

Tapped density: It was determined by placing a graduated cylinder, containing a known mass of powder on mechanical tapping apparatus, which was operated for fixed number of taps (around 250) until the powder bed volume reached a minimum. Using the weight of powder in a cylinder and this minimum volume, the tapped density was computed. From the results of bulk density and tapped density, Carr's index and Hausner's ratio were calculated.

Angle of repose: For the measurement of angle of repose, a glass funnel was secured with its tip at a given height (h) above a piece of graph paper placed on a horizontal surface. Powder was poured through the funnel until the apex of the conical pile touched the tip of the funnel. The angle of repose was calculated with the formula tan Θ= h/r, where Θ is the angle of repose and r is the radius of the conical pile.

FTIR Spectral analysis: To investigate the possibility of chemical interaction between drug and polymer FTIR spectra of pure drug and polymers were analysed over the range of 4000-500 cm^{-1}. It showed that there was no significant interaction between the drug and polymer and were compatible with each other. The IR- spectrum of pure drug and polymer are given in Fig 2 & 3.

DSC Studies: Thermograms of the pure drug and the optimized formulation F8 were shown in Fig 4. A sharp melting transition of Diltiazem hydrochloride pure drug was observed at 216.20°C. In Formulation F8 melting endoderm at 214.08°C was observed. This confirmed that the presence of other excipient did not affect the drug nature and it was well maintained in the selected formulation.

Evaluation of DTZ HCL Mouth dissolving tablets:

Weight Variation: Ten tablets were selected at a random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight.

Hardness: The tablet crushing load, which is the force required to break a tablet by compression in the radial direction, was determined using a Monsanto hardness tester.

Friability: Friability of tablets was measured by using Roche Friabilator. Friability was evaluated from the percentage weight loss of 20 tablets tumbled in a friabilator at 25 rpm for 4 minutes. The tablets were dedusted, and the loss in weight caused by fracture or abrasion was recorded as the percentage weight loss. Friability below 1% was considered acceptable.

Content uniformity:

***In-vitro* disintegration time**: The *in-vitro* disintegration time was determined using disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus and one tablet was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.

***In-vitro* dissolution study:** *In-vitro* dissolution studies for all the prepared tablets was carried out using USP. Paddle method at 50rpm in 900ml of phosphate buffer pH 6.8 as dissolution medium, maintained at 37±0.5ºC. 5 ml aliquots were withdrawn at the specified time intervals, filtered through whatmann filter paper and assayed spectrophotometrically at 237nm. An equal volume of fresh medium, which was pre-warmed at 37± 0.5ºC, was replaced into the dissolution medium after each sampling to maintain the constant volume though out the test. Dissolution rate was studied for all designed formulations.

Table.1.Formulae of Mouth dissolving tablets

Ingredient(mg/tab)	F1	F2	F3	F4	F5	F6	F7	F8	PD
Drug	60	60	60	60	60	60	60	60	60
Mannitol	172	97	-	-	-	-	-	-	-
Maltitol	-	-	97	-	-	-	-	-	-
Erytritol	-	-	-	97	97	97	97	97	-
Crospovidone	25	25	25	25	-	-	29	33	-
Sodium starch glycolate	-	-	-	-	25	-	-	-	-
Croscarmellose sodium	-	-	-	-	-	25	-	-	-
Magnesium stearate	27	27	27	27	27	27	27	27	-
Talc	6	6	6	6	6	6	6	6	-
Micro crystalline cellulose	6	6	6	6	6	6	6	6	-
Sweetener	4	4	4	4	4	4	4	4	-
Total weight	300	225	225	225	225	225	225	225	60

