Formulation Design and Optimization of Fast Dissolving Effervescent Tablets of Clonazepam

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ABSTRACT

Fast dissolving tablets of clonazepam were prepared by effervescent method with a view to enhance patient compliance. A 3² full factorial design was applied to investigate the combined effect of two formulation variables: amount of crospovidone and 1:1 mixture of sodium bicarbonate and anhydrous citric acid. Crospovidone (2-8% w/w) was used as superdisintegrant and mixture of sodium bicarbonate and anhydrous citric acid (16-48% w/w) as effervescent material, along with directly compressible mannitol to enhance mouth feel. The tablets were evaluated for hardness, friability, thickness, drug content uniformity and in vitro dispersion time. Based on in vitro dispersion time (approximately 10 sec); the formulation containing 8% w/w crospovidone and 48% w/w effervescent material was found to be promising and tested for in vitro drug release pattern (in pH 6.8 phosphate buffer), accelerated stability (at 40ºC/75% relative humidity for 6 months) and drug-excipient interaction (FT-IR analysis). Surface response plots are presented to graphically represent the effect of independent variables on the in vitro dispersion time. The validity of the generated mathematical model was tested by preparing two extra-design check point formulations. The optimized tablet formulation was compared with conventional commercial tablet for drug release profiles. This formulation showed nearly nine-fold faster drug release (tₚ₅₀ 1.9 min) compared to the conventional commercial tablet formulation (tₚ₅₀ 16.4 min). Short-term stability studies on the formulation indicated that there are no significant changes in drug content and in vitro dispersion time (p<0.05).

Keywords: Fast dissolving tablets, clonazepam, crospovidone, sodium bicarbonate, citric acid, 3² full factorial design.

INTRODUCTION

Fast dissolving tablets are continuously gaining great success in the pharmaceutical market. Many patients have difficulty in swallowing tablets and hard gelatin capsules, so that they do not take medications as prescribed. It is estimated that 50% of the population is affected by this problem, which results in a high incidence of non-compliance and ineffective therapy.¹ The pediatric and geriatric populations are of particular concern. Working patients who are busy or traveling, especially those who have no access to water, but also patients who prefer a readily administered dosage form, greatly appreciate this fast-dissolving form. It can indeed dissolve and / or suspend in water, be chewed, or rapidly disperse in mouth. In addition, the bioavailability of this form is undoubtedly greater than conventional tablets or hard gelatin capsules. Another advantage, interesting for pharmaceutical industries, is cost savings, particularly when these solid dosage forms are compared with similar fast-dissolving tablets such as effervescent tablets, which require particular care to maintain very low relative humidity percentage during the entire tablet production and to guarantee an appropriate first packaging choice.

Several fast dissolving drug delivery systems have been investigated in an attempt to overcome the above limitations of conventional solid dosage form. Scientists at Wyeth Laboratories in the UK pioneered fast dissolving drug delivery during the late 1970s.² During the last decade, fast dissolving tablet (FDT) technology has drawn a great deal of attention.³ FDTs are also known as fast disintegrating, fast dispersing, rapid dissolving, and rapid melting and / or orodisperse tablets. The European Pharmacopoeia defines the term orodisperse tablet as a tablet that can be placed in the mouth where it disperses or disintegrates rapidly before swallowing.⁴ FDTs approved by United States Food & Drug Administration are classified as orally disintegrating tablets. The advantages of this dosage form over conventional tablets or capsules include ease of administration, patient compliance and palatability. The fast disintegration of tablets inside the mouth renders possibly a certain degree of absorption, throughout the sublingual or the buccal mucosa. Moreover, the drug candidates that undergoes pre-gastric absorption, when formulated as FDTs may show increased oral bioavailability.
The key parameters that are to be considered in the process of formulating FDT are taste and the disintegration time. Both of these are related either directly or indirectly to the oral cavity. The mucosa in the oral cavity presents a surface area of 100 cm² and three different types of oral mucosa are recognized: the masticatory mucosa, the lining mucosa and the specialized mucosa. Out of total oral mucosa, 15% of it consists of specialized mucosa, which is present on the dorsum of the tongue. It is mainly involved in identifying the taste of the formulation. The saliva plays an important role in the disintegration of FDTs and is primarily secreted in the oral cavity by parotid, sub-mandibular (sub-maxillary), sublingual glands, and also by numerous minor glands. Saliva is mainly constituted by water (99.5% w/v) and the remaining 0.5% w/v is constituted by dissolved compounds. The principal components of saliva are inorganic electrolytes (0.2% w/v), gases (CO₂, N₂ and O₂), nitrogen products such as urea and ammonia, vitamin-C, creatinine and mucins (glycoprotein with high molecular weight which renders the saliva viscous and adhesive). The accepted range of normal salivary flow is comprised from about 0.1 to 0.2 ml/min and reaches 7 ml/min upon stimulation.

