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Formulation and Characterization of Diltiazem Hydrochloride Oral Fast Dissolving Films

Sudhir Maddela[1*], Naveena Chukka[1], Alekhya M[1], Sruthi Vemuri[1], Pamula Reddy B[1]

[1*]Associate Professor, Department of Pharmaceutics, Nirmala College of Pharmacy, Atmakur, Mangalagiri-522503.

***Corresponding Author**:

Sudhir Maddela,Associate Professor of Pharmaceutics, Nirmala College of Pharmacy.
E-mail: sudhir.spark@gmail.com

ABSTRACT:

The present investigation was aimed with an objective to formulate and evaluate Diltiazem HCl (DTZ) oral fast dissolving films (OFDFs) to improve convenience and compliance of elderly and pediatric patients. In the present investigation OFDFs were prepared by using film forming agents like Hydroxyl propyl methylcellulose (HPMC) E15, HPMC K4M, Methyl cellulose (MC) and Sodium carboxy methyl cellulose (Na CMC), surfactants like Sodium lauryl sulphate (SLS) and Poly vinyl pyrrolidone (PVP) and Polyethylene glycol (PEG 400) as plasticizer. The OFDFs were prepared in petri plates employing solvent casting technique. The prepared OFDFs were characterized for DTZ content, thickness, weight variation, folding endurance and *in vitro* drug release studies. The compatibility between DTZ and excipients was confirmed by FTIR in OFDFs. The DTZ OFDFs prepared with HPMC E15 as film forming agent showed superior DTZ release compared to other film forming agents. The DTZ OFDFs containing PVP showed slight increased DTZ release compared to OFDFs containing SLS as solubilizing agent. All the prepared OFDFs showed 100 percent cumulative of DTZ release within 30 minutes.

KEYWORDS: Diltiazem HCl, Oral Fast Dissolving Films, Solvent Casting Method and Compatibility.

INTRODUCTION:

DTZ is a calcium channel blocker used in the treatment of hypertension and angina pectoris. DTZ blocks voltage sensitive calcium channels in blood vessels by inhibiting ion control gating mechanism, there preventing calcium levels in blood. Hypertension (HT) is defined as a condition in which blood vessels have persistently raised blood pressure (1). For the time being, HT became more chronic to the maximum extent caused at the middle age of patients. HT is of two types; primary HT is caused due to nonspecific lifestyle, whereas secondary HT caused due to preexisting medical condition like congestive heart failure, kidney failure. Formulation of dosage forms for chronic disease is major task to researches. So, they were formulating various types of dosage forms with different route of administration.

Oral route is most acceptable for dosage form administration compared to other routes because of its simplicity in self-administration. A wide range of research activity is involved in reformulating existing drugs into new dosage forms (2). In that one of new dosage form is OFDFs prepared by using hydrophilic polymers to attain faster onset of action. Recently, the trans mucosal route has gained a significant scope and potential to reduce the problems associated with other solid oral formulations (3). Developing formulations for pediatric has been a challenging task amongst other factors palatability is one of significant factor influencing patient convenience. So, taking in consideration about ease of administration and swallowing, these impediments led to development of Oral Disintegrating Tablets (ODTs). ODTs are defined as "A solid dosage form that consists of active pharmaceutical substance which disintegrates rapidly within seconds, when placed upon tongue without drinking water". For pediatric patients the fear of choking is a big task so, again it remained as a drawback for ODTs especially for these age specific patients (4). Therefore, the development of OFDFs has gained popularity for the delivery of OFDFs when placed on tongue requires no water or chewing for release of active ingredient from dosage form (5).

Need for formulating OFDFs is there especially for age specific patients like pediatrics and geriatrics to overcome the choking fear and unwillingness to take other oral dosage forms like tablets and pills (6). Due to more flexibility and comfort OFDFs are leading form of oral dosage forms in terms of formulation aspects. OFDFs gains consumer acceptance by fast dissolution rate, self-administration and with these dosage forms there is no fear of choking. OFDFs have some special features compared to other dosage forms such as these are thin elegant films, unobstructive, quick dissolving and fast disintegrating.

There are some formulation considerations in formulating of OFDFs such as taste masking, physical appearance and palatability for improving consumer compliance (7). For improving palatability sweetening and coloring agents were used and to increase the dissolution and disintegration of film surfactants were used. The OFDFs can be prepared by employing different methods like solvent casting method, semisolid casting, hot melt extrusion, solid dispersion extrusion and rolling

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method. In the present investigation solvent dispersion technique was used with an objective of formulation and evaluation of DTZ OFDFs to attain quicker onset of action and better therapeutic efficacy.

