Abstract

Background: The main objective of present research work is to formulate the Carbamazepine Fast Dissolving tablets. Carbamazepine, an antiepileptic, belongs to BCS Class-II and used to control some types of seizures in the treatment of epilepsy and Neuropathic Pain by blocking use-dependent sodium channels. Methods: The Fast Dissolving tablets of Carbamazepine were prepared employing different concentrations of Crospovidone and Croscarmellose sodium in different combinations as a Sperdisintegrants by Direct Compression technique using factorial design. The concentration of Crospovidone and Croscarmellose sodium was selected as independent variables, X₁ and X₂ respectively whereas, wetting time, Disintegration time, t₅₀% and t₉₀% were selected as dependent variables. Results and Discussion: Totally nine formulations were designed and are evaluated for hardness, friability, thickness, Assay, Wetting time, Disintegration time, In-vitro drug release. From the Results concluded that all the formulation were found to be with in the Pharmacopoeial limits and the In-vitro dissolution profiles of all formulations were fitted in to different Kinetic models, the statistical parameters like intercept (a), slope (b) & regression coefficient (r) were calculated. Polynomial equations were developed for Wetting time, Disintegration time, t₅₀%, t₉₀%. Validity of developed polynomial equations were verified by designing 2 check point formulations (C₁, C₂). According to SUPAC guidelines the formulation (F₅) containing combination of 9.375% Crospovidone and 9.375% Croscarmellose, is the most similar formulation (similarity factor f₂=82.675, dissimilarity factor f₁= 2.049 & No significant difference, t= 0.041) to marketed product (TEGRETOL-100). Conclusion: The selected formulation (F₅) follows First order, Higuchi’s kinetics, mechanism of drug release was found to be Non-Fickian Diffusion (n= 0.665).

Keywords: Carbamazepine, Factorial Design, Crospovidone, croscarmellose Sodium, Wetting Time, Disintegration Time.

Introduction

Difficulty in swallowing (Dysphasia) is a common problem of all age groups, especially elderly and pediatrics, because of physiological changes associated with these groups of patients. Researchers throughout the world are focusing intensively on the methods for the development of new drug delivery systems to enhance patient’s compliance. Tablets are the most popular oral solidformulations available in the market and are preferred by patients and physicians alike. Recently fast dissolving formulation is popular as Novel Drug Delivery Systems because they are easy to administer and lead to Patient Compliance.

Fast dissolving tablets become an emerging trend in the Pharmaceutical industry. Fast dissolving tablets are ideal for all types of people, including for people who have swallowing difficulties, pediatric, geriatric, and bedridden patients. It is also for active patients who are busy, travelling and may not have access to water. Fast dissolving tablets are also known as orodispersible tablets, mouth-dissolving tablets, orally disintegrating tablets, melt-in mouth tablets, rapimelts, porous tablets, quick dissolving etc. Many drugs have the potentials to be made into orodispersible tablets. They vary from analgesics to neuroleptics and anti-psychotic drugs. However only a small percentage of them are researched on and some have been manufactured and marketed.

Fast-dissolving drug-delivery systems were initially developed in the late 1970s as an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experiences difficulties in swallowing traditional oral solid-dosage forms¹. The speed of solubility of drug affects the rate of absorption of the drug. The faster the drug dissolve into solution, quicker the absorption and onset of clinical effect. They
should readily dissolve or disintegrate in the saliva generally within <60 seconds. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach. The significance of orodispersible dosage forms are progressively being recognized in both, industry and academics. The small volume of saliva is usually sufficient to result in tablet disintegration in the oral cavity. The medication can then be absorbed partially or entirely into the systemic circulation from blood vessels in the sublingual mucosa, or it can be swallowed as a solution to be absorbed from the gastrointestinal tract. The sublingual route usually produces a faster onset of action than orally ingested tablets and the portion absorbed through the sublingual blood vessels bypasses the hepatic first-pass metabolic processes. The performance of ODT depends on the technology used in their manufacture. The orally disintegrating property of the tablet is attributable to a quick intake of water into the tablet matrix, which creates porous structures and results in rapid disintegration. Hence the basic approaches to develop ODT include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water soluble excipients in the formulation. Orally disintegrating tablets are formulated by utilizing several processes, which differ in their methodologies and the ODTs formed vary in various properties such as, mechanical strength of tablet, taste and mouth feel, swallowability, drug dissolution in saliva, bioavailability and stability. Various processes employed in formulating ODTs include Freeze-Drying or Lyophilization, cotton candy process, molding, spray drying, mass extrusion and compaction (wet granulation, dry granulation, direct compression).