Advantages of Effervescent Tablets

Effervescent tablets are outstanding because (a) they offer an attractive administration and also improve the absorption of the active drug by previous dissolution in a buffered medium, (b) effervescent system can buffer the aqueous solution of drug, so that the stomach pH increases (becomes less acidic) and thus prevent the degradation or inactivation of the active ingredient. This buffering effect (via carbonation) induces the stomach to empty quickly—usually within 20 minutes into small intestine and results in maximum absorption of active ingredient, (c) effervescent tablets have major advantage that the drug product is already in solution at the time it is consumed. Thus, the absorption is faster and more complete than with conventional tablet, (d) they dissolve fully in a buffered solution. Reduced localized contact in upper GIT leads to less irritation and greater tolerability. Buffering also prevents gastric acids from interacting with drugs themselves, which can be a major cause of stomach and esophageal upsets, (e) they retain their palatability after lengthy storage, essentially flavourings so they taste much better than a non-effervescent in water. Moreover, they produce fizzy tablets, which may have better consumer appeal than the traditional dosage forms, (f) excellent stability is inherent with effervescent formulations, particularly surpassing liquid forms, (g) drugs delivered using effervescent technology have predictable and reproducible pharmacokinetic profiles that are more consistent than tablets or capsules, (h) effervescent components aid in improving the therapeutic profiles of active ingredients. They also help in solubilization of poorly soluble drugs, (i) effervescence induces penetration enhancement of broad range of compounds ranging in size structure and other physiological properties. Effervescent blend can be used to obtain programmed drug delivery, (j) in remote areas, especially where parenteral forms are not available due to prohibitive cost, lack of qualified medical staff, effervescent tablets could become an alternative e.g., the use of chloroquine phosphate effervescent tablets for epidemic diseases like malaria and viral fever, (k) to solve the problems of physicochemical stability and high cost of transporting syrups, effervescent tablets provide a realistic solution.

Clonazepam is a benzodiazepine derivative with marked anti-epileptic properties. It may be used in the treatment of all types of epilepsy and seizures. Since epileptic patients have to strictly follow the dosage regimen for preventing sub-therapeutic concentration, FDT will avoid missing out of a dose even during travelling or other situations, where there is no access to water; offers a suitable and practical approach in serving desired objective of faster disintegration and dissolution characteristics with increased bioavailability. The objective of the present study was to develop and optimize such a novel drug delivery system for clonazepam by simple and cost-effective method having sufficient mechanical integrity, good content uniformity and acceptable palatability.

MATERIALS

Clonazepam (CZ) and crospovidone (CP) were gift samples from Torrent Pharma, Ahmedabad (India) and Wockhardt Research Centre, Aurangabad (India) respectively. Directly compressible mannitol (Pearlitol SD 200), and sodium stearyl fumarate (SSF) were generous gifts from Strides Arcolabs, Bangalore (India). All the other chemicals used were of analytical reagent grade.

