WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 5.990
Volume 4, Issue 5, 2534-2549. Research Article ISSN 2277– 7105

# FORMULATION AND EVALUATION OF MODIFIED RELEASE TABLET OF DONEPEZIL HYDROCHLORIDE

***Dr. Patel Bhavik N., Patel Devyani B., Dr. Patel Chhagan N.**

Department of Pharmaceutics and Pharmaceutical Technology, Shri Sarvajanik Pharmacy College, Near Arvind Baug, Mehsana, Gujarat, India.

Article Received on
15 March 2015,

Revised on 06 April 2015,
Accepted on 30 April 2015

***Correspondence for Author**
**Dr. Patel Bhavik N**
Department of Pharmaceutics and Pharmaceutical Technology, Shri Sarvajanik Pharmacy College, Near Arvind Baug, Mehsana, Gujarat, India.

## ABSTRACT

The purpose of present work was a developed sustained release matrix tablet of Donepezil hydrochloride stable and provide sustained therapeutically effective plasma level over a 24 hour period with reduced undesired side effects, and developed dosage form shows better in-vitro drug release than that of marketed available (SR) formulation. Donepezil hydrochloride matrix tablet were prepared by wet-granulation technique using natural polymers Guar gum, Xanthan gum, Karaya gum and pectin a release controlled polymer. The prepared SR tablets were evaluated for thickness, Hardness, friability, drug content and in-vitro drug release.Using experiment design, the prepared formulations evaluated. The optimized formulation E7 containing guar gum and PVP-K30 showed good in-vitro drug release and grater similarity factor with marketed (SR) formulation profile (76.22), and other physicochemical properties that were suitable for SR tablet. Stability study of optimized formulation showed that optimized formulation was stable at accelerated environment conditions.

**KEYWORDS:** Donepezil hydrochloride, Sustained release, in-vitro drug release, similarity factor (*f*2), Guar gum

## INTRODUCTION

Over the Past 30 years, as the expense and complications involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantages of Sustained drug delivery, greater attention is being paid on development of oral sustained release drug delivery systems. The goal in designing sustained release drug delivery system is to reduce the frequency of the dosing, reducing the dose & providing uniform drug delivery.

So, Sustained release dosage form is a dosage form that releases one or more drugs continuously in predetermined pattern for a fixed period of time, either systemically or locally to specified target organ.[1-3] Sustained release dosage forms provide better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery.

Immediate release dosage forms result in a quick rise of blood plasma levels with a subsequent decrease due to elimination. The use of sustained release medication could be beneficial in order to maintain therapeutic plasma levels. Furthermore, it would improve the patient compliance with the use of once daily drug administration. Although initial development costs may be high, controlled release dosage forms have the potential to enhance clinical efficacy and reduce the total treatment cost as compared to immediate release dosage forms.

Donepezil Hydrochloride (DH) is a second-generation cholinesterase inhibitor (ChEI), used for the treatment of Alziemers disease (AD) having greater specificity for the brain acetyl cholinesterase enzyme (AchE). This compound characterized by a long plasma half-life (70h) and a bioavailability of 100%2. Initially DH was available in immediate release dosage forms, which resulted in spikes in the patient's blood plasma levels within 2 to 5 hrs after the drug administration. Eisai Research Institute discloses a sustained release formulation of Donepezil Hydrochloride that overcomes the side effects of the immediate release formulations.

## MATERIALS AND METHODS

### Materials

Donepezil hydrochloride was gifted Astron research Ltd, Gandhinagar. Guar gum was supplied by yarrow chem, Mumbai, India. Xanthan gum was supplied by yarrow chem, Mumbai, India. Pectin was supplied by chem, Mumbai, India. Polyvinyl pyrrolidone K30 (PVP K30) was supplied by Fine Chemical Limited, Mumbai, India. All the materials used were of Pharmaceutical or analytical grade.

### Methods

#### Preparation of matrix tablets by Direct-compression technique

Matrix tablets of Donepezil HCL with other excipients were prepared by direct compression technique. The weight of Donepezil HCL was kept constant in all the prepared tablets at

23mg/tablet. Using various polymers viz; Guar Gum, Xanthan Gum, Karaya Gum, and Pectin. microcrystalline cellulose was selected as tablet diluent and Magnesium stearate and talc were used as a lubricant.to make powder mixtures, the drug, polymer, microcrystalline cellulose were thoroughly mixed in polybag for 20min.This powder mixture was the lubricated with Magnesium stearate and talc then compressed into tablets in 8mm flat punch rotary tablet compression machine. The tablet weight was 200mg.

**Preliminary screening**

Preliminary screening was carried out to select a natural controlled release polymers viz; Guar gum, Xanthan gum, Karaya gum, and pectin were used in the study.

**Table 1: Preliminary trial for selection of polymer (by direct-compression method)**

| Ingredients | F1 | F2 | F3 | F4 |
|---|---|---|---|---|
| Donepezil HCL | 23 | 23 | 23 | 23 |
| Guar Gum(30%w/w) | 60 | - | - | - |
| Xanthan Gum(30%w/w) | - | 60 | - | - |
| Karaya Gum(30%w/w | - | - | 60 | - |
| Pectin(30%w/w) | - | - | - | 60 |
| MCC | 111 | 111 | 111 | 111 |
| Talc | 4 | 4 | 4 | 4 |
| Mg. Stearate | 2 | 2 | 2 | 2 |

All quantities are in mg. Total weight of tablet =200 mg

From above Preliminary trials it has been concluded that natural polymers by direct compression method is not able to achieve sufficient sustained release action, so wet granulation method was selected for matrix tablets.