In the present study the direct compression method was adopted to manufacture the ODT tablets, since it is very simple and do not require any sophisticated equipment’s. The direct compression represents the simplest and most cost effective tablet manufacturing technique.

**Criteria for Fast Disintegrating Drug Delivery System**

- Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- Be harder and less friable.
- Be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasant mouth feel.
- Leave minimum or no residue in the mouth after oral administration.
- Exhibit low sensitive to environmental condition as temperature and humidity.
- Allow the manufacture of the tablet using conventional processing and packaging equipment’s at low cost.

**Criteria for excipient used in the formulation of FDTs**

- It must be able to disintegrate quickly.
- Their individual properties should not affect the FDTs.
- It should not have any interactions with drug and other excipients.
- It should not interfere in the efficacy and organoleptic properties of the product.
- When the final integrity and stability of the product.
- The melting points of excipients used will be in the range of 30-35°C.

The binders may be in liquid, semi liquid, solid or Polymeric mixtures. (Ex: Polyethylene glycol, coca butter, hydrogenated vegetable oils) ODT by direct compression technique is a simple approach of drug delivery systems that proved to be rational in the pharmaceutical arena for its ease, compliance, faster production, avoid hydrolytic or oxidative reactions occurred during processing of dosage forms.

**Drug Profile and Rationality For Experimental Design:**

Carbamazepine, a dibenzapine derivative with structure resembling the tricyclic antidepressants, is used to control some types of seizures in the treatment of epilepsy. One of the major problems with this drug is its very low solubility in biological fluids and its biological half-life between 18 to 65 h that results into poor bioavailability after oral administration. It shows erratic dissolution profile in gastric and intestinal fluid due to its poor water solubility. The peak plasma concentration (C max) and the time taken to reach C max (t max) depend upon extent and rate of dissolution of drug respectively. The rate of dissolution can be increased by increasing the surface area of available drug by various methods (micronization, complexation and solid dispersion). The dissolution of a drug can also be influenced by disintegration time of the tablets. Faster disintegration of tablets delivers a fine suspension of drug particles resulting in a higher surface area and faster dissolution. The bioavailability of the extended-release tablet is 89%, compared to the suspension. Plasma levels of carbamazepine are variable. The time to peak concentration for the different formulations are as follows: Suspension = 1.5 hours; Conventional tablets = 4-5 hours; Extended-release tablets = 3-12 hours. Hence the drug is selected for formulating Fast Dissolving Tablets by Direct compression method.

It is an important issue to design an optimized formulation with an appropriate dissolution rate in a short time period and minimum trials. Many statistical experimental designs have been recognized as useful techniques to optimize the process variables. For this purpose, response surface methodology (RSM) utilizing a polynomial
equation has been widely used. Different types of RSM designs include 3-level factorial design, central composite design (CCD), Box-Behnken design and D-optimal design. Response surface methodology (RSM) is used when only a few significant factors are involved in experimental optimization. The technique requires less experimentation and time, thus proving to be far more effective and cost-effective than the conventional methods of formulating sustained release dosage forms.

Hence an attempt is made in this research work to formulate Fast Dissolving Tablets of Carbamazepine using Crospovidone and Croscarmellose sodium. Instead of normal and trial method, a standard statistical tool design of experiments is employed to study the effect of formulation variables on the release properties. Large scale production needs more simplicity in the formulation with economic and cheapest dosage form. The Fast Dissolving tablets formulation by direct compression method is most acceptable in large scale production.