METHODS

Preparation and Evaluation of FDT

Fast dissolving tablets of clonazepam were prepared by effervescent method according to the formulae given in Table 1.

The drug (CZ), directly compressible mannitol (Pearlitol SD 200), spray dried pineapple flavour (Trusil), aspartame and crospovidone were separately passed through # 44 mesh (British Standard wire-mesh sieve) and weighed accurately. Sodium bicarbonate and anhydrous citric acid were pre-dried at a temperature of 80°C for 2 hours, to remove residual/absorbed moisture and were thoroughly mixed in a
mortar to get a uniform powder and then added to other ingredients by mixing in geometrical order. Then sodium stearyl fumarate and purified talc (# 200 mesh) were added and mixed for further 5 min. The blend thus obtained was directly compressed using 7 mm flat round punches in to tablets of 150 mg on a 10-station rotary tablet machine (Clit, Ahmedabad, India).

**Weight Variation**
Twenty tablets were selected randomly from each formulation and weighed individually using a Shimadzu digital balance (BL-220H). The individual weights were compared with the average weight for the weight variation.

**Thickness variation**
Ten tablets from each formulation were taken randomly and their thickness was measured with a micrometer screw gauge.

**Hardness and Friability**
Hardness of the tablets was measured using the Monsanto Hardness Tester (Pharmalab, Ahmedabad, India). The friability of a sample of twenty tablets was measured using a USP type Roche friabilator (Pharmalab, Ahmedabad, India). Pre-weighed tablets were placed in a plastic chambered friabilator attached to a motor revolving at a speed of 25 rpm for 4 min. The tablets were then dusted, reweighed and percentage weight loss (friability) was calculated.

**Drug Content Uniformity**
For the content uniformity test, ten tablets were weighed and pulverized to a fine powder, a quantity of powder equivalent to 2 mg of clonazepam was extracted into methanol and liquid was filtered (0.22µm membrane filter disc (Millipore Corporation). The CZ content was determined by measuring the absorbance at 308 nm (using UV-vis spectrophotometer, Shimadzu 1700) after appropriate dilution with methanol. The drug content was determined using standard calibration curve. The mean percent drug content was calculated as an average of six determinations.

**In Vitro Dispersion Time**
One tablet was placed in a beaker containing 10 ml of pH 6.8 phosphate buffer at 37±0.5ºC and the time required for complete dispersion was determined.

**Wetting Time**
Twice folded tissue paper was placed in a petri-dish having an internal diameter of 5 cm containing 6 ml of water. A tablet was carefully placed on the surface of the tissue paper in the petri-dish. The time required for water to reach the upper surface of the tablet and to completely wet it was noted as the wetting time.

**Water Absorption Ratio (R)**
The weight of the tablet prior to placement in the petri-dish was noted (w) utilizing a Shimadzu digital balance (ELB 300). The wetted tablet was removed and reweighed (w'). Water absorption ratio (R) was then determined according to the following equation:

\[
R = \frac{100 \times (w' - w)}{w}
\]

Where, \( w \) and \( w' \) were tablet weights before and after water absorption, respectively.

**In Vitro Drug Release Study**
In vitro dissolution studies of the optimized fast dissolving tablets of clonazepam, control and commercial conventional tablet formulations were performed according to USP XXIII.
Type-II dissolution apparatus (Electrolab, model TDT-06N) employing a paddle stirrer at 50 rpm using 900 ml of pH 6.8 phosphate buffer at 37±0.5ºC as dissolution medium. One tablet was used in each test. Aliquots of the dissolution medium (5 ml) were withdrawn at specific time intervals (2, 4, 6, 8, 10, 15 & 30 min) and replaced immediately with equal volume of fresh medium. The samples were filtered through 0.22µm membrane filter disc and analyzed for drug content by measuring the absorbance at 307.5 nm. Drug concentration was calculated from the standard calibration curve and expressed as cumulative percent drug dissolved. The release studies were performed in replicates of six.

