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Formulation of Controlled Release Glipizide Pellets Using Pan Coating Method

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Introduction

Glipizide depicted in Figure 1, belonging to the sulfonylurea group, is one of the major active substances used for the treatment of non insulin dependent diabetes mellitus (NIDDM). It is a white odourless powder which is water insoluble. On the other hand, it is sparingly soluble in acetone and soluble in methylene chloride and chloroform[1-3]. It is also bound to the plasma proteins with a ratio of 98% having a pKa value of 5.9[4, 5]. Glipizide was administered once or twice daily in doses of 5 to 20 mg[6].

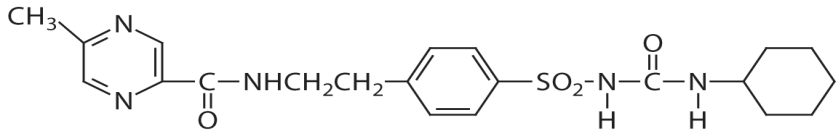

Figure 1
Chemical structure of glipizide

Microparticulate dosage forms are the general group term used to define several small dosage units. Oral administration of microparticulate dosage forms is generally realized by application of dosage units containing required active substance for treatment in hard gelatin capsule caches of a disintegrating tablet. The general method for obtaining the

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controlled release of the active ingredient is encapsulation in a swellable matrix of the coating of the dosage unit by suitable polymer solutions[7].

Pelletization is a term used to define agglomeration of drug substances in either powder or granule form resulting in the form of semi-spherical and spherical agglomerates having good flow properties. Generally, the particle sizes of the resulting pellets are between 0.5 and 1.5 mm depending on the preparation technique[8].

Pellets provide a reduction in the dosage regimen and gastrointestinal irritation moreover controlling the drug release and increasing the absorption of the active ingredient. Also one of the advantageous properties of the pellet formulations is being good candidates for the delivery of the drug substances due to minimizing the dose dumping effect. The reproducibility of the release characteristics from pellet formulations is also much better with respect to the single-unit dosage forms[9-11]. They are suitable systems for film coating with respect to the low surface area-volume ratios. Also, resistance to external factors such as moisture, air and light are the most advantageous properties of these dosage forms[12-20].

Pan coating is a method for the preparation of the coated pellets. In pan coating method; a core material is coated with the drug substance following a secondary coating process in which the release controlling polymer material is introduced. In previous studies, different Eudragit types are used as the polymer coating materials providing the release of the drug substance with respect to various pH values either used as individually or in combination at different ratios[21-23].

In this study, the pellet formulations are prepared by pan coating method described by Bodea et al.[24]. We prepared formulation in order to decrease the dosage regimen which is twice daily for conventional tablet formulation of Glipizide thus the pellet formulation are aimed to maintain the necessary blood Glipizide concentration for the treatment. The in vitro characterization of the pellet formulations are evaluated as well as microscopic investigations.

Materials and Methods

Materials

The active substance glipizide is generously obtained from Carlo Erba (Turkey). The non-pareil seeds used in the preparation of pellet formula-

tions as a core material were obtained from Deva Holding A.Ş. (Turkey). The polymers used in the coating were Eudragit RL 100 PM and Eudragit RS 100 PM (Rhöm Pharm-Germany) and PEG 4000 (Eczacıbaşı, Turkey). All other chemicals are used without further purification. Minidiab® 5 mg (Batch 6116567) tablets were kindly supplied from Carlo Erba Turkey.

Preparation of Controlled Release Glipizide Pellets

As a manufacturing method, pan coating was used in order to prepare spherical pellets. Glipizide was incorporated into non-pareil seeds by spraying glipizide in a solution in methylene chloride containing polyvinyl pyrolidone (PVP 30K) as a binder and talc as antisticking agent. The coating solution parameters are stated in Table I.