A $3^2$ full factorial design was employed to systematically study the drug release profile. A $3^2$ full factorial design was employed to investigate the effect of two independent variables (factors), i.e the amounts of Crospovidone and Croscarmellose on the dependent variables, i.e. Disintegration time, Wetting Time, $t_{50\%}$, $t_{90\%}$, (Time taken to release 50%, 90% respectively).

MATERIALS AND METHODS
Materials used in this study were obtained from the different sources. Carbamazepine was a gift sample from Dr.Reddy’s Laboratories, Hyderabad, India. Crospovidone, Croscarmellose, Di Calcium Phosphate, were procured from LobaChemie Pvt. Ltd, Mumbai. Other excipients such as Magnesium Stearate and talc were procured from S.D. Fine Chem. Ltd., Mumbai.

Formulation Development of Carbamazepine Fast Dissolving Tablets:
The factorial design is a technique that allows identification of factors involved in a process and assesses their relative importance. In addition, any interaction between factors chosen can be identified. Construction of a factorial design involves the selection of parameters and the choice of responses.

A selected three level, two factor experimental design ($3^2$ factorial design) describe the proportion in which the independent variables Crospovidone and Croscarmellose were used in formulation of Carbamazepine Fast Dissolving Tablets. The time required for 50% ($t_{50\%}$), 90% ($t_{90\%}$) drug dissolution, Disintegration Time and Wetting Time were selected as dependent variables. Significance terms were chosen at 95% confidence interval ($p<0.05$) for Final Equations. Polynomial equations were developed for $t_{50\%}$, $t_{90\%}$, Disintegration Time and Wetting Time (step-wise backward Linear Regression Analysis).

The three levels of factor $X_1$ (Crospovidone) at a concentration of 6.25%, 9.375%, 12.5%. Three levels of factor $X_2$ (Croscarmellose) at a concentration of 6.25%, 9.375%, 12.5%. (%) with respect to average weight of Tablet, i.e 200 mg was taken as the rationale for the design of the Carbamazepine Fast Dissolving tablet formulation. Totally nine Carbamazepine Fast Dissolving tablet formulations were prepared employing selected combinations of the two factors i.e $X_1$, $X_2$ as per $3^2$ Factorial and evaluated to find out the significance of combined effects of $X_1$, $X_2$ to select the best combination and the concentration required to achieve the desired Fast release/ Dissolution of drug (by providing large Surface area and Improved Solubility) from the dosage form.

Preparation of Carbamazepine Fast Dissolving Tablets:
Carbamazepine Tablets were prepared by direct compression method. The composition of each tablet is shown in Table No 2. The drug, diluents, superdisintegrants were passed through sieve #40. All the above ingredients were properly mixed together (in a poly-bag). Talc and Magnesium stearate were passed through mesh #80, mixed and blended with initial mixture in a poly-bag. The powder blend was compressed into tablets on a 8 station rotary punch tabletting machine (mini press) using 8 mm circular punches and same hardness was used for the required number tablets. Compressed tablets were examined as per official standards and unofficial tests. Tablets were packaged in well closed light resistance and moisture proof containers.

Experimental Design:
Experimental design utilized in present investigation for the optimization of Superdisintegrant concentration such as, concentration of Crospovidone was taken as $X_1$ and concentration of Croscarmellose sodium was taken as $X_2$. Experimental design was given in the Table 1. Three levels for the Concentration of Crospovidone were selected and coded as -1 = 6.25%, 0 = 9.375%, +1 = 12.5%. Three levels for the Concentration of Croscarmellose sodium were selected and coded as -1 = 6.25%, 0 = 9.375%, +1 = 12.5%. Formulæ for all the experimental batches were given in Table 2.
Dissolving Tablets as Per Experimental Design

Table 2: Formulae for the Preparation of Carbamazepine Fast Dissolving Tablets as Per Experimental Design

<table>
<thead>
<tr>
<th>Name of Ingredients</th>
<th>Quantity of Ingredients per each Tablet (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F₁</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>100</td>
</tr>
<tr>
<td>Di Calcium Phosphate</td>
<td>46</td>
</tr>
<tr>
<td>Crospovidone</td>
<td>25</td>
</tr>
<tr>
<td>Croscarmellose sodium</td>
<td>25</td>
</tr>
<tr>
<td>Magnesium Stearate</td>
<td>2</td>
</tr>
<tr>
<td>Talc</td>
<td>2</td>
</tr>
<tr>
<td>Total Weight</td>
<td>200</td>
</tr>
</tbody>
</table>

Friability

Friability of the tablets was measured in a Roche friabilator (Campbell Electronics, Mumbai). 20 Tablets were taken, Weighed and Initial weight was noted (Wᵢ) and dedusted in a drum for a fixed time (100 revolutions, in a Roche Friabilator) and weighed (W) again. Percentage friability was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1 %.

