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MODIFICATION OF DISSOLVING STUDIES OF GLİCLAZİDE IN LONG RELEASE TABLET FORM USING DIFFERENT POLYMERS

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ABSTRACT

The main purpose of this study is to obtain an long release tablet formulation of gliclazide utilizing wet granulation production method after evaluation of different polymer structures. In order to provide the long release profile of the gliclazide, trial studies were carried out with xanthan gum, hydroxypropylmethylcellulose (HPMC K100M), povidone K30 and povidone K90 polymers, which have different viscosity properties. Dissolution rate (In vitro) test was applied to each trial run. In this study, Diamicron MR 60 mg Tablet was used as reference product for dissolution rate tests. As a result of dissolution rate (in vitro) studies, dissolution rate profile was obtained by plotting the dissolution amount of gliclazide versus time. To conclude, it was determined that the polymers providing long release of gliclazide were Povidone K30 and Povidone K90 mixture, and it was proved by the dissolution rate test.

KEYWORDS: Gliclazide, Dissolution Rate, Long Release, Wet Granulation, Polymer.

INTRODUCTION

Controlled-release drug forms offer many advantages such as reducing the frequency of dosage intake during the day, convenience in the compliance of the patients, and a significant reduction in drug plasma concentration fluctuations and side effects.[1] Long-release dosage forms have systemic structures; therefore, it ensures that the drug form is released slowly in the gastrointestinal tract, ensuring that the drug concentration in the gastric circulation remains constant for a long time. In normally developed drug forms, the drug release cannot be completed in a healthy way due to the short residence time in the stomach, staying in the upper part of the stomach and intestinal canal, and dissolution and absorption in the non-targeted area.[2] The bioavailability of the drugs decreases due to the drug that does not have a controlled release in the targeted area. As a result of studies, it has been observed that the bioavailability of the drug increases in patients using drugs with controlled release systems, as a result of the dissolution profile in the targeted region and time, and the effects expected from the drug used are faster.[3] As a result of all these, drug development projects with controlled release systems are very trendy in companies today.

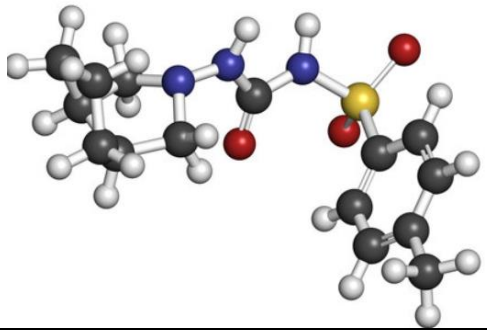
Drugs with controlled-release systems differ from other drugs in terms of dosage amounts, rates of absorption, duration of action, route of elimination, and binding sites on the target pancreatic beta-cell receptor.[4] The rate of absorption may differ depending on both the preparations and the patient. Raw materials in the gliclazide class are generally metabolized by the liver.[5]

High-density systems, systems where the drug is retained in the lower stomach[4], low-density systems floating in gastric juice[6,7], mucoadhesive[8] systems, systems that open and expand by providing swelling to restrict passage through the pyloric sphincter[9,10], multi-porous hydrogels[11], magnetic systems[12] are formulations developed within the scope of these controlled release drugs.

As a model for our studies, it is aimed to develop drugs with controlled release systems. In this context, gliclazide, which is widely used in the treatment of diabetes, was chosen. Four different polymers were used to gain similarities in terms of in-vitro, permeability, bioequivalence with reference products taken in Turkiye and abroad.

GLİCLAZİDE

Table 1: Physical, Chemical and Characteristic Properties of Gliclazide.

Physical, Chemical and Characteristics of Gliclazide	
Apperance	White-whitish colored homogenous powder
Solubility	While it is not freely soluble in water, it is freely soluble in Methylene Chloride. It is slightly soluble in Acet1 and 96% Ethanol.
Structural Formula	
BCS Class	It is in Class II Drugs Category. (Low Solubility, High Permeability)
Molecular Weight	323,41
Chemical Formula	$C_{15}H_{21}N_3O_3S$
Melting Point	181° C
Elimination half-life	10.4 Hours
Storage Conditions	Gliclazide should be stored at controlled room temperature between 15-30°C and in tightly closed airtight containers.
CAS Number	21187-98-4
Pharmacological Group	Antidiabetic Drugs ⟶ Oral Antidiabetic Drugs ⟶ Sulfonylureas
ATC Number	A10 ⟶ Drugs Used in Diabetes Treatment A10B ⟶ Drugs that Lower Blood Sugar, Excluding Insulins A10BB ⟶ Sulfonamides (Urea Derivatives) A10BB09 ⟶ Gliclazide
Indication Information	It is indicated for Type II diabetes disease as approved. It should be used only in patients with diabetes who are not insulin dependent, where hyperglycemia cannot be controlled by diet and exercise.
Posology	Adults should initially take 40-80 mg/day as a dose. It can be gradually increased to 320 mg/day as needed doses above 160 mg should be given divided into two.
Contraindication	The situations in which drugs containing glycosides should definitely not