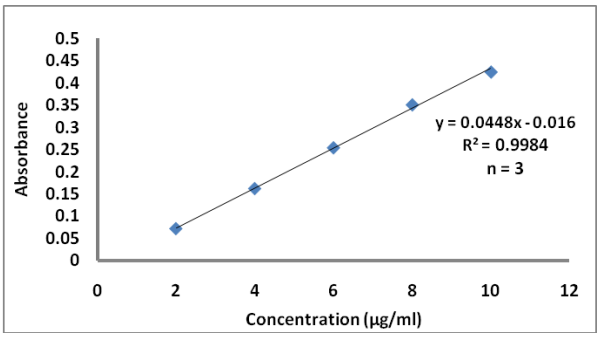

Figure.1.Calibration curve for DTZ HCL in pH 6.8 phosphate buffer

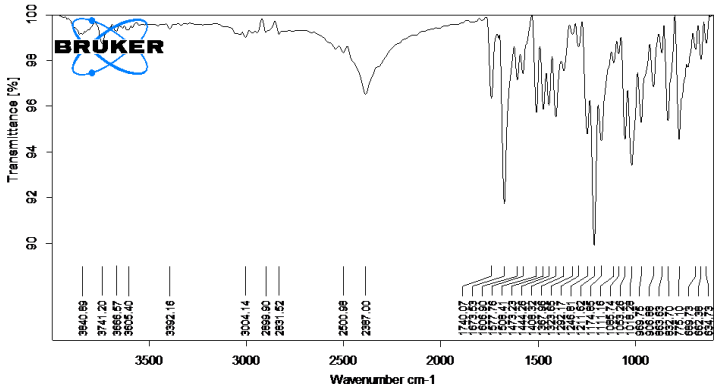

Figure.2.FT- IR Spectra of DTZ HCL

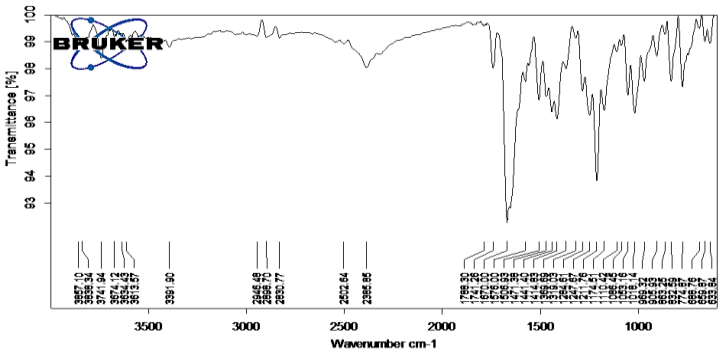

Figure.3.FT- IR Spectra of optimized formulae (F8)

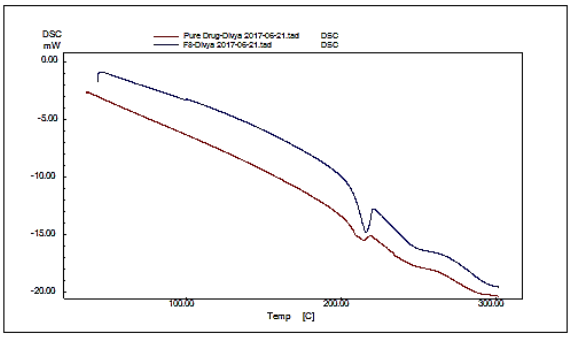

Figure.4.DSC of pure drug and formulation F8

Table.2.Pre-compressional characteristics of the powder blends

Formulation code	Parameters (Mean ±SD)				
	Bulk density (gm/cc)	Tapped density (gm/cc)	%Compressibility index	Hausner's ratio	Angle of repose (degrees)
F1	0.46±0.12	0.54±0.42	21.02±0.81	1.19±0.49	26.43±0.61
F2	0.39±0.56	0.41±0.16	17.54±0.74	1.20±0.94	24.98±0.59
F3	0.38±0.41	0.50±0.17	19.31±0.96	1.14±0.65	23.72±0.87
F4	0.40±0.23	0.49±0.49	15.36±0.61	1.13±1.17	27.46±0.64
F5	0.38±0.39	0.51±0.49	15.69±0.71	1.14±0.94	23.13±0.49
F6	0.41±0.18	0.42±0.36	16.01±0.67	1.17±0.93	27.10±1.67
F7	0.38±0.12	0.46±0.11	18.79±0.98	1.16±0.83	24.02±1.39
F8	0.38±0.25	0.48±0.26	15.95±0.73	1.13±0.69	24.98±1.79

Table.3.Post compression characteristics of the DTZ HCL MDTs

Formulation code	Parameters (Mean ±SD)			
	Mean weight ± % variation	Hardness (Kg/cm^2)	Friability (%)	Content uniformity (%)
F1	300±0.97	3.5±0.32	0.19±0.42	99.92±1.26
F2	224.1±0.21	3.1±0.68	0.12±0.96	97.69±0.52
F3	226.0±1.8	3.5±0.91	0.14±0.48	98.9±0.34
F4	225.1±0.94	3.01±0.56	0.15±0.71	98.01±0.42
F5	223.9±0.79	3.0±0.42	0.14±0.38	100.01±0.29
F6	224.6±0.67	2.9±1.93	0.11±0.63	99.81±0.79
F7	224.7±0.19	2.9±0.93	0.12±0.16	100.19±0.29
F8	224.8±0.31	3.0±0.21	0.12±0.19	99.96±0.64

Table.4.In-vitro disintegration data of MDTs

Formulation code	Disintegration time(sec)
F1	31
F2	27
F3	29
F4	26
F5	29
F6	28
F7	29
F8	25