Friability (%) = [(Initial weight - Final weight) / (Initial weight)] x 100

Content Uniformity

In this test, 20 tablets were randomly selected and the percent drug content was determined, the tablets contained not less than 85% or not more than 115% (100±15%) of the labeled drug content can be considered as the test was passed.

Assay

Drug content was determined by weighing randomly selected tablets, pulverizing to a fine powder. The powder equivalent to 10 mg Carbamazepine was weighed and dissolved in 10 ml of methanol in volumetric flask using magnetic stirrer, the volume was adjusted to 100 ml with Phosphate buffer pH 6.8 and the solution was filtered. An aliquot of 1.0 ml of solution were diluted to 10 ml Phosphate buffer pH 6.8 in separate volumetric flask. The drug content in was determined spectrophotometrically at 285 nm.

Thickness

Thickness of the all tablet formulations were measured using vernier calipers by placing tablet between two arms of the vernier calipers.

Wetting time

To measure Wetting time of the Tablet, a piece of Tissue paper folded twice was placed in a small petri dish (Internal Diameter is= 6.5 cm) containing 5 ml of Distilled water. A Tablet placed on the paper, and the time for complete wetting of the tablet was measured in seconds.

In-vitro Dissolution Study

The In-vitro dissolution study for the Carbamazepine Fast Dissolving tablets were carried out in USP XXIII type-II dissolution test apparatus (Paddle type) using 900 ml of Phosphate buffer pH 6.8 as dissolution medium at 50 rpm and temperature 37±0.5°C. At predetermined time intervals, 5 ml of the samples were withdrawn by means of a syringe fitted with a pre-filter, the volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The resultant samples were analyzed for the presence of the drug release by measuring the absorbance at 285 nm using UV Visible spectrophotometer after suitable dilutions. The determinations were performed in triplicate (n=3).

Disintegration test

Disintegration of fast disintegrating tablets is achieved in the mouth owing to the action of saliva, however amount of saliva in the mouth is limited and no tablet disintegration test was found in USP and IP to simulate in vivo conditions. A modified method was used to determine disintegration time of the tablets. A cylindrical vessel was used in which 10 mesh screen was placed in such way that only 2 ml of disintegrating or dissolution medium would be placed below the sieve. To determine disintegration time, 6 ml of Sorenson’s buffer (pH 6.8), was placed inside the vessel in such way that 4 ml of the media was below the sieve and 2 ml above the sieve. Tablet was placed on the sieve and the whole assembly was then placed on a shaker. The time at which all the particles pass through the sieve was taken as a disintegration time of the tablet. Six tablets were chosen randomly from the composite samples and the average value was determined. Following Figure shows modified disintegration apparatus.
Kinetic modeling of drug release

The dissolution profile of all the formulations was fitted into zero-order, first-order, Higuchi and Korsmeyer-Peppas models to ascertain the kinetic modeling of drug release.