TABLE I
Formulation of pan coating solution

Inactive and Active Ingradients	Amounts
Glipizide	0.7 g
Polyvinylpyrolidone (PVP) 30K	20 g
Talc	20 g
Methylene Chloride qs	300 mL

The stated amounts of glipizide and PVP 30 K were dissolved in methylene chloride solution separately. After mixing each solution for a certain period of time, these two solutions were mixed together and necessary amount of methylene chloride up to the desired volume was added. The coating solution was sprayed over the non-pareil seed by using Erweka AR 400 coating pan rotating with a speed of 20 rpm. The pressure of the spray gun was set to 4 atm and 1200 mL coating solution was sprayed over 70 g of non-pareil seeds. No heating was applied during the preparation for the drying of the pellets during preparation. The pellets were dried at room temperature up to a constant weight.

Upper layer coating was evaluated for proving the controlled release of glipizide from pellet formulations. For this purpose, Eudragit RS 100 PM and Eudragit RL 100 PM polymers were used which provide the release of the active ingredients independent of pH of the environment[25-26]. Three different coating solutions with the formulation codes PI, PII and PIII were prepared for the upper layer coating. The formulation parameters for upper layer coating solutions are given in Table 2. PEG 4000

was added to the coating formulations as the plasticizer. As the solvent for these coating solutions ethanol was selected since the active ingredient glipizide has no solubility in this solvent. These formulations were sprayed over the 70 g of glipizide coated pellets in the coating pan set to 20 rpm with a spray gun at 4 atm pressure. After coating, the coated pellets were dried at room temperature until constant weight is reached.

TABLE II

Upper Layer Coating Formulations

Ingradients	Amounts		
	PI	PII	PIII
Eudragit RS 100 PM	7,5 g	12,5 g	17,5 g
Eudragit RL 100 PM	5 g	-	-
PEG 4000	10 g	5 g	5 g
Talc	10 g	5 g	5 g
Etanol qs	200 mL	100 mL	100 mL

As an other formulation parameter the amount of these three upper layer coating polymer solutions were varied in order to provide different release rates of the glipizide. These parameters are summarized in Table 3.

TABLE III

Upper Layer Coating Solution Amounts

Coating Solution	Sprayed Amount (mL)			
PI	100	200	400	600
PII	150	300	450	-
PIII	100	200	-	-

Particle Size Determination

In order to determine the particle size distributions of the prepared pellets containing glipizide, standard sieve method was used[27]. Endecott standard sieves between apertures 355-2000 µm were used by using

all the amount of pellets prepared. The fraction collected on each of the sieves was calculated by the percentage value.

Microscopic Evaluations

The morphological properties of the pellet formulations were investigated by the Nikon polarizing microscope (Japan) directly. In addition, the cross sectional investigations of the formulations was also evaluated.

Friability of the Formulations

Friability of all pellets (eudragit coated pellet formulations, glipizide coated non-pareil seeds and uncoted non-pareil seeds) were determined by using USP friability test. Friability of the pellet formulations was evaluated over 10 g of samples in Roche Friabilator (Hoffman la Roche, Basel) at 25 rpm for 4 minutes[27]. Prior to and following the test, the weights of the formulations were accurately recorded and the friability ratios were calculated with Equation 1 where w_1 is the initial weight and w_2 is the final weight of the formulation. The results are expressed in terms of the percentage of weight lost during the process.

$$F = \frac{W_1 - W_2}{W_1} * 100 \quad \text{(Equation 1)}$$

Drug Loading and Content Uniformity

The glipizide content of the pellet formulations were evaluated over accurately weighed 100 mg pellets. After completely powdering pellets in mortar, the complete residue was transferred into a volumetric flask and added up to 100 mL with pH 7.4 phosphate buffer solution. This solution was kept in the ultrasonic bath for 15 minutes and centrifuged for 30 minutes at 5000 rpm. The UV absorbance of the supernatant was measured at λ=276 nm. The content uniformity test was evaluated six times for each of the formulations and the results are expressed with the standard deviations and variation coefficients.