**Stability Studies**

The tablets of the optimized formulation EF, were subjected to accelerated stability studies, by storing in amber coloured rubber stopper glass vials at 40ºC/75% RH over a period of 6 months. At intervals of 3 months, the tablets were visually examined for any physical changes and evaluated for changes in drug content and in vitro dispersion time. Drug-excipient interactions were ruled out by FT-IR spectroscopic studies on the samples stored at the above conditions.

**Factorial Design**

A randomized 3² full factorial design was adopted to optimize the variables. In this design two factors were evaluated, each at three levels, and experimental trials were performed at all nine possible combinations. Based on the results of preliminary trial formulations obtained from the 15 batches of the three super-disintegrants (i.e., crospovidone, croscarmellose sodium and sodium starch glycolate), crospovidone was found to be superior compared to the other two super-disintegrants, and it was used for the optimization of the formulation by effervescent method. The amounts of crospovidone (X₁) and 1:1 mixture of sodium bicarbonate and anhydrous citric acid (X₂) were selected as independent variables and in vitro dispersion time as dependent/response variable (Y).

**RESULTS AND DISCUSSION**

Fast dissolving tablets of clonazepam were prepared and optimized by effervescent method using crospovidone as super-disintegrant and 1:1 mixture of sodium bicarbonate and anhydrous citric acid as an effervescent material along with directly compressible mannitol (Pearlitol SD 200), which was used to enhance the mouth feel. A total of nine formulations along with a control formulation (EF₀ without super-disintegrant) and two extra design check point formulations (C₁ and C₂) were designed.

As the material was free flowing (angle of repose value <30º and Carr’s index <15%, Table 2), tablets obtained were of uniform weight (due to uniform die fill), with acceptable variation as per Indian Pharmacopoeial specifications (average weight±7.5%). Drug content was found to be in the range of 96.35 - 101.60%, which is within acceptable limits. Hardness of the tablets was found to be 2.6 to 2.92 kg/cm². Friability below 1% was an indication of good mechanical resistance of the tablets (Table 3). Formulation EF, was found to be promising and displayed an in vitro dispersion time of 10 sec, which facilitates faster dispersion in the mouth (Fig. 1)
In order to investigate the factors systematically, a factorial design was employed in the present investigation. Formulation optimization has been done by using $3^2$ full factorial design, preparing nine batches of formulations (EF$_1$ to EF$_9$). A polynomial equation was derived for in vitro dispersion time, by backward stepwise regression analysis, using PCP Disso 2000 V3 software (developed by Bharati Vidya Peeth Deemed University's College of Pharmacy, Pune, India). Formulation EF$_9$ containing 8% w/w crospovidone and 48% w/w effervescent material was found to be promising with an in vitro dispersion time of 10 sec against the 192 sec displayed by control formulation (EF$_0$), which does not contain the super-disintegrant crospovidone.

In vitro dissolution studies on the promising formulation (EF$_9$), the control (EF$_0$) and commercial conventional tablet formulation (CCF) were carried out in pH 6.8 phosphate buffer and the various dissolution parameter values, viz., percent drug dissolved in 5 min (D$_5$), 10 min (D$_{10}$), dissolution efficiency at 10 min (DE$_{10}$), t$_{50\%}$, t$_{70\%}$, t$_{90\%}$, are shown in Table 4 and the dissolution profiles depicted in Fig. 2. This data reveals that, overall, the formulation EF$_9$ has shown nearly nine-fold faster drug release (t$_{90\%}$, 1.9 min) when compared to CCF (t$_{90\%}$, 16.4 min). This highly enhanced dissolution rate of CZ from EF$_9$ can be attributed to the acidic micro-environment created by the effervescence for the weakly basic drug (pKa 10.5).