Table 3: Post-Compression Parameters for the Formulations

<table>
<thead>
<tr>
<th>S.No</th>
<th>Formulation Code</th>
<th>Hardness (kg/cm²)</th>
<th>Thickness (mm)</th>
<th>Friability (%)</th>
<th>Weight Variation</th>
<th>Drug Content (%)</th>
<th>Wetting Time (sec)</th>
<th>Disintegration Time (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F₁</td>
<td>3.1±0.12</td>
<td>3.4±0.8</td>
<td>0.58±0.2</td>
<td>200.69±0.9</td>
<td>99.45±1.1</td>
<td>12.18±1.3</td>
<td>9.13±0.5</td>
</tr>
<tr>
<td>2</td>
<td>F₂</td>
<td>3.2±0.15</td>
<td>3.45±0.7</td>
<td>0.64±0.3</td>
<td>201.46±1.9</td>
<td>99.28±0.7</td>
<td>14.09±1.3</td>
<td>9.32±0.6</td>
</tr>
<tr>
<td>3</td>
<td>F₃</td>
<td>3.2±0.11</td>
<td>3.6±0.5</td>
<td>0.62±0.1</td>
<td>200.67±1.1</td>
<td>99.41±0.5</td>
<td>18.10±1.7</td>
<td>10.30±0.7</td>
</tr>
<tr>
<td>4</td>
<td>F₄</td>
<td>3.2±0.14</td>
<td>3.5±0.6</td>
<td>0.62±0.19</td>
<td>200.55±2.2</td>
<td>99.53±0.4</td>
<td>38.23±1.5</td>
<td>12.5±0.9</td>
</tr>
<tr>
<td>5</td>
<td>F₅</td>
<td>3.1±0.16</td>
<td>3.5±0.4</td>
<td>0.52±0.3</td>
<td>201.48±1.1</td>
<td>99.39±0.6</td>
<td>42.31±1.1</td>
<td>12.8±0.8</td>
</tr>
<tr>
<td>6</td>
<td>F₆</td>
<td>3.5±0.10</td>
<td>3.7±0.2</td>
<td>0.65±0.04</td>
<td>201.04±2.0</td>
<td>99.92±0.4</td>
<td>48.2±1.2</td>
<td>13.21±0.7</td>
</tr>
<tr>
<td>7</td>
<td>F₇</td>
<td>3.3±0.15</td>
<td>3.5±0.6</td>
<td>0.61±0.3</td>
<td>200.48±1.4</td>
<td>99.23±1.0</td>
<td>51.16±1.5</td>
<td>28.18±1.2</td>
</tr>
<tr>
<td>8</td>
<td>F₈</td>
<td>3.3±0.12</td>
<td>3.6±0.4</td>
<td>0.57±0.4</td>
<td>199.68±0.3</td>
<td>99.51±0.8</td>
<td>78.11±1.9</td>
<td>42.39±0.5</td>
</tr>
<tr>
<td>9</td>
<td>F₉</td>
<td>3.2±0.13</td>
<td>3.7±0.1</td>
<td>0.62±0.4</td>
<td>200.45±0.9</td>
<td>99.49±0.9</td>
<td>88.04±1.2</td>
<td>53.20±2.2</td>
</tr>
</tbody>
</table>

Table 4: Regression Analysis Data of 3² Factorial Design Formulations of Carbamazepine Fast Dissolving Tablets