Information	be used are as follows. 1- It should not be used during surgical operations. 2-It should definitely not be used as Diabetic Ketoacidosis. 3- It should not be used as an infection reliever. 4- It should not be used for Renal Weakness. 5 -It should not be used in traumas. 6- It should not be used in the treatment of thyroid disease. 7- It should not be used on patients with hypersensitivity to sulfonylurea.

Gliclazide is a second-generation oral antidiabetic of the sulfonylurea group with a medium duration of action. The duration of action is approximately 12 hours.[13] It is used in the treatment of non-insulin dependent diabetes mellitus cases. Since the effect is shorter than chlorpropamide and glibenclamide, it is preferred in elderly patients with a tendency to hypoglycemia when using long-acting sulfonylureas.[13] Increases the effectiveness of tissue plasminogen activator in a reduced state in patients with diabetes. Regular examinations have shown that it delays the development of diabetic microangiopathy and diabetic retinopathy.[14]

Gliclazide, like all other sulfonylureas, provides an insulin-like effect by increasing the secretion of insulin from pancreatic beta cells.[15] Increases insulin secretion, both basal and caused by glucose loading or eating. It is believed that sulfonylureas bind to ATP-sensitive "potassium channel receptors" located on the surface of pancreatic cells and thereby reduce potassium conductance (permeability), causing depolarization of the membrane. Potassium channels are closed by inhibiting ATP, which is made naturally inside the cell, while they are opened by ADP. These channels are indirectly closed by glucose, which is the natural stimulus of beta cells. Sulfonylureas perform depolarization in the pancreatic cell by selectively blocking potassium channels by their direct action. Depolarization stimulates the entry of calcium ions into the cell through voltage-sensitive calcium channels, which allows the intracellular concentration of these ions to increase. An increase in intracellular calcium concentration allows insulin secretion by exocytosis.[16] Gliclazide is not effective in patients with "type I diabetics" who do not have functional b-cells, or in cases where the number of b-cells is insufficient (as in severe "type II diabetes" patients). Gliclazide also has non-pancreatic effects that contribute to its hypoglycemic activity. The most important of these is to increase the sensitivity to insulin in the periphery. Its effect on increasing sensitivity to insulin in the periphery depends on either increasing the number of insulin receptors or events that follow insulin-receptor binding. The relative importance of each of these effects in the total effect varies between oral decongestants, as well as from patient to patient. For this reason, the potencies of this group of drugs may differ significantly between patients decently.[17] Sulfonylurea group antidiabetic drugs show their main effects by inhibiting the secretion of insulin in the first, but they also stimulate insulin secretion that continues throughout the meal. It increases the effectiveness of tissue plasminogen activator in a reduced state in patients with diabetes. In controlled studies, it has been shown to delay the development of diabetic microangiopathy and diabetic retinopathy.

Although gliclazide is practically insoluble in water, it is a white-whitish powder that is slightly soluble in alcohol and acetone and freely soluble in dichloromethane[18] Gliclazide is a sulfonylurea derivative used in the treatment of diabetes mellitus through the inhibition of ATP-dependent potassium channels. It is given orally in the treatment of type 2 diabetes and has a duration of action of 12-24 hours. Since its effects are shorter-lasting than chlorpropamide or glibenclamide, it may be more suitable for elderly patients who may have hypoglycemia with longer-acting sulfonylureas.[18,19]

The visual showing the mechanism of action of Gliclazide, which is in the group of antidiabetic Drugs, is as follows.