An effervescent system in the formulation$^{19-22}$ facilitate a mild effervescent reaction when the tablets contact saliva, reaction accelerates the disintegration of tablet through the release of carbon dioxide, water and salt. Due to evolution of carbon dioxide, pleasant mouth feel is felt.

Drug-excipient interactions were ruled out by FT-IR spectroscopic studies on the samples (formulation EF$_9$) stored for six months at 40±2°C/75±5% relative humidity. FT-IR spectrum of clonazepam pure drug shows the characteristic peaks at 1692 and 3185 cm$^{-1}$ due to C=O stretching of carbonyl group and NH stretching (bonded NH) respectively. FT-IR spectrum of formulation EF$_9$ shows peaks at 1664 cm$^{-1}$ due to C=O stretching of carbonyl group whereas the peak at 3288.63 cm$^{-1}$ due to NH stretching. This confirms undisturbed structure of drug in the formulation and that the drug is compatible with all the excipients. Accelerated stability studies of the above formulation indicated that there are no significant changes in drug content and in vitro dispersion time at the end of 6 months period (p<0.05).

### Development of polynomial equation

From the data of in vitro dispersion time of the factorial formulations EF$_i$ to EF$_9$, polynomial equation for in vitro dispersion time has been derived using ‘PCP Disso 2000 V3 software’. Polynomial equation for $3^2$ full factorial design with

<table>
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<th>Formulation code</th>
<th>D$_5$ (%)</th>
<th>D$_{10}$ (%)</th>
<th>D$_{15}$ (%)</th>
<th>DE$_{10}$ (%)</th>
<th>t$_{50%}$ (min)</th>
<th>t$_{70%}$ (min)</th>
<th>t$_{90%}$ (min)</th>
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<td>6.3</td>
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EF$_i$ is control formulation, EF$_9$ is promising fast dissolving tablet formulation, CCF is conventional commercial tablet formulation, D$_i$ is percent drug released in 5 min, D$_{10}$ is percent drug release in 10 min, D$_{15}$ is percent drug release in 15 min, DE$_{10}$ is dissolution efficiency at 10 min, t$_{50\%}$ is time for 50% drug dissolution, t$_{70\%}$ is time for 70% drug dissolution, t$_{90\%}$ is time for 90% drug dissolution.
two independent variables i.e., proportion of crospovidone ($X_1$) and proportion of sodium bicarbonate and citric acid (1:1 ratio) as effervescent material ($X_2$), at three levels is:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \ldots .................1$$

Where, $Y$ is dependent variable, $b_0$ arithmetic mean response of nine batches, and $b_i$ estimated coefficient for factor $X_i$. The main effects ($X_1$ and $X_2$) represent the average results of changing one factor at a time from its low to high value. The interaction term ($X_1X_2$) 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.

The equation derived for in vitro dispersion time of the factorial formulations is:

$$Y_i = 39.11 – 7.34 X_1 – 8.16 X_2 \ldots .........................2$$

The negative sign for coefficients of $X_1$ and $X_2$ indicate that as the concentration of disintegrants increases, in vitro dispersion time decreases.

Validity of the above equation was verified by designing two extra design check point formulations ($C_1$ and $C_2$) and determining the in vitro dispersion time. The in vitro dispersion time values predicted from the equation for these formulations are 56.59 and 23.61 sec, whereas those observed from experimental results are 54.61 and 23.61 sec, respectively. The closeness of the predicted and observed values for $C_1$ and $C_2$ in the method indicates validity of derived equation for the dependent variable (in vitro dispersion time).

The computer generated response surface and contour plots for the dependent variable are shown in Fig. 3 and Fig. 4, respectively.

**CONCLUSION**

The results of a $3^2$ full factorial design revealed that the amounts of crospovidone and effervescent material significantly affect the dependent variable, in vitro dispersion time. It is thus concluded that by adopting a systematic formulation approach, an optimum point can be reached in the shortest time with minimum efforts.

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