<table>
<thead>
<tr>
<th>S.No</th>
<th>Formulation Code</th>
<th>Zero-Order a</th>
<th>First-Order a</th>
<th>Higuchi a</th>
<th>Korsmeyer-Peppas a</th>
<th>b</th>
<th>r</th>
<th>a</th>
<th>b</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F₁</td>
<td>49.509</td>
<td>1.150</td>
<td>0.689</td>
<td>1.678</td>
<td>0.031</td>
<td>0.948</td>
<td>24.919</td>
<td>12.157</td>
<td>0.876</td>
</tr>
<tr>
<td>2</td>
<td>F₂</td>
<td>46.956</td>
<td>1.178</td>
<td>0.710</td>
<td>1.678</td>
<td>0.027</td>
<td>0.912</td>
<td>22.494</td>
<td>12.282</td>
<td>0.889</td>
</tr>
<tr>
<td>3</td>
<td>F₃</td>
<td>44.339</td>
<td>1.212</td>
<td>0.733</td>
<td>1.730</td>
<td>0.026</td>
<td>0.934</td>
<td>20.077</td>
<td>12.420</td>
<td>0.903</td>
</tr>
<tr>
<td>4</td>
<td>F₄</td>
<td>48.056</td>
<td>1.173</td>
<td>0.696</td>
<td>1.630</td>
<td>0.028</td>
<td>0.879</td>
<td>23.282</td>
<td>12.334</td>
<td>0.879</td>
</tr>
<tr>
<td>5</td>
<td>F₅</td>
<td>45.183</td>
<td>1.240</td>
<td>0.731</td>
<td>1.776</td>
<td>0.035</td>
<td>0.967</td>
<td>20.307</td>
<td>12.723</td>
<td>0.901</td>
</tr>
<tr>
<td>6</td>
<td>F₆</td>
<td>42.482</td>
<td>1.261</td>
<td>0.749</td>
<td>1.762</td>
<td>0.028</td>
<td>0.941</td>
<td>17.915</td>
<td>12.765</td>
<td>0.911</td>
</tr>
<tr>
<td>7</td>
<td>F₇</td>
<td>46.380</td>
<td>1.178</td>
<td>0.710</td>
<td>1.682</td>
<td>0.025</td>
<td>0.914</td>
<td>21.993</td>
<td>12.266</td>
<td>0.888</td>
</tr>
<tr>
<td>8</td>
<td>F₈</td>
<td>43.237</td>
<td>1.233</td>
<td>0.739</td>
<td>1.737</td>
<td>0.025</td>
<td>0.931</td>
<td>18.836</td>
<td>12.570</td>
<td>0.905</td>
</tr>
<tr>
<td>9</td>
<td>F₉</td>
<td>42.399</td>
<td>1.217</td>
<td>0.712</td>
<td>1.725</td>
<td>0.022</td>
<td>0.906</td>
<td>18.324</td>
<td>12.406</td>
<td>0.904</td>
</tr>
<tr>
<td>10</td>
<td>MP</td>
<td>44.971</td>
<td>1.219</td>
<td>0.727</td>
<td>1.757</td>
<td>0.030</td>
<td>0.950</td>
<td>20.433</td>
<td>12.524</td>
<td>0.898</td>
</tr>
</tbody>
</table>

F₁ to F₉ are factorial formulations, r-correlation coefficient, a-Intercept, b-Slope and MP-Markedeted Product.
53.20 sec. Results for all Post-compression parameters were tabulated or shown in Table 3. In-vitro Dissolution studies were performed for prepared tablets using Phosphate buffer pH 6.8 as a dissolution media at 50 rpm and temperature 37±0.5°C. The In-vitro dissolution profiles of tablets are shown in Fig.1 and the dissolution parameters are given in Table 4. Cumulative % Drug release of Factorial Design Formulations F\textsubscript{1}-F\textsubscript{9} at 1 Hr were found to be in the range of 95.34-99.24 %. From the result it reveals that the release rate was higher for formulations containing High level of Crospovidone / Croscarmellose sodium compared with other Formulations containing Lower level, due to High concentration of Superdisintegrant in combination, shows various disintegration mechanism such as wicking and swelling etc more compared with lower concentration and alone, drug may release rapidly and shows improved bioavailability. Therefore, required release of drug can be obtained by manipulating the composition of Crospovidone and Croscarmellose sodium.

Much variation was observed in the Wetting time, Disintegrating time, \(t_{50\%}\) and \(t_{90\%}\) due to formulation variables. Formulation F\textsubscript{5} containing 18.75 mg of Crospovidone, 18.75 mg of Croscarmellose sodium showed promising dissolution parameter (Wetting time = 42.31±1.1 sec, Disintegrating time = 12.8±0.8 sec, \(t_{50\%} = 8.671\) min, \(t_{90\%} = 28.813\) min). The difference in burst effect of the initial time is a result of the difference in the Concentration of Superdisintegrants mixtures. This reveals that increased concentration of superdisintegrants resulted in a corresponding decrease in the Wetting Time, which might be due to the result of wicking and other possible disintegrating mechanisms. Disintegration time is directly proportional to wetting time.