In-vitro Release Studies

In-vitro release of Glipizide from pellet formulations and Minidiab® commercial dosage form was investigated by the USP apparatus I (Basket

method) and USP apparatus II (Pedal Method) respectively. The release medium was 900 mL pH 7.4 phosphate buffer solution at 37±0.5°C and the rotating speed of the apparatus was set to 100 rpm for all formulations (pellets and Minidiab®). At certain time intervals, 5 mL of samples were withdrawn and immediately, same amount of fresh medium (37±0.5°C) was added. For the determination of glipizide amount, the UV absorbancies of the samples were measured at λ=276 nm and total amount of glipizide contents were calculated with the previously determined calibration curve (r^2=0.9999).

Results and Discussion

Particle Size Determination

The particle size distribution results obtained by standard sieve method for each of the formulations are given in Figure 2. According to the experimental findings, average particle sizes of the pellets were nearly 1200 µm and narrow distribution range was observed which is between 1000-1400 µm.

Microscopic Evaluations

The pellet formulations were examined by polarizing microscopy for the evaluation of the surface characteristics as previously described. For all formulations, the surfaces of the pellets were rough and spherical. The coating layer of the pellet formulations were observed with the cross-sectional observation of the pellets under microscope starting with the core in the center and the outer coating layer levels towards the outside as shown in Figure 3.

Friability of the Formulations

Friability results for all pellet formulations (Eudragit coated pellet formulations, glipizide coated non-pareil seeds and uncoated non-pareil seeds) as a characterization parameter were evaluated and the results were in a range between ratios of 0.02-1 %. Detailed results for all pellet formulations are expressed in Table 4. PII 300 mL formulation showed friability value equal 1% USP limit for tablets[27, 28]. All other pellet formulations achieved friability values less than 0.4%. Thus all pellets passed the USP friability test.

