Solubility and Dissolution Properties of Gliclazide

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Summary

Gliclazide is a second generation sulfonylurea drug, characterized by poor solubility and, hence, by a low dissolution rate in water. This property causes inter-individual variations of its bioavailability. The major drawback in the therapeutic application and efficacy of gliclazide as oral dosage forms is its very low aqueous solubility because of its hydrophobic nature.

Statistical experimental design is the methodology of how to conduct and plan experiments in order to extract the maximum amount of information in the fewest number of runs. With the rapidly rising cost of conducting experiments, it is essential that optimization be achieved with as few experiments as possible. This is one important reason why statistical experimental design is needed. Most experimentation today is done by changing levels of one factor (variable) at a time in a non-systematic way in order to try and find the optimum conditions of a complex system. It is not a good strategy because of its low efficacy, non-rationality and expense. A key concept often employed in optimization methodology is the response surface graphic. The response surface graphic is a geometrical representation of the response and the factor levels similar to a contour graphic. The formulation or a region in which its response has optimal characteristics based on the experimenter's specifications can be chosen in this way. Results of this study indicate the low aqueous solubility and low dissolution rate of gliclazide. A factorial design study was used to investigate the results, and the polynomial equations were constructed for further investigations.

Key Words : *Gliclazide, factorial design, optimization, dissolution.*

Gliklazidin Çözünürlük ve Çözünme Hızı Özellikleri

Özet

Gliklazid zayıf çözünürlüğü ve bu özelliğine bağlı olarak sudaki yavaş çözünme hızı ile karakterize olan ikinci jenerasyon sülfonilüre grubu bir ilaçtır. Bu özelliği, biyoyaralanımında bireylerarası değişkenliğe neden olmaktadır. Gliklazidin oral dozaj şeklinde terapötik uygulamasında ve etkililiğindeki en büyük sorun hidrofobik yapısı nedeniyle sudaki çözünürlüğünün çok düşük olmasıdır.

İstatistiksel deney tasarımı, en az sayıdaki deneyle maksimum miktarda bilginin elde edilebilmesi için deneylerin nasıl yönetilip planlanacağını ortaya koyan yöntem bilimidir. Deneylerin hızla artan maliyeti nedeniyle, mümkün olan en az deneyle yapılacak optimizasyon esastır. Bu sonuç istatistiksel deney tasarımına duyulan ihtiyacı gösteren önemli bir nedendir. Bugün çoğu deney tasarımı, kompleks bir sistemin optimum koşullarını deneme ve bulma yoluyla, herhangi bir zamandaki faktörün (değişken) düzeylerinin değiştirilmesi gibi sistematik olmayan bir şekilde yapılmaktadır. Bu düşük etkinliği, gerçekçi olmaması ve maliyeti nedeniyle iyi bir strateji değildir. Optimizasyon yönteminde sıklıkla kullanılan anahtar kavram yüzey cevap grafiğidir. Yüzey cevap grafiği kontur grafiğine benzer olarak cevap ve faktör düzeylerinin geometrik bir gösterimidir. Bu yol ile deneyi düzenleyen kişinin spesifikasyonlarına dayanan formülasyon veya uygun özelliklere sahip cevapların yeraldığı bölge seçilebilir. Bu çalışma sonuçları gliklazidin sudaki düşük çözünürlüğünü ve çözünme hızını göstermektedir. Sonuçların araştırılmasında faktöriyel tasarım kullanılmış ve daha ileri araştırmalar için polinomial denklemler ortaya konmuştur.

Anahtar Kelimeler : *Gliklazid, faktöriyel tasarım, optimizasyon, çözünme hızı.*

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INTRODUCTION

Gliclazide is a second generation sulfonylurea group oral hypoglycemic agent which is used in the treatment of non-insulin-dependent diabetes mellitus (NIDDM). Gliclazide has been well tolerated by most patients with the most frequently reported side effects being gastrointestinal in nature, which occurred in less than 2% of patients. The drug shows good general tolerability, low incidence of hypoglycemia and a low rate of secondary failure. In addition, it has potential for slowing the progression of diabetic retinopathy. For these reasons, gliclazide appears to be a drug of choice in long-term sulfonylurea therapy for the control of NIDDM[1-3].

The drug is currently prescribed in the dose range of 40-320 mg per day as tablets, one to three times daily. Indeed, high inter-subject variation in the oral absorption of Diamicron® in both type 2 diabetic patients and healthy volunteers has been observed[4]. This had no effect on the efficacy or safety of the compound, both of which have been well established[4]. The variability in absorption can be due to the physicochemical properties of gliclazide, which belongs to Class II of the biopharmaceutical classification system. That means it has low solubility and high permeability. As a result, the dissolution rate is the controlling step in drug absorption. For gliclazide, the dissolution rate depends on the gastric emptying time and the dissolution rate in the small intestine, where the compound is soluble[4-7].