**Preparation of matrix tablets by wet-granulation technique**

A tablet containing 23mg Donepezil hydrochloride were prepared by wet-granulation technique with composition detailed in table 2. All the ingredients were weighed and passed through sieve no 80#. The mixture was prepared by mixing Donepezil hydrochloride, guar gum and lactose. Binder solution was prepared by mixing PVP-K30 in water. The binder solution was added to mixture to prepare a uniform mass. The wet mass was passed through sieve no 22/44#. The granules were dried at hot air oven. Magnesium stearate and talc was used as lubricant. The final granules were compressed using a tablet compression machine using 8mm flat punch. The tablet average weight of 200 mg.

**Table 2: Preliminary trial for selection of polymer (by wet-granulation method)**

| Ingredients | FA1 | FA2 | FA3 | FA4 |
|---|---|---|---|---|
| Donepezil HCL | 23 | 23 | 23 | 23 |
| Guar Gum(30%w/w) | 60 | - | - | - |
| Xanthan Gum(30%w/w) | - | 60 | - | - |
| Karaya Gum(30%w/w) | - | - | 60 | - |
| Pectin(30%w/w) | - | - | - | 60 |
| PVP-K-30 in water (5%) | 10 | 10 | 10 | 10 |
| Lactose | 101 | 101 | 101 | 101 |
| Talc (2%) | 4 | 4 | 4 | 4 |
| Mg. Stearate | 2 | 2 | 2 | 2 |

All quantities are in mg. Total weight of tablet =200 mg.

**Optimization by $3^2$full factorial Design**

A $3^2$ randomized full‑factorial design was used in the present investigation. In this design, two factors were evaluated, each at three levels, and experimental trials were performed at all night possible combinations. Ration of Polymer and Ratio of Binder were chosen as independent variables in the $3^2$ full‑factorial design, where as Q0.5( drug release at 0.5hr), Q10 ( drug release at the 10hr), Q18 (drug release at 18hr), and *f2* value were selected as dependent variables (responses). Different levels and their respective values are depicted in Table 3. The formulation layout of the factorial batches (E1‑E9) is shown in Table 4. Tablets of all the factorial batches were evaluated for weight variation, hardness, drug content, friability, and in vitro drug release. The polynomial equations can be used to draw conclusions after considering the magnitude of the coefficient and the mathematical sign it carries (i.e., negative or positive). Data were analyzed for regression using Microsoft Excel.

**Table 3: Coding of variables**

| Level | Factor X1: Concentration of Polymer(Guar gum) | Factor X2:Concentration of binder(PVP-K30) |
|---|---|---|
| -1 | 18% | 3% |
| 0 | 20% | 4% |
| +1 | 22% | 5% |

**Table 4: Experimental design by using 32 full factorial design**

| Batch code | Coded Value | | Actual Value | |
|---|---|---|---|---|
| | X1 | X2 | X1 Concentration of polymer (%) | X2 Concentration of binder (%) |
| E1 | -1 | -1 | 18 | 3 |
| E2 | 0 | -1 | 20 | 3 |
| E3 | +1 | -1 | 22 | 3 |
| E4 | -1 | 0 | 18 | 4 |
| E5 | 0 | 0 | 20 | 4 |
| E6 | +1 | 0 | 22 | 4 |
| E7 | -1 | +1 | 18 | 5 |
| E8 | 0 | +1 | 20 | 5 |
| E9 | +1 | +1 | 22 | 5 |

**Table 5: Formulations of 32 full factorial design batches**

| Ingredients (mg/tab) | E1 | E2 | E3 | E4 | E5 | E6 | E7 | E8 | E9 |
|---|---|---|---|---|---|---|---|---|---|
| **Donepezil HCL** | 23 | 23 | 23 | 23 | 23 | 23 | 23 | 23 | 23 |
| **Guar Gum** | 36 | 40 | 44 | 36 | 40 | 44 | 36 | 40 | 44 |
| **PVP-K30** | 6 | 6 | 6 | 8 | 8 | 8 | 10 | 10 | 10 |
| **Lactose** | 129 | 125 | 121 | 127 | 123 | 119 | 125 | 121 | 117 |
| **Talc (2%)** | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| **Mg. Stearate (1%)** | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| **Total** | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |

**Evaluation of matrix tablets**

- **Weight variation test**

Twenty tablets were selected at random, weighed and the average weight was calculated. Not more than two of the individual weights should deviate from the average weight by more than 10 %.

- **Friability**

For each formulation, pre weighed tablet sample (20 tablets) were placed in the Roche friabilator (Electro lab, Mumbai, India) which is then operated for 100 revolutions. The tablets were deducted and reweighed. Conventional compressed tablets that loose < 0.5 to 1% of their weight are considered acceptable.

- **Hardness**

Hardness of tablet was determined using Pfizer hardness tester (Campbell Electronics, Mumbai, India).

- **Content Uniformity**

Ten tablets were weighed and powdered in a glass mortar. Weigh accurately about 10mg and transferred in a 100 ml volumetric flask add 20 ml distilled water shake well for 5 min. Add remaining volume of the distilled Water and adjust the final volume in the flask up to 100 ml and filter it. From the resulting solution 10 ml of the sample withdrawn and adjust final volume in volumetric flask up to 100 ml using distilled water. Measure the absorbance of the resulting solution using UV Visible spectrophotometer at of λ max 270 nm & calculate the amount of the Donepezil HCL using the calibration curve method.

- **In Vitro dissolution study**

Dissolution rate studies were performed using a USP Type II (paddle type) dissolution test apparatus.

**ACID STAGE:** Place 750 ml of 0.1N hydrochloric acid in the vessel for 2 hours, After 2 hours the acid medium withdraw an aliquot of liquid and proceed immediately as directed under buffer stage.