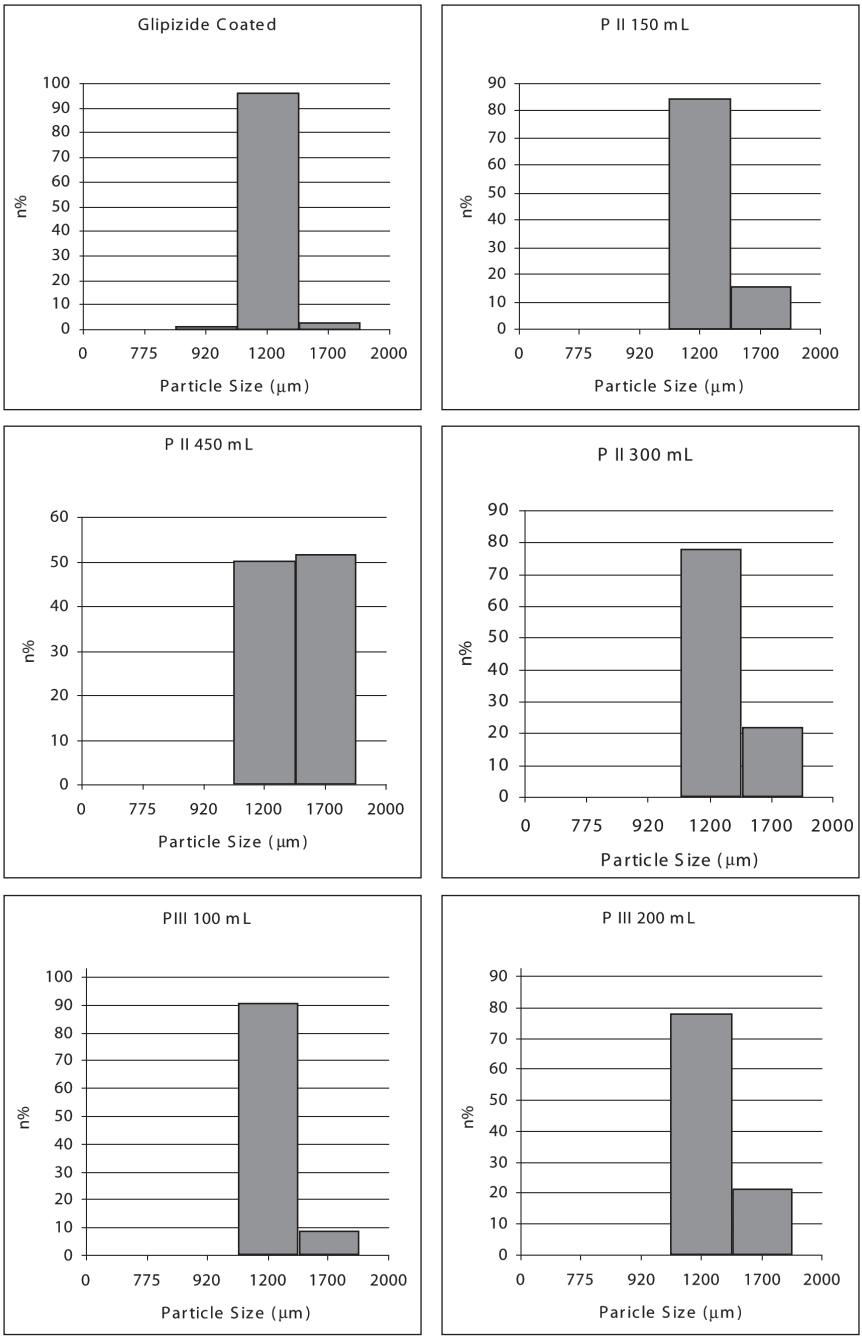


Figure 2
Particle size distribution of formulations

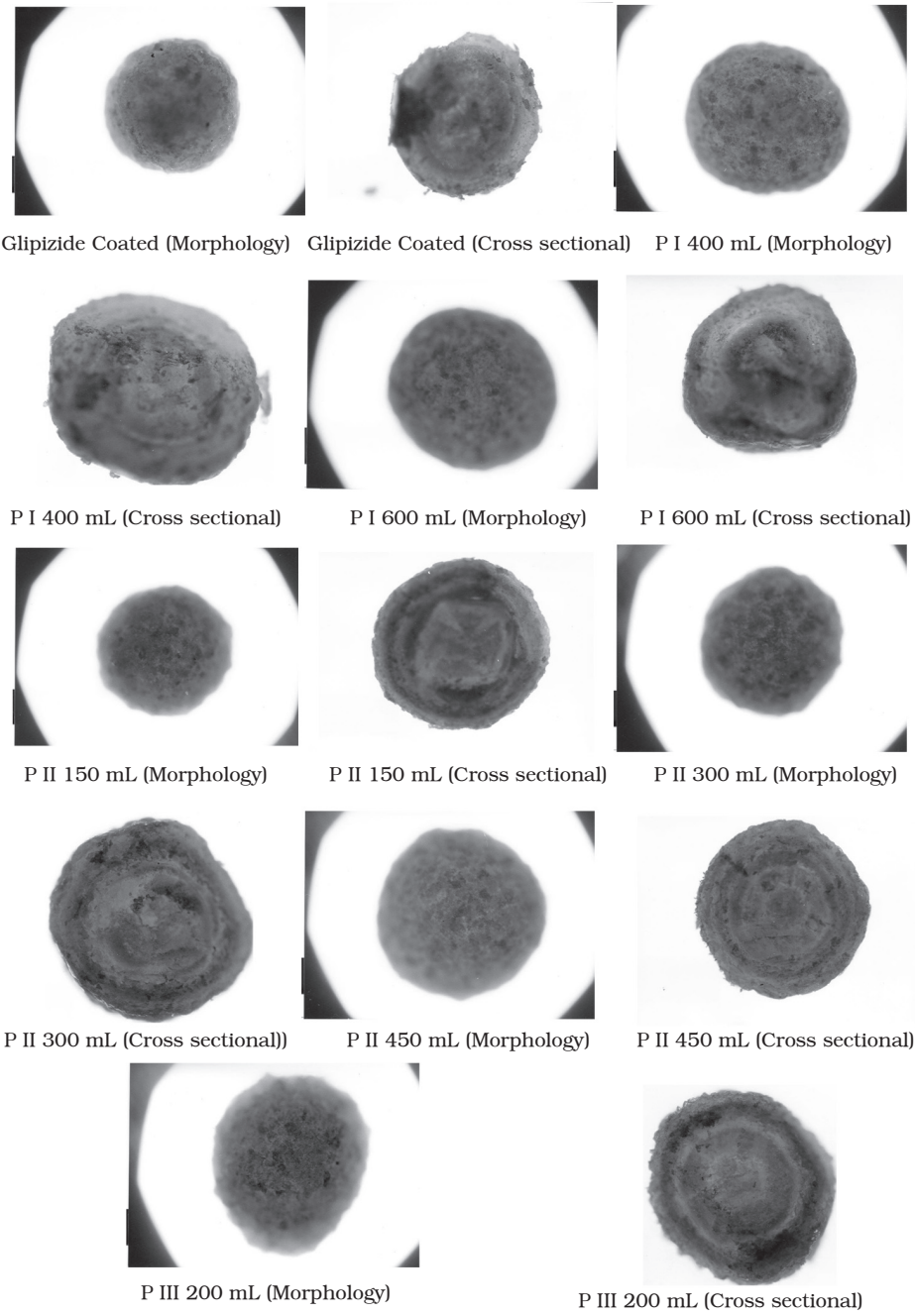


Figure 3
Morphological and cross sectional microscope photographs of glipizide pellet formulations (magnification X4)

TABLE IV

Friability Results of Formulations

Sample		**Friability (%)**
PI	100 mL Coated	0,03
	200 mL Coated	0,04
	400 mL Coated	0,06
	600 mL Coated	0,07
PII	150 mL Coated	0,02
	300 mL Coated	1,00
	450 mL Coated	0,05
PIII	100 mL Coated	0,40
	200 mL Coated	0,20
Glipizide Coated Non-Pareil Seeds		0,10
Uncoated Non-pareil Seeds		0,20

Drug Loading and Content Uniformity

The results for the drug loading of the pellet formulations were evaluated statistically by calculating the standard deviations and variation coefficients. For every single formulation, the drug content results were evaluated six different times and variation coefficients were all in the range below 5% except only one formulation coded PIII-100 mL with the coefficient 6.7%. The overall results for all formulations are summarized in Table 5.

In-vitro Release Studies

The in vitro release experiments were evaluated in order to investigate the effect of the type of coating polymer and the amount of the polymer regardless from the type. Eudragit RS and Eudragit RL were the two types of ammonioalkyl methacrylate copolymers that have the property of pH independent release, used for the aim of sustained drug delivery. Eudragit RS and RL are two types of. Although they are insoluble in water, they have the capacity to permeate water through swellable porous structure that they form[26, 29-33]. This property results in the release the active ingredient as a consequence of diffusion through the coating layer.