1. MATERIALS AND METHODOLOGY:

2.1. Materials:

DTZ was obtained from Aurobindo Pharma (Hyderabad), HPMC E15, HPMC K4M, Na CMC, and MC were purchased from Loba Chemie Pvt. Ltd, SLS was obtained from Finar Chemicals Pvt. Ltd and other excipients used in formulation were of analytical grade.

2.2. Preparation of Artificial Saliva Buffer:

Artificial saliva is prepared by accurately weighing 0.844 gm of sodium chloride, 1.2 gm of potassium chloride, 0.93 gm of calcium chloride, 0.11 gm of magnesium chloride, and 0.342 gm of potassium phosphate and dissolved in 1000 mL of distilled water. The pH was adjusted with 0.1N hydrochloric acid to 5.7 (8).

2.3. Construction of calibration curve for DTZ:

Accurately weigh 10 mg of pure DTZ and transfer it in to 10 mL volumetric flask containing ethanol to sufficiently dissolve the DTZ and make up the volume to the mark with distilled water. From this, subsequent dilutions were made to prepare a series of standard solutions 2, 4, 6, 8, 10 µg/mL solutions with artificial saliva. The absorbance of these solutions was measured using UV-Visible spectrophotometer at 228 nm against blank.

2.4. Preparation of DTZ OFDFs:

The DTZ OFDFs were prepared using various film forming agents like HPMC E15 LV, HPMC K4M, Na. CMC, MC and solubilizing agents like SLS and PVP were used. The OFDFs were prepared by employing solvent casting technique. Initially, the drug was dissolved in a mixture of solvents (methanol, and water). To this required amounted remaining ingredients were added with continuous stirring. Finally, the polymer was added and the stirring was continued till a homogenous and a clear solution is obtained. The solution is then casted in petri plates and were dried at 50^{o}C for 4 hours. The OFDFs prepared were peeled and stored in desiccator till further use (9).

2.5. FTIR Studies:

The FTIR studies were carried out using ATR FTIR spectrometer (Bruker, Germany). The FTIR spectra were measured at 4000 – 5000 cm^{-1} at a resolution of 1 cm^{-1}. The powder or film sample was simply placed on the ATR and the spectra were collected.

2.6. EVALUATION OF ORAL FAST DISSOLVING FILMS:

2.6.1. Morphological studies:

The DTZ OFDFs prepared were tested visually for color, homogeneity, transparency and texture. The OFDFs were stored at 25^{0}C and 75% RH for 6 months. The OFDFs were tested periodically for morphological properties (10).

2.6.2. Variation of Mass:

1 cm^2 OFDF cut from different areas of OFDFs among different batches and mass was measured to determine mass variation. The estimations were carried out in triplicate (11).

2.6.3. Thickness:

The thickness was measured with film gauge at different places of OFDFs to evaluate the reproducibility of the preparation method. The dial reading of the film gauge was adjusted to zero and then the film was held on the anvil and the reading on the dial was noted. The estimations were carried out in triplicate (12,13).

2.6.4. Folding Endurance:

The folding endurance was measured manually for the prepared films to measure the brittleness of the film. A strip of film of specific size (1*1 cm^2) was cut and repeatedly folded at the same place till it breaks. The number of times the film could be folded at the same place without breaking gives the folding endurance value (14-16).

2.6.5. DTZ content:

Three 1 cm^2 films were taken in 10 ml volumetric flask and dissolved in 5 ml of distilled water and the final volume was made up to the mark with artificial saliva and then analyzed by UV Visible spectrophotometer at 228 nm (17-19).

2.6.6. Invitro drug release studies:

The in vitro dissolution studies were performed with modified USP Type V rate testing apparatus using 500 ml of artificial saliva as dissolution medium. Each film with a dimension of appropriate size (1*1.6 cm^2) equivalent to 30 mg of DTZ was placed on a watch glass covered with nylon wire mesh. 5 mL of samples were withdrawn periodically at 1, 2, 3, 4, 5, 10, 20, and 30. minutes and every time replaced with 5 ml of fresh dissolution medium to maintain sink conditions (20,21). The samples were analyzed by measuring absorbance at 228 nm by UV Visible spectrophotometer. The experiment was carried out in triplicate.

3. RESULTS AND DISCUSSION:

3.1. Preparation of DTZ OFDFs:

The OFDFs were prepared as per the formula given in Table 1. The OFDFs were prepared by using various film modifiers like HPMC E15, HPMC K4M, Na CMC, MC and PEG 400 as plasticizer and observed for their film forming capacities and morphology. The polymers showed good film forming properties and the OFDFs obtained were transparent with

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faster drying rates and good mechanical properties. Moreover, the OFDFs prepared were easily peeled from petri plates after casting. The obtained OFDFs were stored in desiccator till further use.