**BUFFER STAGE:** Adding the buffer and adjusting the pH within 5 min with the apparatus operating at the rate specified add to the medium in the vessel 250ml of a 0.2M solution of tri-sodium phosphate dodecahydrate, adjust if necessary with 2M hydrochloric acid or 2M sodium hydroxide to a pH of 6.8±0.05 dissolution media was maintained at 37±0.5°C and stirred at 50 rpm. Samples were withdrawn at appropriate time intervals and replaced with fresh dissolution medium, after filtration through whatman filter paper, the absorbance was measured at 270nm, the dissolution study were carried out for 24 hrs.

**Drug–excipient compatibility study**

**Fourier transforms infrared spectrophotometry**

A drug–excipient interaction plays a vital role in the release of drug from the formulation. Fourier transform infrared (FTIR) spectroscopy has been used to study the physical and chemical interactions between drugs and excipients. The FTIR spectra of Donepezil HCL and a mixture of Donepezil HCL with major excipients were recorded using the KBr mixing method using an FTIR instrument (FTIR‑8400S; Shimadzu).

**Stability studies of the optimized formulation**

Stability testing of drug products begins as a part of drug discovery and ends with the demise of the compound or commercial product. To assess drug and formulation stability, short‑term stability studies were done for 1 month. The stability studies were carried out on the most satisfactory formulations (batch E7). The most satisfactory formulations were sealed in aluminium packaging and kept in a humid chamber maintained at 40 ± 2°C/75 ± 5%. relative humidity (RH) for 1 month. The optimized formulation sealed in aluminum foil was also kept at room temperature and humid condition. At the end of the storage time, the samples were analysed for in vitro drug release and % drug content.The in vitro drug release profiles for both formulations (initial and after storage at 40 ± 2°C/75 ± 5% RH for 1 month) were compared by the similarity factor (f2).

## RESULTS AND DISCUSSION

**Results of preliminary screening**

The tablets prepared sustained release matrix tablets by direct compression method were evaluated in-vitro drug release studies, thickness, hardness, friability, and average weight.

**Table 6: Results of evaluation of tablets of trial batches**

| Batch Code | Thicknes s(mm) | Hardness (kg/cm²) | Friability (%) | Average weight(mg) |
|---|---|---|---|---|
| F1 | 3.2±0.1 | 6±0.05 | 0.16 | 200.82±0.42 |
| F2 | 3.1±0.1 | 7±0.05 | 0.13 | 199.05±0.84 |
| F3 | 3±0.05 | 5.8±0.1 | 0.15 | 198.1±2.20 |
| F4 | 3.1±0.1 | 6±0.1 | 0.07 | 201.07±1.08 |

All values are mean ± SD (n=3)

**Table 7: In-vitro drug release studies of trial batches**

| TIME (hr) | F1 | F2 | F3 | F4 |
|---|---|---|---|---|
| 0.5 | 35.75±0.1 | 91.96±1.18 | 94.03±0.02 | 43.10±0.07 |
| 1 | 48.34±0.05 | 98.67±0.001 | 96.11±0.01 | 74.01±0.1 |
| 1.5 | 65.13±0.02 | 97.39±0.35 | 102.04±1.16 | 104.39±0.02 |
| 2 | 69.29±1.16 | 101.1±0.05 | 101.29±3.12 | 107.41±0.45 |
| 3 | 78.50±0.08 | 108.3±0.1 | | |
| 4 | 98.49±0.76 | | | |
| 6 | 98.43±2.16 | | | |
| 8 | 113.77±0.05 | | | |
| 10 | 111.36±1.25 | | | |
| 12 | 101.97±0.25 | | | |
| 18 | 102.45±0.78 | | | |
| 24 | 105.35±0.1 | | | |

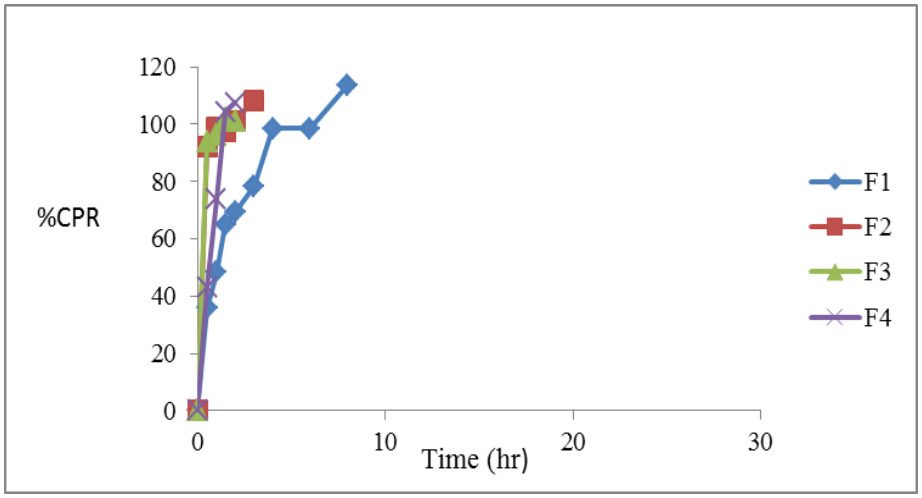


**Figure 1: Comparative Dissolution Profile**

Form the above preliminary trials it was found that Guar gum, Xanthan gum, Pectin, Karaya gum (30%) by direct compression method is not able to achieve sufficient in-vitro drug release, so further studies with wet-granulation method for matrix tablets.

**Evaluation of Preliminary Trial Batches**

Prepared sustained release matrix tablets by wet-granulation method were evaluated in-vitro drug release studies, thickness, hardness, friability, and average weight.