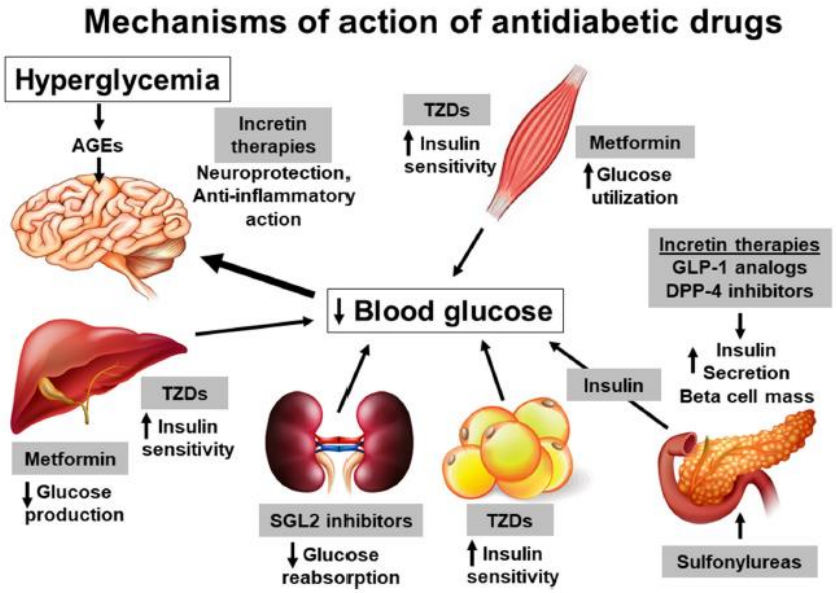


Figure 1: Mechanisms of action of antidiabetic drugs.[20]

MATERIAL AND METHOD

Material

Gliclazide active substance was procured by (Zhejiang, China). The excipient which are used as respectively; Maltodextrin (Roquette, France), Calcium Hydrogen Phosphate Dihydrate (Sudeep, India), Xanthan Gum (Jungbunzlauer, Switzerland), HPMC K100M (Colorcon, Germany), Povidone K-90 (ISP, Germany), Povidone K-30(BASF, Germany), Ethanol (96%) (Merck, Germany), and Magnesium Stearate (Peter Greven, Germany) supplied. All raw materials used are suitable for European Pharmacopoeia.

Method

Tablet Formulation Trial Studies

Trial studies have been conducted to develop a long-release tablet formulation with gliclazide. The formulation table of the trial studies is given in detail below.

Table 2: Formulations for trials.

Raw material	Trial 1 (mg/tablet)	Trial 2 (mg/tablet)	Trial 3 (mg/tablet)	Trial 4 (mg/tablet)	Trial 5 (mg/tablet)
Gliclazide	60,000	60,000	60,000	60,000	60,000
Maltodextrin	*	*	*	*	*
Calcium Hydrogen Phosphate Dihydrate	*	*	*	*	*
Xanthan Gum	*	-	-	-	-
HPMC K100M	-	*	-	-	-
Povidone K-90	-	-	*	-	*
Povidone K-30				*	*
Ethanol (96%)	*	*	*	*	*
Magnesium Stearate	*	*	*	*	*

*Raw materials used in the formulation of the experiments

-Raw materials not found in the trials

Trial 1: Production Method

Batch Size: 1000 Tablets

- Raw materials are weighed in accordance with the production formula.

Table 3: Trial 1 Premix Parameters.

Premix Parameters		Process Steps
Mixer Speed	25rpm	Premix Stage
Chopper Speed	Closed	
Mixing Time	10 min	

- Gliclazide, Maltodextrin, Calcium Hydrogen Phosphate Dihydrate and Xanthan Gum are loaded into the High Shear Mixer and the pre-mixing process is applied with the following parameters.

Table 4: Trial 1 Wet Granulation Parameters.

Wet Granulation Parameters		Process Steps
Mixer Speed	25rpm	Wet Granulation Stage
Mixing Time	3 min	
Pump Speed	25rpm	
Chopper Speed	1500rpm	
Mixer Speed	25rpm	After Wet Granulation Stage
Mixing Time	1 min	
Chopper Speed	1500rpm	
Compression force	5-10 kW	

- The resulting powder mixture is granulated with 96% Ethanol with the following parameters.

Table 5: Trial 1 Wet Sieving Parameters.

Wet Sieving Parameters		
Sieve Size	9525µ	Wet Sieving Stage
Sieve Speed	1000rpm	

- In order to provide a homogeneous drying to the obtained granules, the following parameters are applied by Wet Sieving process.

Table 6: Trial 1 Wet Sieving Parameters.

Wet Sieving Parameters		
Sieve Size	9525µ	Wet Sieving Stage
Sieve Speed	1000rpm	

- The obtained wet granules are dried in a fluidized bed dryer with the following parameters so that the humidity is in the range of 1%-3%.

Table 7: Drying Parameters.

Drying Parameters		Process Steps
Inlet Air Temperature	50°C	Drying Stage
Inlet Air Amount	60 CFM	
Shaking Period	5 seconds	
Product Temperature	35-40°C	
Outlet Air Temperature	30-35°C	

- The resulting dry granules are sifted through an osulator-type sieve.

Table 8: Trial 1 Dry Sieving Parameters.

Sieving Parameters		Process Steps
Sieve Size	1.2mm	Dry Sieving Stage
Sieving Speed	3m/s	

- The final mixing process is applied by adding Magnesium Stearate sifted in the following parameters to the sifted mixture.