Factorial designs are the designs of choice for simultaneous determination of the effects of several factors and their interactions. The choice of factors to be included in an experiment depends on experimental objectives and is predetermined by the experimenter. A factor can be qualitative or quantitative. The levels of a factor are the values or designations assigned to the factor. In factorial designs, levels of factors are independently varied, each factor at two or more levels. The optimization procedure is facilated by construction of an equation that describes the experimental results as a function of the factor levels. A polynomial equation can be constructed, in the case of a factorial design, where the coefficients in the equation are related to the effects and interactions of the factors[8,9].

When an experimenter is interested in the effects of two or more independent variables, it is usually more efficient to manipulate these variables in one experiment than to run a separate experiment for each variable. Moreover, only in experiments with more than one independent variable it is possible to test for interactions among variables. Optimization of experiments, such as those used in the formulation development stage, can lead to useful savings of scientific resources[10-16].

The objective of this study was to investigate the solubility and dissolution properties of gliclazide by using a 4x2 and 5x7 factorial design, respectively[17]. Factorial designs are used in experiments where the effects of different levels of different factors on experimental results are elucidated.

MATERIALS and METHODS

Materials

Gliclazide (Servier, Turkey) was used as the active ingredient. Potassium dihydrogen phosphate, sodium hydroxide, hydrochloric acid, sodium acetate, acetic acid, citric acid and disodium phosphate (Merck, Germany) were used to prepare the buffer solutions.

Methods

Solubility of Gliclazide
The pH solubility was investigated by measuring solubility of gliclazide using buffers of various pH (1.5, 2.5, 3.5, 4.5, 5.5, 6.5, 7.5). Weighted test sample of about 80 mg of gliclazide was added to 250 mL of buffer solution and stirred magnetically in a water bath at 37°C. One hour later 5 mL were withdrawn and assayed spectrophotometrically.

Effect of Rotation Speed on the Dissolution Rate of Gliclazide

A 4x2 factorial design was used to investigate the dissolution properties of the gliclazide active ingredient.

Independent variables were rotation speed (X) and pH of the dissolution medium (Y). The dependent variable included percent dissolved at 30 min, 45

min and 60 min. The second order polynomial equations were calculated by the Graftool, Version 3.3 computer software program (3-D Visions, Torrance, CA) and this program was employed to produce the response surface and contour graphics.

Table 1. Levels of the independent variables investigated

Variables	Levels
pH	6.5 7.5
Rotation Speed (rpm)	50 75 100 125

Effect of pH on the Dissolution Rate of Gliclazide

A 5x7 factorial design was used to investigate the dissolution properties of the gliclazide active ingredient.

Independent variables were pH of the dissolution medium (X) and dissolution time (Y). The dependent variable included percent of gliclazide dissolved in the dissolution medium. The second order polynomial equations were calculated by the same program and the response surface and contour graphics were produced.

Table 2. Levels of the independent variables investigated

Variables	Levels
pH	1.5 2.5 3.5 4.5 5.5 6.5 7.5
Dissolution Time (min)	0 30 60 90 120

RESULTS and DISCUSSION

Solubility of Gliclazide

The solubility results of gliclazide are summarized in Table 3.

Table 3. Solubility results of gliclazide

pH 1.5	pH 2.5	pH 3.5	pH 4.5	pH 5.5	pH 6.5	pH 7.5
46.37 %	30.21 %	24. 11%	2.43 %	13.98 %	76.42 %	98.93 %

Effect of Rotation Speed on the Dissolution Rate of Gliclazide
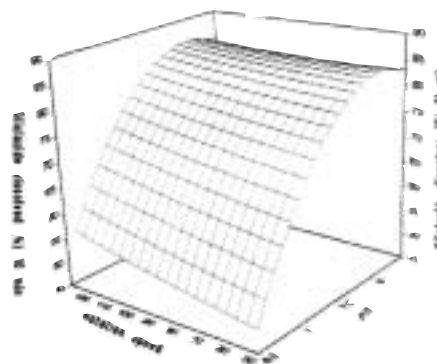
The second order polynomi

30 min.

$$Z_{30} = -808.60 + 217.49X + 0.37Y - 13.22X^2 + 309.10^{-4}Y^2 - 0.05XY \qquad \text{Eq. 1}$$
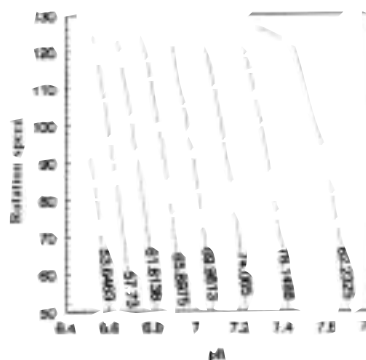
Multiple Correlation Coefficient = 0.957

Standard Error = 5.996

The response surface and contour graphic described by Eq. 1 are shown in Fig. 1 and Fig. 2, respectively.

Fig. 1. The response surface graphic of gliclazide dissolved in 30 min.

Fig. 2. The contour graphic of gliclazide dissolved in 30 min.