**Table 8: Results of evaluation of tablets of trial batches**

| Batch Code | Thickness( mm) | Hardness(kg/cm²) | Friability (%) | Average weight(mg) |
|---|---|---|---|---|
| F5 | 3.2±0.1 | 6±0.05 | 0.08 | 200.22±0.98 |
| F6 | 3.2±0.1 | 7.5±0.1 | 0.16 | 199.20±0.49 |
| F7 | 3±0.05 | 7±0.05 | 0.14 | 198.75±0.35 |
| F8 | 3.2±0.1 | 6±0.1 | 0.12 | 198.80±1.06 |

**Table 9: In-vitro drug release studies of trial batches**

| TIME(hr) | F5 | F6 | F7 | F8 | Marketed profile |
|---|---|---|---|---|---|
| 0 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 0.5 | 10.08±1.05 | 16.81±0.50 | 72.40±3.62 | 32.96±0.1 | 17.94 |
| 1 | 16.42±2.20 | 21.79±0.05 | 85.78±0.20 | 60.00±0.1 | 25.77 |
| 1.5 | 20.68±0.1 | 32.64±0.08 | 97.37±0.005 | 75.18±0.06 | 31.88 |
| 2 | 27.06±1.03 | 42.50±1.27 | 102.84±1.17 | 92.42±0.78 | 36.50 |
| 3 | 43.17±0.49 | 52.95±0.005 | 145.13±0.65 | 135.12±0.03 | 48.70 |
| 4 | 53.21±1.32 | 73.22±0.76 | | 144.77±0.2 | 53.66 |
| 6 | 58.64±1.18 | 98.01±0.01 | | | 61.55 |
| 8 | 63.71±0.98 | 113.49±0.88 | | | 72.96 |
| 10 | 71.74±0.79 | | | | 80.10 |

| | | | | | |
|---|---|---|---|---|---|
| 12 | 83.47±1.66 | | | | 89.54 |
| 18 | 87.17±2.08 | | | | 94.21 |
| 24 | 92.40±1.00 | | | | 97.82 |

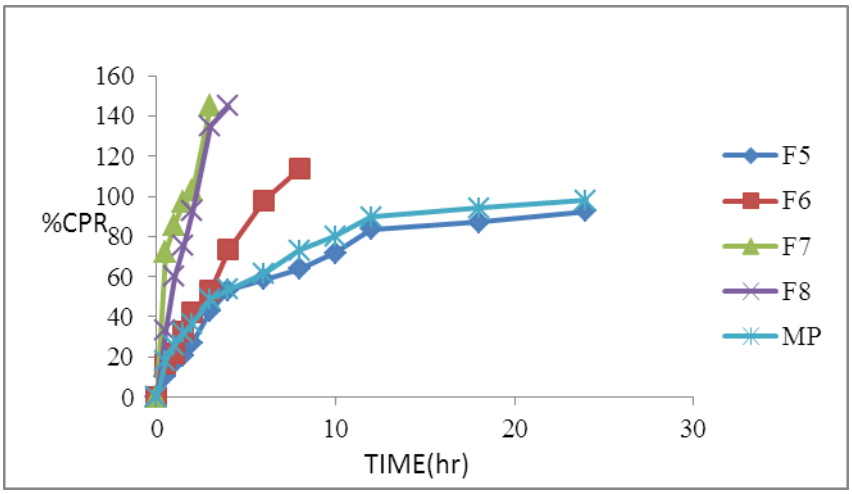


**Figure 2: Comparative Dissolution Profile**

Form the in-vitro drug release study it was found that guar gum have more sustaining effect on release of drug than Xanthan gum, Pectin, Karaya gum. By calculating the similarity factor f2 value Hence Guar gum is suitable for sustain release in low concentration. Form the above studies, it was concluded that low concentration (18%, 20%, 22%) is optimized for further studies with full factorial experimental design.

**FTIR spectroscopy**

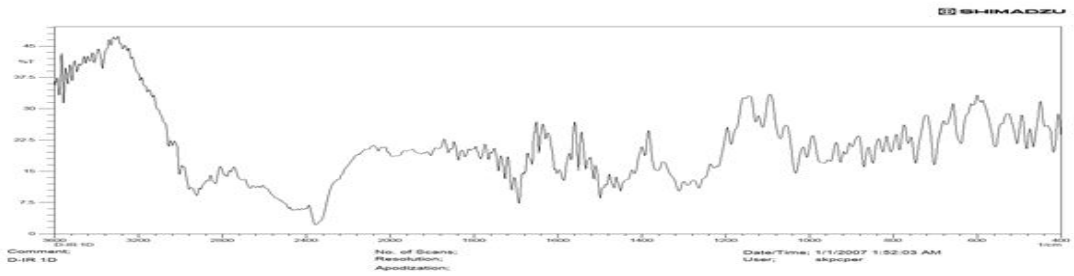

**Figure 3: FT-IR spectrum of pure drug**

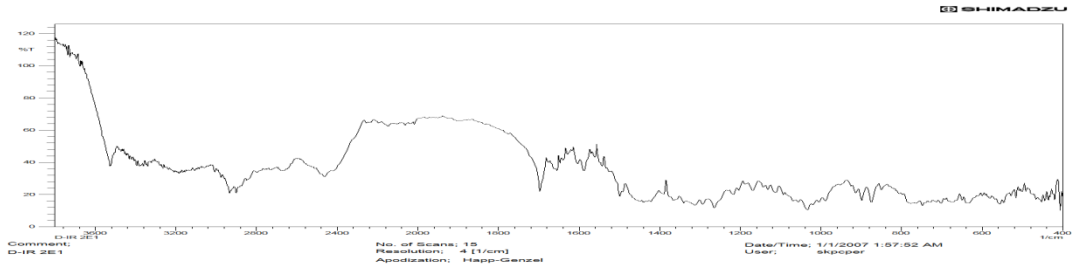

**Figure 4: FTIR Spectrum of Drug and Mixture**

It was observed that there were no changes in these major peaks in the IR spectra of mixture of drug and excipients.