Similar to this perspective, our results correlate with the previous data. For the formulations PI-100mL, PI-200 mL, PI-400 mL and PI-600 mL, as

TABLE V
The amount of glipizide in 100 mg pellets in different formulations

Formulation		**Mean***	**Standard Deviation**	**Variation Coefficient**
PI	100 mL Coated	0,459	0,026	4,790
	200 mL Coated	0,584	0,010	2,370
	400 mL Coated	0,460	0,016	0,011
	600 mL Coated	0,364	0,011	3,265
PII	150 mL Coated	0,880	0,020	2,880
	300 mL Coated	0,580	0,010	2,330
	450 mL Coated	0,500	0,020	4,210
PIII	100 mL Coated	0,790	0,050	6,700
	200 mL Coated	0,730	0,020	2,350

*mg Glipizide /100mg pellet

the amount of the coating layer is increased, the release time of glipizide is significantly increased due to the thickness of the diffusion layer. The released amount of glipizide was 90% in 1.5 hours for PI-100 mL, 85% in 3 hours for PI-200 mL and 81% in 3 hours for PI-400 mL formulation. As the amount of coating layer is increased up to 600 mL, in 4 hours %78 of the glipizide content was released. On the other hand over 95% amount of glipizide was dissolved from Minidiab® tablets in 5 minutes.

PII formulations were prepared only with Eudragit RS, which is less permeable than RL form, and again as the amount of the coating solution is increased, the release of glipizide was significantly prolonged. We found that the released amount of glipizide was 81% in 5 hours for PII-150 mL, 86% in 12 hours for PII-300 mL and 85% in 14 hours for PII-450 mL formulation.

For the PIII formulations, the highest concentration of coating solution, composed of 17.5 g Eudragit RS polymer in 100 mL, was used. Released glipizde amount was found 82% in 4 hours for PIII-100 mL. The release time of glipizide was 9 hours, but on the other hand the released glipizide amount from PIII 200 mL formulation was significantly lower than the previous formulations as a ratio of 70%. The release profiles for all formulations are given in Figure 4.

The lag time observed in coated pharmaceutical dosage forms generally depends on the coating material used in these formulations[34]. As the concentration of the plasticizer is increased, porosity and the permeability

also increase, whereas the lag time is decreased in dissolution studies. This is due to the increase in plasticizer concentration resulting in the formation of the porous structure in the coating layer[35]. In this study, PII-300 mL and PII 450 mL formulations showed a lag time as similar as in dissolution profiles. This lag time can be avoided by increasing the PEG 4000 concentration in the PII-300 mL and PII 450 mL coating formulations.

Conclusion

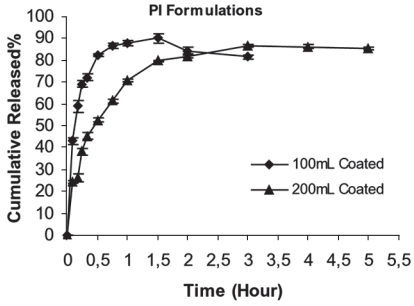
The aim in formulating glipizide pellet formulations, which was determined as extending the release, was successfully achieved. As a result of this study, it was shown that the release time may be extended by changing the coating layer composition and coating layer. Further studies are needed for determining the in vivo performances of these formulations for the aim of extending the release of glipizide.

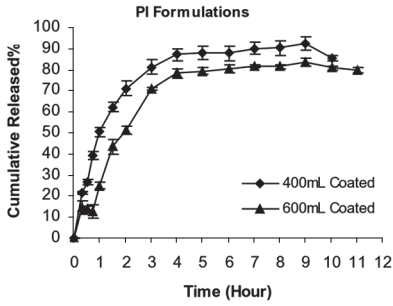
Summary

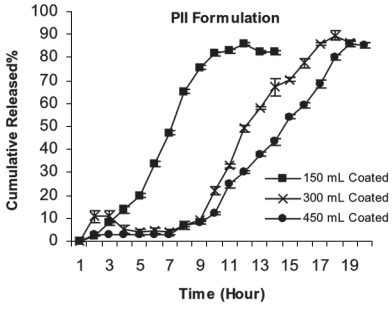
Formulation of Controlled Release Glipizide Pellets Using Pan Coating Method