The In-vitro dissolution data of Carbamazepine Fast Dissolving formulations was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi’s and Korsmeyer-Peppas models to assess the mechanism of drug release. The results of linear regression analysis including regression coefficients are summarized in Table 4 and plots shown in fig.1-4. It was observed from the above that dissolution of all the tablets followed First order kinetics with co-efficient of determination (R\textsuperscript{2}) values in the range of 0.879-0.967. The values of r of factorial formulations for Higuchi’s equation was found to be in the range of 0.876-0.911, which shows that the dissolution data fitted well to Higuchi’s square root of time equation confirming the release followed diffusion mechanism. Kinetic data also treated for Peppas equation, the slope (n) values ranges from 0.634-0.732 that shows Non-Fickian diffusion mechanism. Polynomial equations were derived for Wetting time Disintegrating time, \(t_{50\%}\) and \(t_{90\%}\) values by backward stepwise linear regression analysis using PCP Disso software and Response surface plots were constructed using SIGMAPLOT V13 software. The Linear Contour plots and Response surface plots were shown in Fig.7-14 for Wetting time, Disintegrating time, \(t_{50\%}\) and \(t_{90\%}\) using X\textsubscript{1} and X\textsubscript{2} on both the axes respectively. The dissolution data (Kinetic parameters) of factorial formulations F\textsubscript{1} to F\textsubscript{9} are shown in Table 5.
Fig. 4 Comparative Korsmeyer-Peppas plots for Formulation F₁ - F₉

Fig. 5 Wetting Time Chart for Formulation F₁ - F₉

Fig. 6 Disintegration Time Chart for Formulation F₁ - F₉

Fig. 7 Linear Contour plot for Wetting Time

Fig. 8 Linear Contour plot for Disintegration Time

Fig. 9 Linear Contour plot for $t_{50\%}$

Fig. 10 Linear Contour plot for $t_{90\%}$
Polynomial equation for $3^2$ full factorial designs is given in Equation

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2 + b_{11} X_1^2 + b_{22} X_2^2$$

Where, $Y$ is dependent variable, $b_0$ arithmetic mean response of nine batches, and $b_1$ estimated co-efficient for factor $X_1$. The main effects ($X_1$ and $X_2$) represent the average result of changing one factor at a time from its low to high value. The interaction term ($X_1 X_2$) shows how the response changes when two factors are simultaneously changed. The polynomial terms ($X_1^2$ and $X_2^2$) are included to investigate non-linearity. Validity of derived equations was verified by preparing Two Check point Formulations of Intermediate concentration ($C_1$, $C_2$).

The equations for Wetting time, Disintegrating time, $t_{50\%}$ and $t_{90\%}$ developed as follows,

$$Y_1 = 43.380-28.823X_1 - 8.795X_2 + 7.740X_1 X_2 + 0.70 X_1^2 - 2.185X_2^2 \text{(for Wetting time)}$$

$$Y_2 = 21.225-15.837X_1 - 4.483X_2 + 5.963X_1 X_2 + 12.583X_1^2 - 0.417X_2^2 \text{(for Disintegrating time)}$$

Table 5: Dissolution Parameters of Carbamazepine Fast Dissolving Tablets $3^2$ Full Factorial Design Batches