**Table 10: Physicochemical properties of tablets of factorial batches**

| Batch Code | Diameter (mm) | Thickness (mm) | Weight Variation(mg) | Hardness (kg/cm2) | %Drug Content | % Friability |
|---|---|---|---|---|---|---|
| **E1** | 8.0 ± 0.1 | 3.3 ±0.1 | 200.05 ±3.62 | 7.2 ±0.05 | 97.1 ±0.87 | 0.16 |
| **E2** | 7.99± 0.05 | 3.20 ±0.05 | 199.10±2.20 | 6.5 ±0.2 | 103.97±0.81 | 0.13 |
| **E3** | 8.0 ± 0.1 | 3.1 ±0.2 | 198.20 ±1.08 | 7.4 ±0.1 | 102.61±0.67 | 0.15 |
| **E4** | 8.0 ± 0.1 | 3.4 ±0.1 | 197.40±1.68 | 8.1 ±0.1 | 104.2 ±0.7 | 0.07 |
| **E5** | 7.99± 0.05 | 3.1 ±0.1 | 199.20 ±2.78 | 7.4 ±0.05 | 98.9 ±0.65 | 0.14 |
| **E6** | 8.0 ± 0.1 | 3.1 ±0.05 | 201.0 ± 2.41 | 6.4 ±0.36 | 100 ±1.70 | 0.16 |
| **E7** | 8.0 ± 0.1 | 3.0 ±0.05 | 200.01 ±1.05 | 7.6±0.005 | 99.65 ±0.69 | 0.05 |
| **E8** | 8.0 ± 0.1 | 3.2±0.1 | 198.20±1.08 | 5.5 ±0.36 | 101.1 ±1.2 | 0.12 |
| **E9** | 7.98± 0.05 | 3.4±0.05 | 199.10 ±1.25 | 6.1 ±0.01 | 103.8 ±1.18 | 0.071 |

All values are mean ± SD (n=3)

**Table 11: In-Vitro drug release profile of factorial batches**

| Time (hrs) | CPR | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **E1** | **E2** | **E3** | **E4** | **E5** | **E6** | **E7** | **E8** | **E9** |
| 0 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 |
| 0.5 | 22.81±0.05 | 22.09±2.06 | 20.33±0.70 | 18.26±124 | 17.96±0.49 | 14.22±1.03 | 16.60±0.57 | 14.63±1.27 | 13.80±0.70 |
| 1 | 30.57±0.01 | 27.25±1.30 | 25.15±1.47 | 23.05±0.32 | 22.01±0.25 | 20.83±0.89 | 21.48±0.49 | 20.94±1.18 | 20.20±1.47 |
| 1.5 | 32.32±0.0 | 31.75±1.98 | 29.73±1.66 | 28.74±0.25 | 29.14±0.58 | 25.35±1.18 | 27.66±0.57 | 27.11±0.01 | 23.88±1.36 |
| 2 | 37.50±0.01 | 36.75±0.36 | 32.70±1.36 | 34.19±0.33 | 32.52±0.58 | 31.58±0.69 | 32.58±0.49 | 31.61±0.006 | 29.89±0.98 |
| 3 | 55.88±0.2 | 54.00±0.70 | 53.18±0.01 | 48.97±0.40 | 48.94±0.15 | 46.73±0.93 | 48.20±0.12 | 47.31±0.1 | 43.90±1.17 |
| 4 | 66.06±0.05 | 64.44±0.11 | 62.48±0.01 | 61.15±0.42 | 59.87±0.58 | 54.45±0.69 | 58.71±0.43 | 57.31±0.89 | 53.39±1.31 |
| 6 | 74.12±0.1 | 72.48±1.08 | 71.49±0.05 | 65.56±0.75 | 66.21±0.15 | 60.31±0.01 | 63.23±1.16 | 62.47±0.12 | 59.80±1.66 |
| 8 | 92.26±0.02 | 88.24±0.01 | 81.97±0.98 | 73.75±0.52 | 72.60±0.91 | 71.78±0.50 | 72.51±0.17 | 71.46±0.45 | 70.43±0.76 |
| 10 | 101.98±0.005 | 92.38±1.64 | 90.06±1.00 | 79.39±0.93 | 78.65±0.57 | 76.01±0.12 | 78.28±0.05 | 77.77±0.88 | 74.43±1.00 |
| 12 | 104.73±0.01 | 102.51±0.05 | 99.34±0.79 | 90.77±1.91 | 90.30±0.18 | 89.44±0.09 | 90.34±0.20 | 89.00±0.76 | 87.51±0.44 |
| 18 | 106.80±0.0 | 105.25±0.1 | 103.71±1.15 | 96.86±0.99 | 95.00±0.28 | 93.85±0.20 | 94.90±0.01 | 94.56±0.01 | 90.37±0.53 |
| 24 | 108.46±0.05 | 108.02±1.88 | 106.40±0.25 | 104.12±0.45 | 101.12±1.41 | 99.83±0.05 | 100.83±0.10 | 98.68±0.98 | 93.96±0.08 |