3.2. Morphological Properties:

OFDFs prepared were tested for homogeneity, transparency, color and smoothness. All the OFDFs prepared were stable and exhibited good morphological properties and were elegant in appearance. Moreover, no recrystallization of DTZ was observed.

3.3. FT-IR Analysis:

The compatibility between DTZ and excipients used in formulation of OFDFs was studied using FTIR studies. The DTZ showed characteristic peaks at 1679.99 cm^{-1} (C=O stretching) and N-H stretching at 1607.21 cm^{-1} (C=O stretching) wave number. The peaks of DTZ were well retained in OFDFs and results indicate there is no interaction between DTZ and excipients used in the preparation of OFDFs. The FTIR spectra of DTZ and selected OFDFs were shown in Fig 1.

3.4. Variation of Mass:

Formulated OFDFs were subjected for weight variation with random batches. In all formulations same mass of film was obtained indicating reproducibility of method of preparation and spread ability of film. Weight variation result is in between the range of 0.24 - 0.28 gm. The weight variation values were given in the following table 2.

3.5. Thickness Uniformity:

Thickness of film was evaluated by film gauge at different places of OFDFs whole area to evaluate the reproducibility of preparation method. The thickness of OFDFs were found in between 50 to 60µm and values were shown in table no 2. The OFDFs prepared with HPMC K4M (F4) showed higher thickness (59.5±0.707) followed by OFDFs prepared with MC (F8, 57.9±1.414), Na CMC (F6, 55±0.707), and HPMC E15 (F1, 51.5±0.707). The solubilizing agent didn't show any significant effect on thickness of OFDFs.

3.6. DTZ content:

Films from different areas of OFDFs were estimated for DTZ content. The values were given in table 2. The DTZ content in OFDFs were found to be in the range of 9-17 mg. The DTZ OFDFs (F4) showed more drug content values compared to others may be due to its higher thickness, whereas, the OFDFs prepared with HPMC E15 showed less DTZ content.

3.7. Folding Endurance:

A strip of film of specific size (1*1 cm) was cut and repeatedly folded at the same place till it breaks. The film was folded at the same place until the film breaks. DTZ OFDFs F1 showed higher folding endurance values compared to other OFDFs. The results were given the table 2.

3.8. In Vitro Dissolution Studies:

The in vitro dissolution studies were carried out in modified USP Type-V rate testing apparatus using 500 mL of pH 5.7 artificial saliva as dissolution medium. A temperature of 37^0C and 50 rpm was maintained. The cumulative percent of DTZ release from OFDFs containing HPMC E15 (F1) is significantly superior compared to other OFDFs prepared with Na CMC, MC, and HPMC K4M as shown in Fig 2(A). The formulations containing PVP showed a slightly increase in DTZ release rates compared to OFDFs containing SLS as solubilizing agent. The effect of solubilizing agent on DTZ release was shown in FIG 2(B). Overall, OFDFs containing HPMC E15 as film forming agent and PVP a solubilizing agent showed superior dissolution rates compared to other formulations.

4. CONCLUSION:

In the present investigation DTZ was formulated to OFDFs, the OFDFs showed good morphological and mechanical properties with good in vitro dissolution profile indicating faster onset of action and better therapeutic efficacy. The OFDFs were stable even after six months indicating that DTZ in OFDFs has not recrystallized.

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CONFLICT OF INTERESTS:

The authors declare that they have no conflict of interests.

Abbreviations:

OFDF- oral fast dissolving films; DTZ- Diltiazem; HCl- hydrochloric acid; PVP- poly vinyl pyrrolidine; HPMC- hydroxyl propyl methyl cellulose; SLS- sodium lauryl sulphate; Na. CMC- sodium carboxy methyl cellulose; HT- hypertension; ODT- oral disintegrating tablets; FT-IR-Fourier transform infrared spectroscopy.

TABLES:

Table 1: Composition of DTZ OFDFs

Ingredients (%)	F1 (HPMC E 15 LV PVP)	F2 (HPMC E 15 LV SLS)	F3 (HPMC K4M SLS)	F4 (HPMC K4M PVP)	F5 (Na CMC SLS)	F6 (Na CMC PVP)	F7 (MC SLS)	F8 (MC PVP)

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Drug	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Methanol	25	25	25	25	25	25	25	25
Polymer	3.75	3.75	3.75	3.75	3.75	3.75	3.75	3.75
SLS	0.125	-----	0.125	-----	0.125	-----	0.125	-----
PVP	-----	0.125	0.125	-----	0.125	-----	0.125	-----
PEG	0.125	0.125	0.125	0.125	0.125	0.125	0.125	0.125
Citric acid	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06
Mannitol	1.87	1.87	1.87	1.87	1.87	1.87	1.87	1.87
Flavouring agent	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06
Colouring agent	0.06	0.06	0.06	0.06	0.06	0.06	0.06	0.06
Water	62.5	62.5	62.5	62.5	62.5	62.5	62.5	62.5
Total (%)	100	100	100	100	100	100	100	100