<table>
<thead>
<tr>
<th>S.No</th>
<th>Formulation code</th>
<th>$t_{50%}$ (Min)</th>
<th>$t_{90%}$ (Min)</th>
<th>$t_{50%}$ (Min)</th>
<th>$t_{90%}$ (Min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$F_1$</td>
<td>1.464</td>
<td>9.630</td>
<td>19.260</td>
<td>32.001</td>
</tr>
<tr>
<td>2</td>
<td>$F_2$</td>
<td>1.724</td>
<td>11.344</td>
<td>22.687</td>
<td>37.695</td>
</tr>
<tr>
<td>3</td>
<td>$F_3$</td>
<td>1.784</td>
<td>11.739</td>
<td>23.479</td>
<td>39.010</td>
</tr>
<tr>
<td>4</td>
<td>$F_4$</td>
<td>1.652</td>
<td>10.870</td>
<td>21.740</td>
<td>36.121</td>
</tr>
<tr>
<td>5</td>
<td>$F_5$</td>
<td>1.318</td>
<td>8.671</td>
<td>17.342</td>
<td>28.813</td>
</tr>
<tr>
<td>6</td>
<td>$F_6$</td>
<td>1.648</td>
<td>10.841</td>
<td>21.682</td>
<td>36.024</td>
</tr>
<tr>
<td>7</td>
<td>$F_7$</td>
<td>1.832</td>
<td>12.051</td>
<td>24.101</td>
<td>40.044</td>
</tr>
<tr>
<td>8</td>
<td>$F_8$</td>
<td>1.805</td>
<td>11.872</td>
<td>23.744</td>
<td>39.451</td>
</tr>
<tr>
<td>9</td>
<td>$F_9$</td>
<td>2.092</td>
<td>13.762</td>
<td>27.525</td>
<td>45.732</td>
</tr>
<tr>
<td>10</td>
<td>$MP$</td>
<td>1.526</td>
<td>10.042</td>
<td>20.084</td>
<td>33.370</td>
</tr>
</tbody>
</table>
Disintegration time
\[ Y_1 = 11.979 - 0.828X_1 - 0.632X_2 - 0.0995X_3 + 1.605X_4 + 0.853X_5 + 0.798X_6 + 0.136 \times (10^{X_1}) \]
\[ Y_2 = 37.210 - 2.754X_1 - 2.1X_2 - 0.33X_3 + 5.336X_4 - 2.836X_5 \]

The positive sign for co-efficient of \( X_1, X_2, X_3 \) and \( X_4 \) equations indicates that, as the concentration of Crospovidone decreases, wetting time disintegrating time, \( t_{50\%} \) and \( t_{90\%} \) value increases. In other words the data demonstrate that both \( X_1 \) (amount of Crospovidone) and \( X_2 \) (amount of Croscarmellose sodium) affect the time required for drug release (wetting time disintegrating time, \( t_{50\%} \) and \( t_{90\%} \)). From the results it can be concluded that, and increase in the amount of the Superdisintegrant leads to decrease in disintegration time of the Dosage form and drug release pattern may be changed by appropriate selection of the \( X_1 \) and \( X_2 \) levels. The dissolution parameters for predicted from the polynomial equations derived and those actual observed from experimental results are summarized in Table 6. The closeness of Predicted and Observed values for wetting time disintegrating time \( t_{50\%} \) and \( t_{90\%} \) indicates validity of derived equations for dependent variables. The Response surface Plots were presented to show the effects of \( X_1 \) and \( X_2 \) on wetting time disintegrating time \( t_{50\%} \) and \( t_{90\%} \). The final best (Optimized) formulation \( F_0 \) is compared with marketed product (TEGRETOL-100) shows similarity factor \( (f_2) = 82.675 \), difference factor \( (f_1) = 2.048907 \). There is no significant difference in drug release because \( f_1 \) is <0.05.

Table 6: Dissolution Parameters for Predicted and Observed Values for Check Point Formulations

<table>
<thead>
<tr>
<th>Formulation Code</th>
<th>Predicted value</th>
<th>Actual observed value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>WT (Sec)</td>
<td>DT (Sec)</td>
</tr>
<tr>
<td>( C_1 )</td>
<td>63.753</td>
<td>35.917</td>
</tr>
</tbody>
</table>

CONCLUSION

The present research work envisages the applicability of Superdisintegrants such as Crospovidone and Croscarmellose sodium in the design and development of Fast Dissolving tablet formulations of Carbamazepine utilizing the \( 3^2 \) factorial design. From the results it was clearly understand that as the concentration of Superdisintegrant increases the release rate of drug was RAPID (Improved Solubility) and both of these Superdisintegrants can be used in combination since do not interact with the drug which may be more helpful in achieving the desired fast Dissolving of the dosage form for rapid action and improved Bioavailability. The optimized formulation followed Higuchi’s kinetics while the drug release mechanism was found to be Non-Fickian Diffusion, first order release type. On the basis of evaluation parameters, the optimized formulation \( F_0 \) may be used for the effective management of Epilepsy, convulsions, Tremors and Neuropathic Pain. This may improve the patient compliance by showing rapid action via disintegration without difficult in swallowing and side effects which will ultimately improve the therapeutic outcome. we could be able to minimize the per oral cost of the formulation.

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