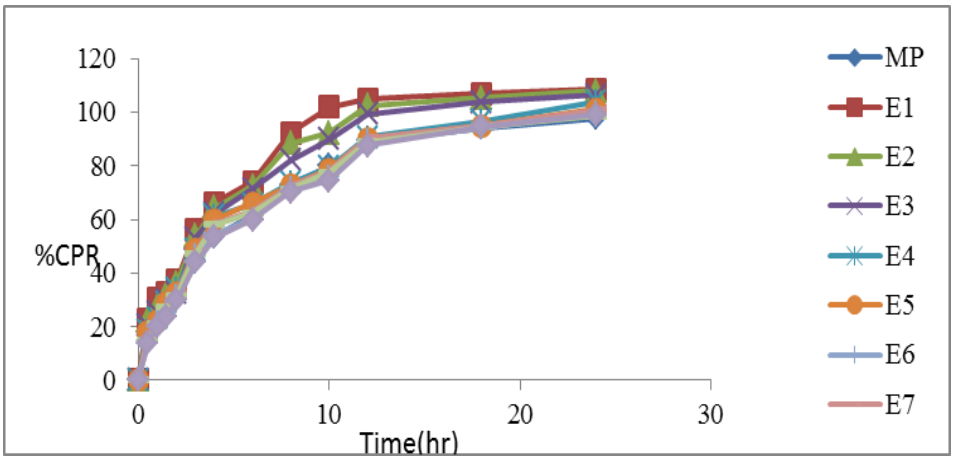


**Figure 5: Comparative Release Profile of factorial batches**

**Table 12: Similarity Factor (*f*2) for E1 to E9**

| Batch | Similarity factor (*f*2) |
|---|---|
| E1 | 44.79 |
| E2 | 50.17 |
| E3 | 55.38 |
| E4 | 72.13 |
| E5 | 74.63 |
| E6 | 73.09 |
| **E7** | **76.22** |
| E8 | 74.72 |
| E9 | 66.39 |

E7 Batch showed maximum similarity(76.22) compared with other batches.

**Table 13: Comparison of dissolution profile of E7 and Marketed release profile**

| Time (hr) | % Release of E7 batch | % Release of marketed formulation |
|---|---|---|
| 0 | 0.00 | 0.00 |
| 0.5 | 16.60 | 17.94 |
| 1 | 21.48 | 25.77 |
| 1.5 | 27.66 | 31.88 |
| 2 | 32.68 | 36.50 |
| 3 | 48.20 | 48.70 |
| 4 | 58.71 | 53.66 |
| 6 | 63.23 | 61.55 |
| 8 | 72.51 | 72.96 |
| 10 | 78.28 | 80.10 |
| 12 | 90.34 | 89.54 |
| 18 | 94.90 | 94.21 |
| 24 | 100.34 | 97.82 |

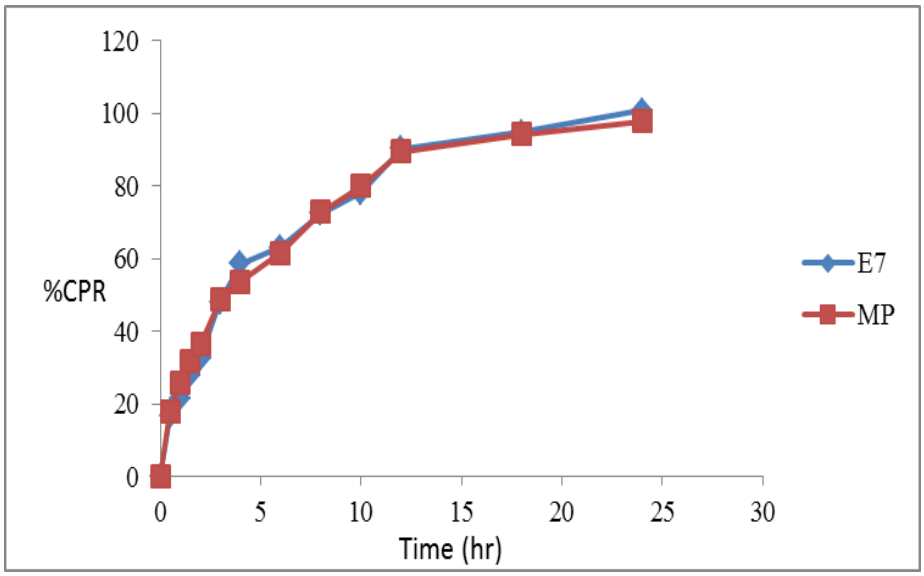


**Figure 6: Comparison of dissolution profile of E7 and Marketed release profile**

## KINETIC MODELING OF DISSOLUTION DATA

The kinetics of the dissolution data were well fitted to zero order, Higuchi model and Korsemeyer-Peppas model as evident from regression coefficients. In case of the controlled or sustained release formulations, diffusion, swelling and erosion are the three most important rate controlling mechanisms. Formulation containing swelling polymers show swelling as well as diffusion mechanism because the kinetic of swelling include relaxation of polymer chains and imbibitions of water, causing the polymer to swell and changing it from a glassy to rubbery state. The diffusion exponent n is the indicative of mechanism of drug release from the formulation. For a swellable cylindrical (tablet) drug delivery system, the n value of 0.45 is indicative of Fickian diffusion controlled drug release, n value between 0.5-0.85 signifies anomalous (non Fickian).E7 batch showed the n value 0.503 so it was signifies non fickian transport.

**Table 13: Statistical analysis of factorial design batches**

| Batch Code | X1 | X2 | Q0.5 (hr) | Q10 (hr) | Q18 (hr) | *f2* |
|---|---|---|---|---|---|---|
| E1 | -1 | -1 | 22.81 | 101.98 | 106.98 | 44.79 |
| E2 | 0 | -1 | 22.09 | 92.38 | 105.25 | 50.17 |
| E3 | 1 | -1 | 20.33 | 90.06 | 103.71 | 55.38 |
| E4 | -1 | 0 | 18.26 | 79.39 | 96.86 | 72.13 |
| E5 | 0 | 0 | 17.95 | 78.65 | 95.00 | 74.63 |
| E6 | 1 | 0 | 14.22 | 76.01 | 93.85 | 73.09 |
| E7 | -1 | 1 | 16.60 | 78.28 | 94.90 | 76.02 |
| E8 | 0 | 1 | 14.63 | 77.77 | 94.56 | 74.72 |
| E9 | 1 | 1 | 13.80 | 74.51 | 90.37 | 66.39 |

The Q0.5, Q10, Q18 and *f*2 of the nine batches showed wide variation. The results depicted in Table clearly indicate that all the dependent variables are strongly dependent on the selected independent variables.