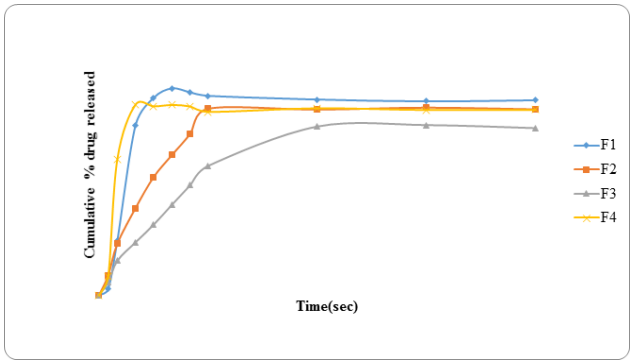

Figure.5.Drug release profile of tablets containing Mannitol, Maltitol, Erytritol as sweeteners

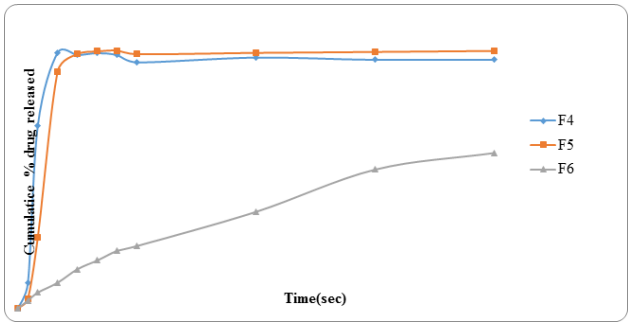

Figure.6.Comparative drug release profiles of formulation tablets containing CP, SSG and CCS as super disintegrants