Table 9: Trial 1 Final Mix Sieving Parameters.

Sieving Parameters		Process Steps
Sieve Size	900 micron	Final Mix Sieving Stage

Final Mixing Parameters		Process Steps
Mixing speed	12rpm	Final Mixing
Mixing time	3 min	

- Tablet pressing process is applied to the final mixture obtained in accordance with the specifications determined on the tablet press machine.

Evaluation: Solubility studies were performed as a result of the formulation of Xanthan Gum polymer with gliclazide. The dissolution study was performed in comparison with the commercially available Diamicron MR 60 mg Film Tablet registered by LES LABORATOIRES. The dissolution rate is determined under sink condition pH 7.4 in phosphate medium. As shown in the table below, the test product (Gliclazide 60 mg Tablet) was compared to the original product (Diamicron MR 60 mg Tablet). As shown in the comparative dissolution rate profile, the dissolution rate of test product is faster than the original product. Based on this result, it was understood that Xanthan Gum is not the appropriate polymer for Gliclazide to provide long release.

Table 10: Dissolution evaluation table for trial 1.

	Time (Hours)								
	0	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**16**
Test Product (%)	0.0	35.00	47.00	65.00	79,00	85.00	93.00	99.00	100.10
Original Product (%)	0.0	13.74	21.34	44.93	62.85	77.52	87.94	92.43	95.25
Similarity factor (f_2)					**40.01**				

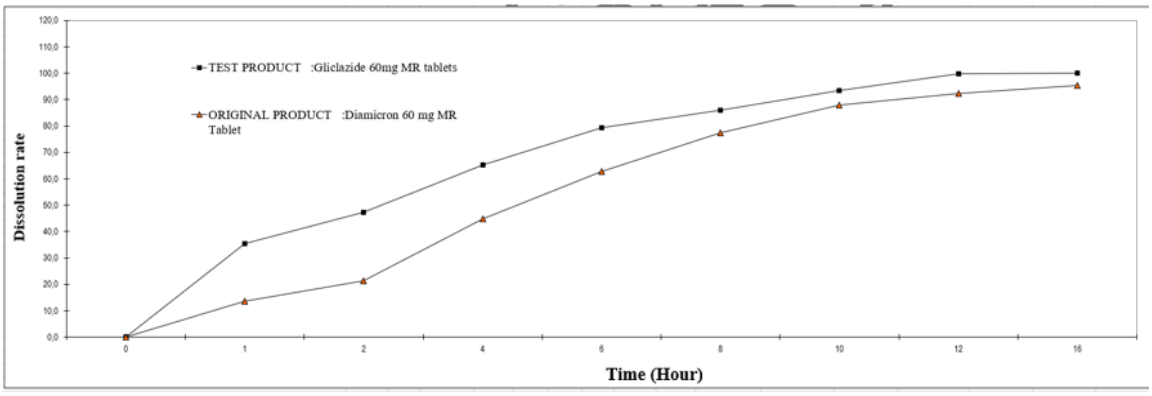


Figure 2: Trial 1 Dissolution rate profile.

Trial 2 Production Method

Series Size: 1000 Tablets

- Raw materials are weighed in accordance with the production formula.
- Gliclazide, Maltodextrin, Calcium Hydrogen Phosphate Dihydrate and Hydroxypropyl methylcellulose (HPMC K100M) are loaded into High Shear Mixer and premix process is applied with the following parameters.

Table 11: Trial 2 Premix Parameters.

Premix Parameters		Process Steps
Mixer Speed	25rpm	Premix Stage
Chopper Speed	Closed	
Mixing Time	10 min	

- The obtained powder mixture is granulated with 96% Ethanol with the following parameters.

Table 12: Trial 2 Wet Granulation Parameters.

Wet Granulation Parameters		Process Steps
Mixer Speed	25rpm	Wet Granulation Stage
Duration	3 min	
Pump Speed	25rpm	
Chopper Speed	1500rpm	
Mixer Speed	25rpm	After Wet Granulation Stage
Duration	1 min	
Chopper Speed	1500rpm	
Compression force	5-10 kW	

- In order to ensure a homogeneous drying of the obtained granules, the Wet Sieving process is applied with the following parameters.

Table 13: Trial 2 Wet Sieving Parameters.

Wet Sieving Parameters		
Sieve Size	9525µ	Wet Sieving Stage
Sieve Speed	1000rpm	

- The wet granules obtained are dried in a fluid bed dryer with the humidity in the range of 1%-3% with the following parameters.

Table 13: Trial 2 Drying Parameters.