**ANOVA table for Dependent variables from $3^2$ full factorial batches**

**Table 14: ANOVA table for Response Q0.5 (In-Vitro drug Release at 0.5hr)**

| | DF | SS | MS | F | P-value Prob > F |
|---|---|---|---|---|---|
| Model | 5 | 88.030 | 17.60 | 22.15 | 0.01422 |
| Residual | 3 | 2.38 | 0.79 | | |
| Total | 8 | 90.41 | | | |

**Table15: ANOVA table for Response Q10 (In-vitro drug release at 10hr)**

| | DF | SS | MS | F | P-value Prob > F |
|---|---|---|---|---|---|
| Model | 5 | 683.18 | 136.63 | 24.17 | 0.012 |
| Residual | 3 | 16.95 | 5.65 | | |
| Total | 8 | 700.13 | | | |

**Table 16: ANOVA table for Response Q18 (In-Vitro drug Release at 18hr)**

| | DF | SS | MS | F | P-value Prob > F |
|---|---|---|---|---|---|
| Model | 5 | 267.51 | 53.50 | 72.186 | 0.002 |
| Residual | 3 | 2.22 | 0.741 | | |
| Total | 8 | 269.73 | | | |

**Table 17: ANOVA table for Response *f*2**

| | DF | SS | MS | F | P-value Prob > F |
|---|---|---|---|---|---|
| Model | 5 | 1143.17 | 228.63 | 170.62 | 0.00070 |
| Residual | 3 | 4.01 | 1.33 | | |
| Total | 8 | 1147.19 | | | |

*df indicates degree of freedom; SS, sum of square; MS, mean of square; F, Fischerûs ratio

The fitted equation relating to the responses Drug release at 0.5hr (Q0.5), Drug release at 10hr (Q10), Drug release at 18hr(Q18) and Similarity factor (*f*2) to the transformed factors are shown in equations 1 to 3 respectively.

$$Q0.5 = 17.18-1.55\ X_1-3.37\ X_2 - 0.080X_1X_2 - 0.53\ X_1^2 + 1.57X_2^2 \quad (1)$$

R-Square = 0.9735

$$Q10= 77.72 -3.18\ X_1-8.98\ X_2+2.04X_1X_2 +0.44\ X_1^2 +7.81\ X_2^2 \quad (2)$$

R-Square = 0.9757

$$Q18= 95.58 -1.77\ X_1-5.99\ X_2-0.36\ X_1X_2 -0.52\ X_1^2 +4.03\ X_2^2 \quad (3)$$

R-Square = 0.9917

$$f2 = 74.53+0.32\ X_1+11.13\ X_2-5.05\ X_1X_2 -1.87\ X_1^2 -12.03\ X_2^2 \quad (4)$$

R-Square = 0.9964

The value of correlation coefficient for Q0.5, Q10, Q18, and *f2* indicate good fit (i.e., good agreement between the dependent and independent variables). The polynomial equations can be used to draw conclusion after considering the magnitude of coefficient and the mathematical sign it carries (i.e. positive or negative)

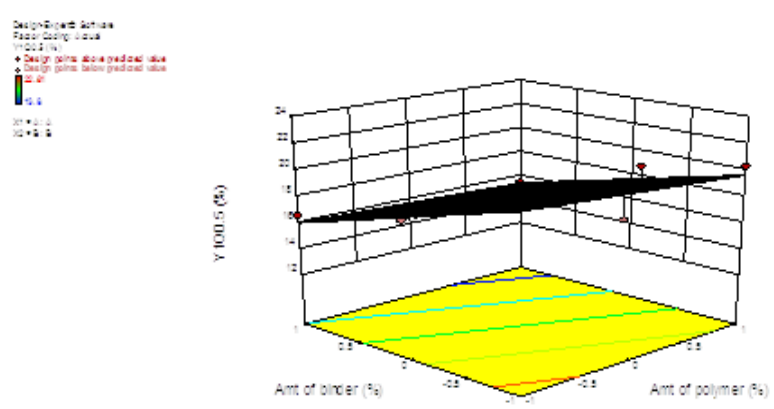


**Figure 7: Response surface plot showing the effect Amt of polymer and Amt of binder on responseQ0.5 (Drug release at 0.5hr)**

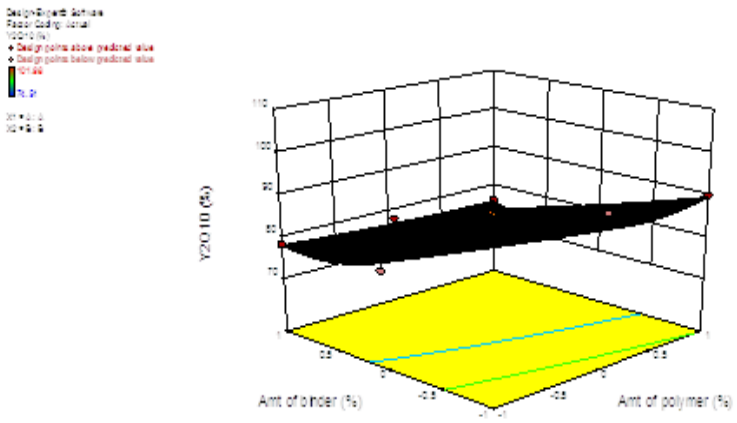


**Figure 8: Response surface plot showing the effect Amt of polymer and Amt of binder on responseQ10 (Drug release at 10hr)**