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Table 2: Physico-chemical and mechanical properties of DTZ OFDFs

FORMULATION OF OFDF's	EVALUATION PARAMETERS			
	Weight Variation±SD	Thickness (µm)±SD	Drug content(mg)±SD	Folding Endurance
F1	0.285±0.0.21	51.5±0.707	15.1±0.32	112
F2	0.275± 0.035	50.5±0.707	15.6±0.67	96
F3	0.285±0.021	58±1.414	23.1±0.18	129
F4	0.26±0.014	59.5±0.707	20.6±0.52	147
F5	0.265±0.035	56±1.414	16.5±0.34	98
F6	0.275±0.013	55±0.707	15.2±0.46	119
F7	0.26±0.033	57.2±1.414	16.5±0.32	92
F8	0.285±0.014	57.9±1.414	19±0.61	81

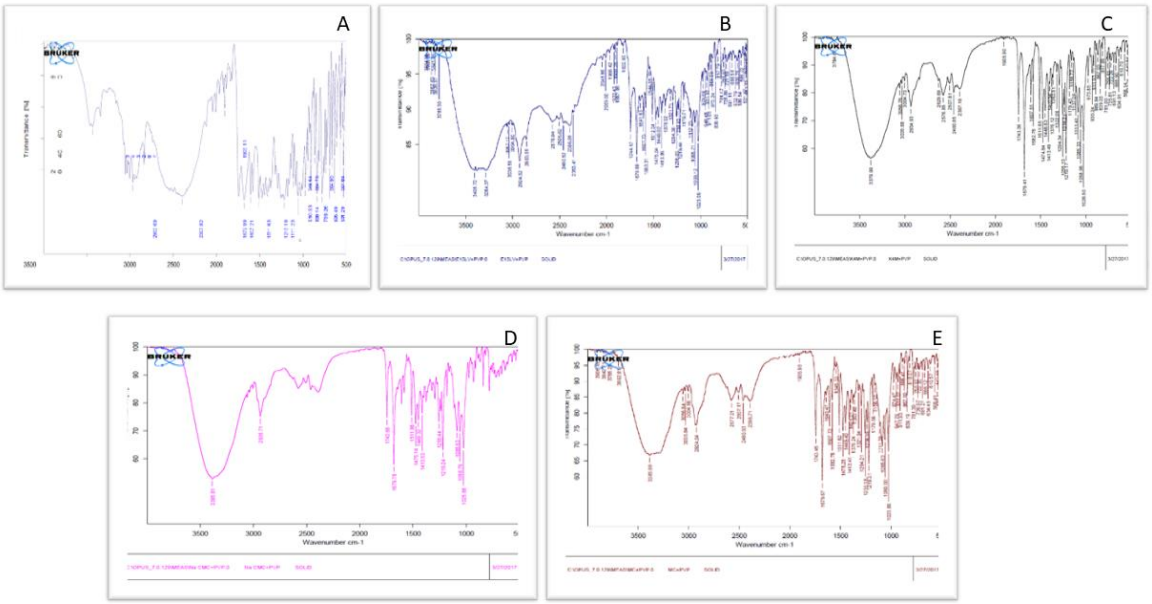

Figure 1: FT-IR spectra of (A) pure DTZ, (B) F1, (C) F4, (D) F6, (E) F8

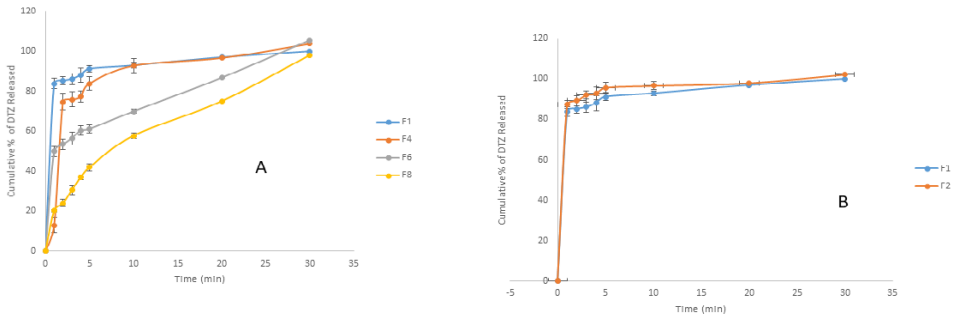

Fig 2: Comparative in vitro drug release profile of DTZ from OFDFs (A) Effect of polymer on DTZ release, (B) Effect of solubilizing agent of DTZ release

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