Drying Parameters		Process Steps
Inlet Air Temperature	50°C	Drying Stage
Inlet Air Amount	60 CFM	
Shaking Period	5 seconds	
Product Temperature	35-40°C	
Outlet Air Temperature	30-35°C	

- The dry granules obtained are sieved through an oscillator type sieve.

Table 14: Trial 2 Dry Sieving Parameters.

Sieving Parameters		Process Steps
Sieve Size	1.2mm	Dry Sieving Stage
Sieving Speed	3m/s	

- The final mixing process is applied by adding sieved Magnesium Stearate with the following parameters on the sieved mixture.

Table 15: Trial 2 Final Mix Sieving Parameters.

Sieving Parameters		**Process Steps**
Sieve Size	900 micron	Final Mix Sieving Stage

Final Mixing Parameters		**Process Steps**
Mixing speed	12rpm	Final Mixing
Mixing time	3 min	

- Tablet pressing process is applied to the final mixture obtained in accordance with the specifications determined in the tablet press machine.

Evaluation: Solubility studies were carried out as a result of the formulation of the gliclazide and the polymer of hydroxypropyl methylcellulose (HPMC K100M). The solubility study was made in comparison with the commercially available Diamicron MR 60 mg Film Tablet registered by LES LABORATOIRES. The dissolution rate is determined in the sink condition, and it is done by the method given in section 3.3 in pH 7.4 Phosphate medium. As shown in the table below, the test product (Gliclazide 60 mg Tablet) was compared to the original product (Diamicron MR 60 mg Tablet). As shown in the comparative dissolution rate profile, the dissolution rate of our test product is slower than the original product. Based on this result, it was understood that hydroxypropyl methylcellulose (HPMC K100M) was not the appropriate polymer for the long release of gliclazide.

Table 16: Dissolution evaluation table for trial 2.

	Time (Hour)								
	0	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**16**
Test Product (%)	0.0	5.06	11.05	17.12	21.87	33.65	37.45	40.75	45.76
Original Product (%)	0.0	13.76	21.97	45.62	63.54	78.12	88.65	93.12	96.91
Similarity Factor (f_2)					***19.97***				

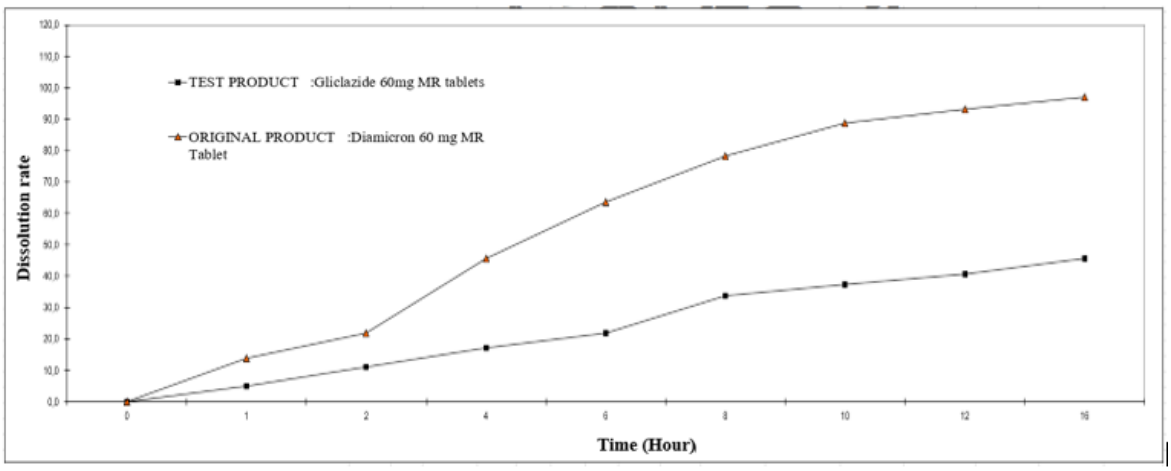


Figure 3: Trial 2 Dissolution rate profile.

Trial 3 Production Method

Series Size: 1000 Tablets

- Raw materials are weighed in accordance with the production formula.
- Gliclazide, Maltodextrin, Calcium Hydrogen Phosphate Dihydrate and Povidone are loaded into K90 High Shear Mixer and premix process is applied with the following parameters.

Table 17: Trial 3 Premix Parameters.

Premix Parameters		Process Steps
Mixer Speed	50rpm	Premix Stage
Chopper Speed	Closed	
Mixing Time	10 min	

- The obtained powder mixture is granulated with 96% Ethanol with the following parameters.

Table 18: Trial 3 Wet Granulation Parameters.