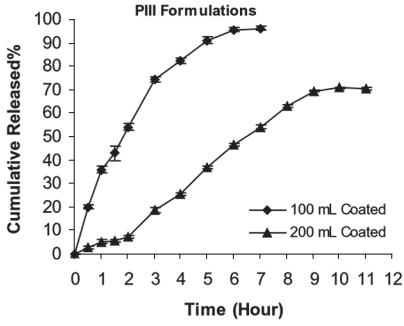
Glipizide is a second generation sulfonylurea used for non insulin dependent diabetes mellitus (NIDDM). The main characteristics of glipizide in the body is, its short half life ($t_{1/2}$=2-4 h) after a rapid absorption from the gastrointestinal tract. The main formulation perspective in pellet formulation is to prepare a controlled release dosage form compared with the commercially available Minidiab® tablets. Pellet formulations were prepared by using pan coating method. Spherical pellets as non-pareil seed were coated by the sprayed solution containing glipizide, polyvinyl pyrolidone, talc and methylene chloride in Erweka AR 400 coating pan. As the polymer coating, Eudragit RS 100 PM, Eudragit RL 100 PM, PEG 4000 and talc with different ratios in alcohol solution was sprayed over the glipizide coated pellets in order to provide controlled release. The dissolution profiles of the manufactured pellets were evaluated in pH 7.4 phosphate buffer solution in USP apparatus 1. The surface morphologies and the cross sectional investigations were evaluated in the polarizing light microscope. As a result, the coated pellet formulations were found to yield the release of glipizide between 3 to 13 hours.

Keywords: Pellet, Glipizide, Controlled release, Pan coating, Eudragit RL, Eudragit RS









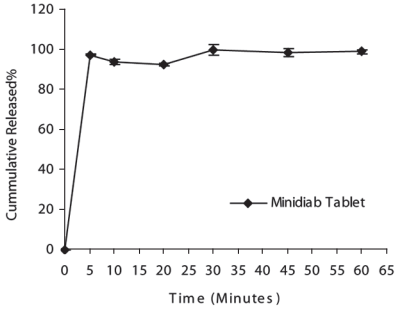


Figure 4
Dissolution profiles of Glipizide from pellet formulations and Minidiab® tablets

Özet

Kazanda Kaplama Yöntemi Kullanılarak Kontrollü Salım Sağlayan Glipizid Pelletlerinin Formülasyonu

Glipizid insülinden bağımsız diabet tedavisinde kullanılan ikinci jenerasyon bir sülfonilüre grubu ilaçtır. Glipizidin vücuttaki ana karakteristiği; mide barsak kanalından hızlı absorpsiyonundan sonra kısa yarılanma ömrüdür ($t_{1/2}$=2-4 saat). Pellet formülasyonu hazırlamadaki ana amaç; Minidiab® adıyla bilinen ticari preparatıyla kıyaslandığında kontrollü salım yapan pellet formülasyonları geliştirmektir. Pellet formülasyonları kazanda kaplama yöntemi kullanılarak hazırlanmıştır. Küresel boş pelletler, glipizid, polivinilpirolidon, talk ve metilenklorid içeren çözelti ile Erweka AR 400 kaplama kazanında püskürtülerek kaplanmıştır. Kontrollü salımı sağlamak amacıyla glipizid kaplı pelletlerin üzerine, polimer kaplaması olarak, Eudragit RS 100 PM, Eudragit RL 100 PM, PEG 4000 ve talkın çeşitli oranlardaki karışımının alkoldeki çözeltisi püskürtülmüştür. Üretilen pelletlerin disolüsyon profilleri pH 7.4 fosfat tamponunda USP yöntem I ile değerlendirilmiştir. Yüzey morfolojisi ve çapraz kesit incelemeleri polarizan ışık mikroskobu ile değerlendirilmiştir. Sonuç olarak, kaplı pellet formülasyonlarından glipizinidin salımı 3-13 saat arasında bulunmuştur.

Anahtar Kelimeler: Glipizid, Kontrollü salım, Kazanda kaplama, Eudragit RL, Eudragit RS

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