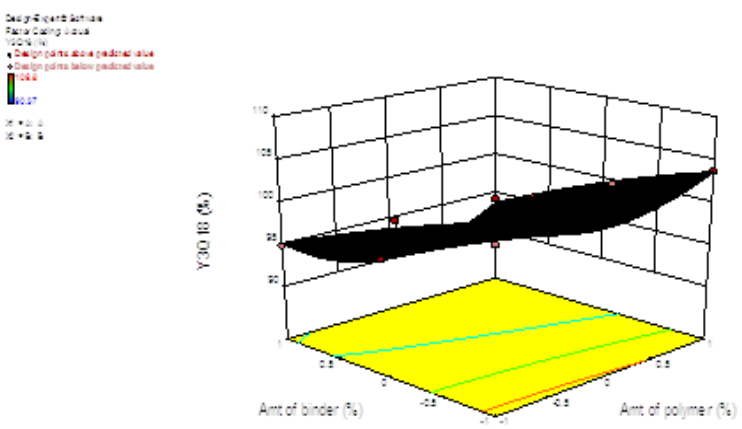


**Figure 9: Response surface plot showing the effect Amt of polymer and Amt of binder on responseQ18 (Drug release at 18hr)**

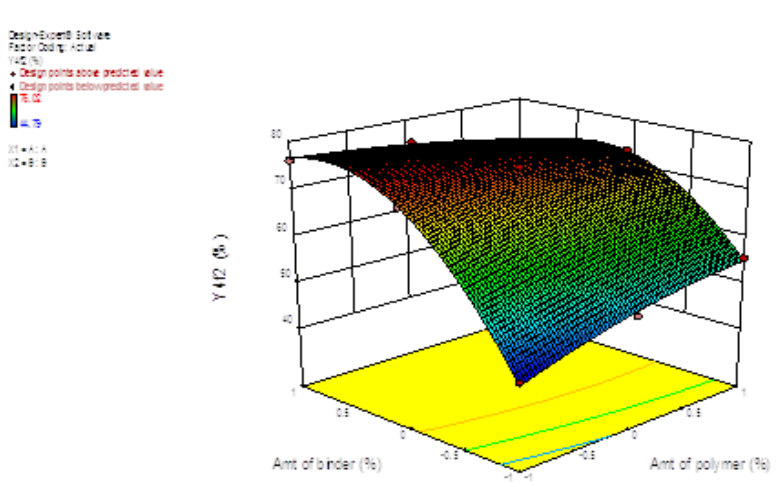


**Figure 10: Response surface plot showing the effect Amt of polymer and Amt of binder on response *f2* (Similarity Factor)**

From the Statistical analysis it was found that variable X1 concentration of polymer and X2 concentration of binder both have negative effect on the in-vitro drug release studies. If concentration of Guar gum and concentration of PVP-K30 decrease the in-vitro drug release increase, so, it can be qualitatively concluded that X1 and X2 both have significant effect on in-vitro drug release. Compare to other batches E7 batch has high similarity factor. So, batch E7 is optimized batch.

Form this research study, it was concluded that development of sustained release matrix tablet of donepezil hydrochloride using guar gum. The optimized formulation E7 showed cumulative release of 100% drug release at the end of the 24$^{th}$ hour in dissolution profile. The optimized formulation batch E7 has high similarity factor (76.22) compared with other batches, by this our objective of sustained release donepezil HCL form matrix tablet has been fulfilled.

**ACKNOWLEDGMENT**

Authors thank Principal of Shri Sarvajanik Pharmacy College, Mehsana for extending laboratory and instrumental facilities to carry out the work.

**REFERENCES**

1. Dixit N, Dutt M and Sagar BP, "Sustained release drug delivery system." Ind. J. of Res. in Pharma. and Biotech., 2013; *1*: 305-310.

2. Singh A, Sharma R and Jamil F, "Sustained release oral drug delivery system – an review." Int. Res. J. of Pharma., 2012; *3*: 21-24.
3. Ratnaparkhi MP and Gupta JP, "Sustained release oral drug delivery system – an overview." Int. J. of Pharma Res. & Rev., 2013; *2*: 11-21.
4. Gummudavelly S, Rao J, "Development and Charcterization of Fast melting tablets of Donepezil Hcl," International Journal of Drug Development & Research, 2010; 2(3).
5. Yi-Dong Yan, Jong soo woo, Joon Heok Kang, Chul soon yong, Han-Gon chol, "Formulation and evaluation of Taste-masked donepezil hydrochloride orally disintegrating tablets," Biol. Pharm. Bull, 2010; 33(8): 1364-1370.
6. Sonica T, Murthy T.E.G.K, "Studies on influence of co-processed excipient on flow and dissolution kinetics of Donepezil Hcl", Journal pharma Educ Research, 2013; 4(1).
7. http://www.accessdata.fda.gov/scripts/cder/dissolution/dsp_SearchResults_Dissolution
8. Higuchi T, "Mechanism of sustained action mediation, theoretical analysis of rate of release of solid drugs dispersed in solid matrices", J. Pharm. Sci., 1963; 52: 1145-1149.
9. Hixon AW and Crowell JH, "Dependence of reaction velocity upon surface and agitation", Ind. Eng. Chem. Res., 1931; 23: 923-931.
10. Korsmeyer RW, Gurny R, Doelker E, Buri P and Peppas NA, "Mechanism of solute release from porous hydrophillic polymers", Int. J. Pharm., 1983; 15: 25-35.