Wet Granulation Parameters		Process Steps
Mixer Speed	50rpm	Wet Granulation Stage
Duration	5 min	
Pump Speed	150rpm	
Chopper Speed	1500rpm	
Mixer Speed	50rpm	After Wet Granulation Stage
Duration	1 min	
Chopper Speed	1500rpm	
Compression force	5-10 kW	

- In order to ensure a homogeneous drying of the obtained granules, the Wet Sieving process is applied with the following parameters.

Table 19: Trial 3 Wet Sieving Parameters.

Wet Sieving Parameters		
Sieve Size	9525µ	Wet Sieving Stage
Sieve Speed	1000rpm	

- The wet granules obtained are dried in a fluid bed dryer with the humidity in the range of 1%-3% with the following parameters.

Table 20: Trials 3 Drying Parameters.

Drying Parameters		Process Steps
Inlet Air Temperature	50°C	Drying Stage
Inlet Air Amount	2500 m^3/hour	
Shaking Period	5 seconds	
Product Temperature	35-40°C	
Outlet Air Temperature	30-35°C	

- The dry granules obtained are sieved through an Oscillator type sieve.

Table 21: Trial 3 Dry Sieving Parameters.

Sieving Parameters		Process Steps
Sieve Size	1.2mm	Dry Sieving Stage
Sieving Speed	3m/s	

- The final mixing process is applied by adding sieved Magnesium Stearate with the following parameters on the sieved mixture.

Table 22: Trial 3 Final Mix Sieving Parameters.

Sieving Parameters		**Process Steps**
Sieve Size	900 micron	Sieving
Final Mixing Parameters		
Mixing speed	12rpm	Final Mixing
Mixing time	3 min	

- Tablet press process is applied to the final mixture obtained in accordance with the specifications determined in the tablet press machine.

Evaluation: Solubility studies were carried out as a result of the formulation of gliclazide and Polyvinylpyrrolidone (Povidone K90) polymer. The solubility study was made in comparison with the commercially available Diamicron MR 60 mg Film Tablet registered by LES LABORATOIRES. The dissolution rate is determined in the sink condition. As shown in the table below, the test product (Gliclazide 60 mg Tablet) was compared to the original product (Diamicron MR 60 mg Tablet). As can be seen in the comparative dissolution rate profile, the dissolution rate of our test product is slower than the original product. Based on this result, it was understood that Polyvinylpyrrolidone (Povidone K90) was not the appropriate polymer for the long release of Gliclazide.

Table 23: f_2 Dissolution evaluation table for trial 3.

	Time (Hour)								
	0	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**16**
Test Product (%)	0.0	8.65	11.54	25.87	29.54	33.65	38.65	43.87	49.98
Original Product (%)	0.0	12.97	19.04	41.98	63.47	78.03	86.95	93.23	97.13
Similarity factor (f_2)					***22.09***				

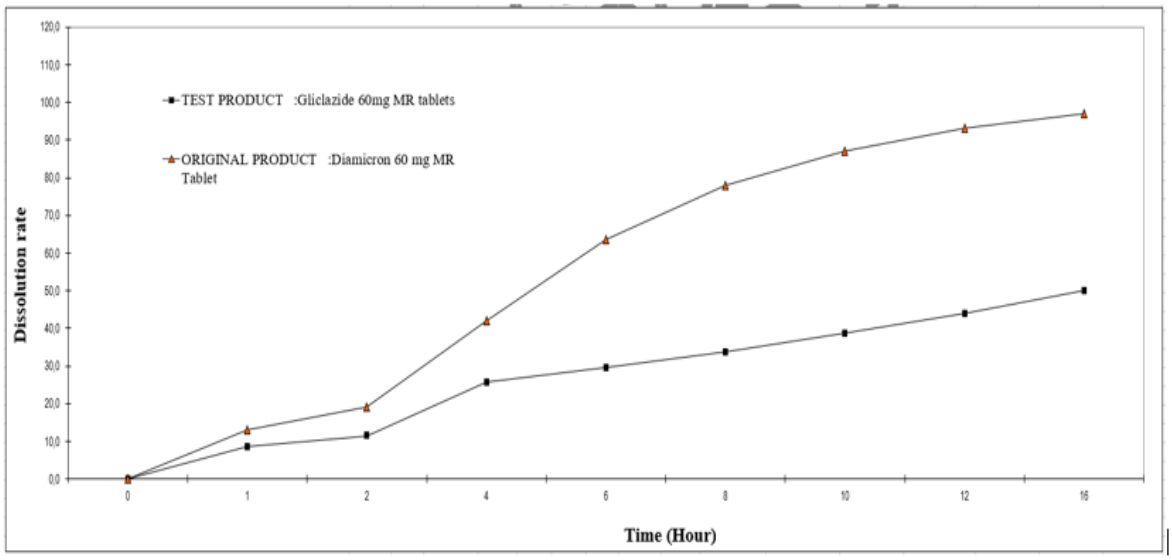


Figure 4: Trial 3 Dissolution rate profile.