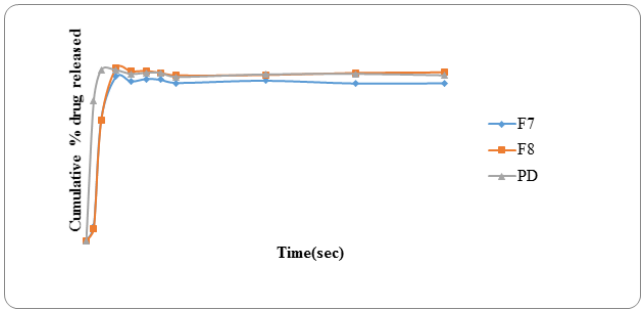

Figure.7.Comparative Drug release profile of optimized formulae

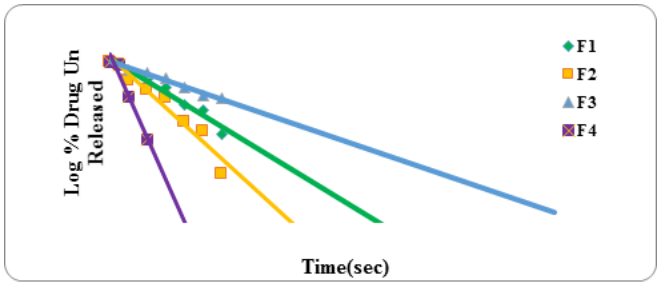

Figure.8.Comparative first order release kinetics of F1, F2, F3 and F4

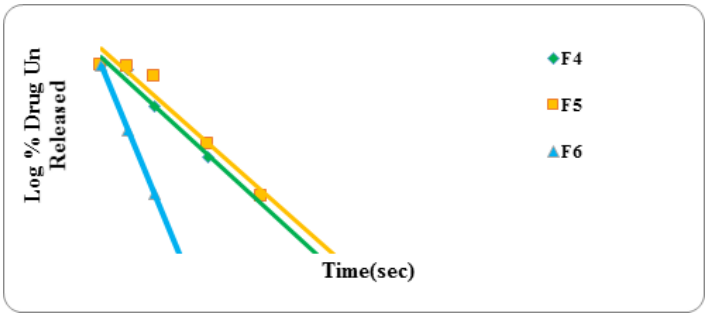

Figure.9.Comparative first order release kinetics of F4, F5 and F6

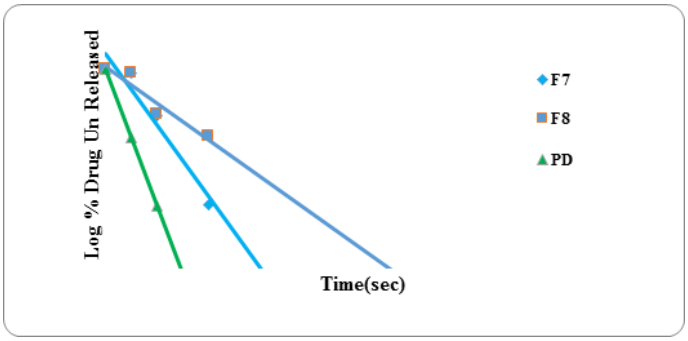

Figure.10.Comparative first order release kinetics of F7, F8 and PD

3. RESULTS AND DISCUSSIONS

The present investigation was undertaken to formulate and evaluate mouth dissolving tablets of DTZ HCL by direct compression method using sweeteners like Mannitol, Maltitol, Erytritol and superdisintegrants like crospovidone, sodium starch glycolate and croscarmellose sodium. Major functional groups present in DTZ HCL showed characteristic peaks in IR spectrum. Figure-2 and 3 shows peaks observed at different wave numbers and the functional group associated with these peaks for drug and drug with different polymer. The major peaks are identical to functional group of DTZ HCL. Hence, it was confirmed that there was no incompatibility between drug and various polymers. The results obtained by evaluating the powder blends of drug and excipients are shown in Table-2. The two most important attributes for the direct compression formula are good flow and good compressibility. The angle of repose <30° indicates free flowing of granules. Values for angle of repose were found in the range of 23° to 27° showing that the blend of powder was free flowing and can be used for direct compression.The value for Carr's index was in between 15-21% (<20), indicating that all the batches of powder blends were having good compressibility.

The results for evaluation of different batches of DTZ HCL MDTs prepared by direct compression method were shown in Table-3. Weight variation was observed within the acceptable limit for uncoated tablets as per United States Pharmacopoeia. One of the primary requirements of immediate release preparation is faster disintegration. It is well known to formulation scientists that the tablets with higher crushing strength show longer disintegration time. Hence the hardness of tablets was determined and was found to be in the range of 2.90 to 3.5 Kg/cm^2. Friability was observed between 0.11 to 0.19%, which were below 1% indicating sufficient mechanical integrity and strength of the prepared tablets. Thus hardness and friability data indicates good mechanical resistance of tablets. In-vitro disintegration time for different batches of MDTs was 25 to 31 seconds and shown in Table- 4. F8 containing erytritol and CP 15% showed minimum disintegration time of 25 seconds.

In-vitro dissolution studies were carried out for all 9 formulations by using pH 6.8 phosphate buffer as dissolution medium. In-vitro dissolution data shows that formulation F8 shows improved dissolution when compared to other formulations. F8 shows 94.93% drug release within 30 seconds. When the data were plotted according to the first-order equation, the formulations showed a fair linearity, with regression values between 0.985 and 0.998. The comparative first order release kinetic profiles of different formulations were shown in Figure 8 to 10 .The order of regression value of optimized formulae (F8) was found to be 0.998. The 'K' value of different formulations were found to be in the following order F8 > F7>F6>F5>F4. F8 formulation was optimized based on disintegration time and dissolution profile. F8 formulation showed 94.93% drug release within 30 sec.

From the above discussion it was concluded that the formulation, F8 containing CP (15%) and erytritol as sweetener can be considered as optimized formulation based on it's release characteristics.

4. CONCLUSION

Mouth dissolving tablets of DTZ HCL were prepared by direct compression method using sodium starch glycolate, croscarmellose sodium and crospovidone as superdisintegrants. The tablets disintegrated rapidly in oral cavity and had acceptable hardness and friability. In-vitro drug release from the tablets shows significantly improved drug dissolution. Hence it could be concluded that the superdisintegrant based mouth dissolving tablets of DTZ HCL would be quite effective in providing quick onset of action without need for water for swallowing or administration.

REFERENCES

1. Lachman L, Liebermann HA, Kaing JL, The theory and practice of industrial pharmacy. 3rd Ed. Bombay: Varghese publishing house, 1987, 293-335.

2. Liebermann HA, Lachman L, Schwartz JB, Pharmaceutical dosage forms tablet volume 1. 2nd Ed. New York: Marcel Dekker Inc, 2005, 75-79.

3. Ghosh TK, P Fister WR, Drug delivery to the oral cavity molecules to market. U.S.A: Taylor and Francis Group, 2005, 261-289.

4. Shukla D, Chakraborty S, Singh S, Mishra B, Mouth dissolving tablets I: An overview of formulation technology. Sci. Pharm, 7(7), 2009, 309 -326.

5. Bhowmik D, Krishnakanth CB, Chandira RM, Fast dissolving tablet: An overview, J. Chem.Pharm. Res, 1(1), 2009, 163-177.

6. Kumaresan C, Orally disintegrating tablet – rapid disintegration, sweet taste and target release profile, 6(5), 2008, 345-358.

7. Bhaskaran S, Narmada GV, Orally disintegrating tablets. Indian Pharmacist, 1(2), 2002, 9-12.

8. Swarbrick J, Boylan J, Encyclopedia of pharmaceutical technology, 2nd Ed. New York: Marcel Dekker; 2002: 2623-2638.