45 min,

$$Z_{45} = -506.32 + 137.68X + 0.51Y - 8.08X^2 - 328.10^{-4}Y^2 - 0.04XY \qquad \text{Eq. 2}$$

Multiple Correlation Coefficient = 0.944

Standard Error = 5.702

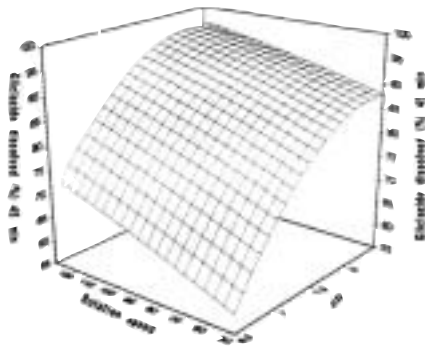The response surface and contour graphic described by Eq. 2 are shown in Fig. 3 and Fig. 4, respectively.

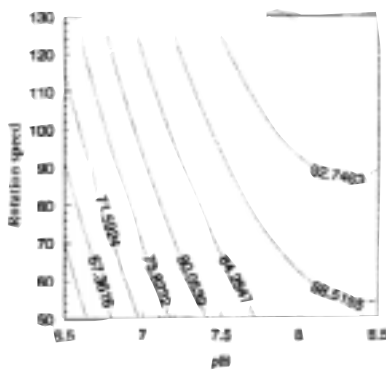**Fig. 3.** The response surface graphic of gliclazide dissolved in 45 min.

Fig. 4. The contour graphic of gliclazide dissolved in 45 min

60 min,

$$Z_{60} = - 535.77 + 146.23 X + 0.69Y - 8.68X^2 - 0.0015Y^2 - 0.05XY \qquad \text{Eq. 3}$$

Multiple Correlation Coefficient = 0.973

Standard Error = 3.663

The response surface and contour graphic described by Eq. 3 are shown in Fig. 5 and Fig. 6, respectively.
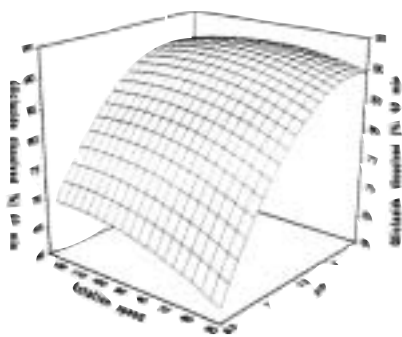

Fig. 5. The response surface graphic of gliclazide dissolved in 60 min.
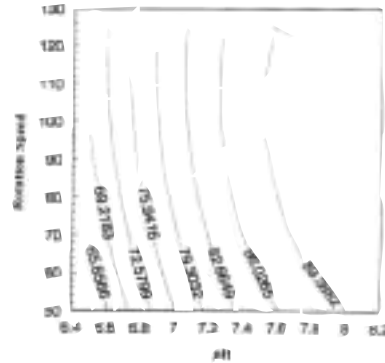

Fig. 6. The contour graphic of gliclazide dissolved in 60 min

Effect of pH on the Dissolution Rate of Gliclazide

The second order polynomial equation is,

$$Z = 49.02 - 28.72 X + 0.88Y + 322X^2 - 0.058Y^2 + 0.05XY \qquad \text{Eq..4}$$

Multiple Correlation Coefficient = 0.891

Standard Error = 16.726

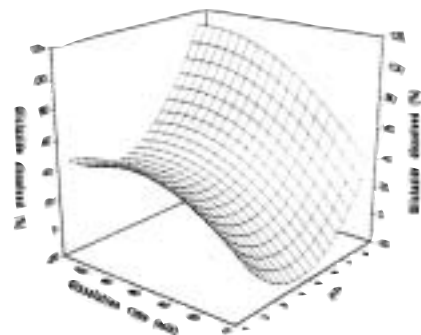The response surface and contour graphic described by Eq. 4 are shown in Fig. 7 and Fig. 8, respectively.

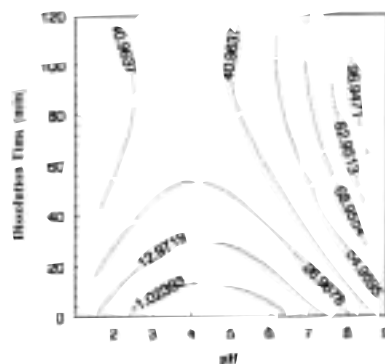**Fig. 7.** The response surface graphic of gliclazide

Fig. 8. The contour graphic of gliclazide

CONCLUSION

One of the most challenging aspects of multivariate analysis is finding the optimal variable settings that maximize or minimize a response. Optimization algorithms are a general name for techniques that are designed to solve such problems. Factorial designs are the simplest and are often adequate enough to achieve the experimental objectives. Frequently, use of these designs is imperative, for the sake of economy. Once the polynomial response equation has been established, an optimum formulation or a region can be found by various techniques[8,9]. Generally, inspection of the experimental results may be sufficient to choose the desired results. Effect of rotation speed and pH of the dissolution medium and also the effect of pH of the dissolution medium and dissolution time on the dissolution rate of gliclazide can be easily estimated by the calculated polynomial equations. Gliclazide is a weak acid with a good lipophilicity. Also, the results showed that the rotation speed, pH and the dissolution time are important factors affecting the dissolution profile of gliclazide. Gliclazide is practically insoluble in acidic media and its solubility increases as the pH becomes more alkaline.

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