Trial 4 Production Method

Series Size: 1000 Tablets

- Raw materials are weighed in accordance with the production formula.
- Gliclazide, Maltodextrin, Calcium Hydrogen Phosphate Dihydrate and Povidone K30 are loaded into the High Shear Mixer and pre-mixing process is applied with the following parameters.

Table 24: Trial 4 Premix Parameters.

Premix Parameters		Process Steps
Mixer Speed	25rpm	Premix Stage
Chopper Speed	Closed	
Mixing Time	10 min	

- The obtained powder mixture is granulated with 96% Ethanol with the following parameters.

Table 25: Trial 4 Wet Granulation Parameters.

Wet Granulation Parameters		Process Steps
Mixer Speed	25rpm	Wet Granulation Stage
Mixing Time	3 min	
Pump Speed	25rpm	
Chopper Speed	1500rpm	
Mixer Speed	25rpm	After Wet Granulation Stage
Mixing Time	1 min	
Chopper Speed	1500rpm	
Compression force	5-10 kW	

- In order to ensure a homogeneous drying of the obtained granules, the Wet Sieving process is applied with the following parameters.

Table 26: Trial 4 Wet Sieving Parameters.

Wet Sieving Parameters		
Sieve Size	9525µ	Wet Sieving Stage
Sieve Speed	1000rpm	

- The wet granules obtained are dried in a fluid bed dryer with the humidity in the range of 1%-3% with the following parameters.

Table 27: Trial 4 Drying Parameters.

Drying Parameters		Process Steps
Inlet Air Temperature	50°C	Drying Stage
Inlet Air Amount	60 CFM	
Shaking Period	5 seconds	
Product Temperature	35-40°C	
Outlet Air Temperature	30-35°C	

- The dry granules obtained are sieved through an Oscillator type sieve.

Table 28: Trial 4 Dry Sieving Parameters.

Sieving Parameters		Process Steps
Sieve Size	1.2mm	Dry Sieving Stage
Sieving Speed	3m/s	

- The final mixing process is applied by adding sieved Magnesium Stearate with the following parameters on the sieved mixture.

Table 29: Trial 4 Final Mix Sieving Parameters.

Sieving Parameters		**Process Steps**
Sieve Size	900 micron	Sieving
Final Mixing Parameters		
Mixing speed	12rpm	Final Mixing
Mixing time	3 min	

- Tablet press process is applied to the final mixture obtained in accordance with the specifications determined in the tablet press machine.

Evaluation: Solubility studies were carried out as a result of the formulation of gliclazide and Polyvinylpyrrolidone (Povidone K30) polymer. The solubility study was made in comparison with the commercially available Diamicron MR 60 mg Film Tablet registered by LES LABORATOIRES. The dissolution rate is determined in the sink condition, and it is done by the method given in section 3.3 in pH 7.4 Phosphate medium. As shown in the table below, the test product (Gliclazide 60 mg Tablet) was compared to the original product (Diamicron MR 60 mg Tablet). As can be seen in the comparative dissolution rate profile, the dissolution rate of our test product is faster than the original product. Based on this result, it was understood that Polyvinylpyrrolidone (Povidone K30) was not the appropriate polymer for the long release of Gliclazide.

Table 30: f_2 Dissolution evaluation table for trial 4.

	Time (Hour)								
	0	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**16**
Test Product (%)	0.0	28.00	43.23	58.51	71.54	86.32	98.34	100.10	100.17
Original Product (%)	0.0	13.23	19.43	42.38	64.23	78.54	87.34	94.67	97.65
Similarity factor (f_2)					***44.53***				

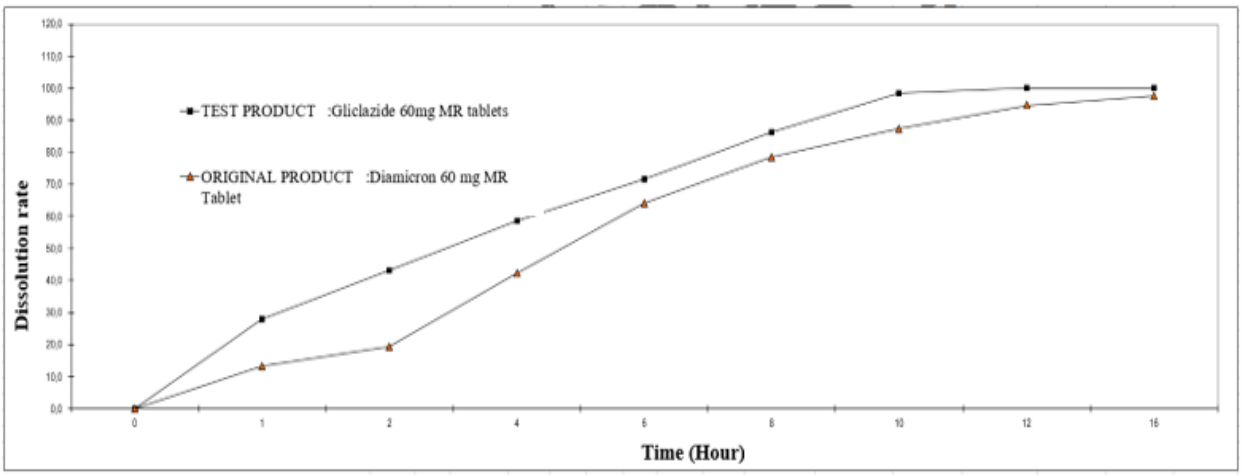


Figure 5: Trial 4 Dissolution rate profile.

Trial 5 Production Method

Series Size: 1000 Tablets

- Raw materials are weighed in accordance with the production formula.
- 16.67% of Gliclazide, Maltodextrin, Calcium Hydrogen Phosphate Dihydrate Povidone K-90 and Povidone K-30 is loaded into High Shear Mixer and premix process is applied with the following parameters.

Table 32: Trial 5 Premix Parameters.

Premix Parameters		Process Steps
Mixer Speed	25rpm	Premix Stage
Chopper Speed	Closed	
Mixing Time	10 min	

- By adding 96% Ethanol to the mixture, granulation is done with the following parameters.

Table 33: Trial 5 Wet Granulation Parameters.

Wet Granulation Parameters		Process Steps
Mixer Speed	25rpm	Wet Granulation
Duration	3 min	
Pump Speed	25rpm	
Chopper Speed	1500rpm	
Mixer Speed	25rpm	After Wet Granulation
Duration	1 min	
Chopper Speed	1500rpm	
Compression force	5-10 kW	

- In order to ensure a homogeneous drying of the granules obtained, the Wet Sieving process is applied with the following parameters.

Table 34: Trial 5 Wet Sieving Parameters.

Wet Sieving Parameters		Process Steps
Sieve Size	9525µ	Wet Sieving Stage
Sieve Speed	1000RPM	

- The wet granules obtained are dried in a fluid bed dryer with the humidity in the range of 1%-3% with the following parameters.

Table 35: Trial 5 Drying Parameters.

Drying Parameters		Process Steps
Inlet Air Temperature	50°C	Drying Stage
Inlet Air Amount	60 CFM	
Shaking Period	5 seconds	
Product Temperature	35-40°C	
Outlet Air Temperature	30-35°C	

- The dry granules obtained are sieved through an oscillator type sieve.

Table 36: Trial 5 Dry Sieving Parameters.

Sieving Parameters		Process Steps
Sieve Size	1.2mm	Dry Sieving Stage
Sieving Speed	3m/s	

- 83.33% of Povidone K-30 is added on the sieved dry granules and mixed.
- The final mixing process is applied by adding sieved Magnesium Stearate with the following parameters on the sieved mixture.

Table 37: Trial 5 Final Mixing and Sieving Parameters.

Sieving Parameters		**Process Steps**
Sieve Size	900 micron	Sieving
Final Mixing Parameters		**Process Steps**
Mixing speed	12rpm	Final Mixing
Mixing time	3 min	

- Tablet press process is applied to the final mixture obtained in accordance with the specifications determined in the tablet press machine.

Evaluation: Solubility studies were carried out as a result of the formulation of gliclazide and Povidone K30 and Povidone K90 polymers. The solubility study was made in comparison with the commercially available Diamicron MR 60 mg Film Tablet registered by LES LABORATOIRES. The dissolution rate is determined in the sink condition, and it is done by the method given in section 3.3 in pH 7.4 Phosphate medium. As shown in the table below, the test product (Gliclazide 60 mg Tablet) was compared to the original product (Diamicron MR 60 mg Tablet). As it can be seen in the comparative dissolution rate profile, the dissolution rate of our test product shows a similar profile with the original product. Based on this result, it was understood that the suitable polymer for the long release of Gliclazide was a mixture of Povidone K30 and Povidone K 90.

Table 38: f_2 Dissolution evaluation table for trial 5.

	time (hour)								
	0	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**16**
Test Product (%)	0.0	12.37	22.97	50.18	63.68	75.93	83.90	92.44	97.49
Original Product (%)	0.0	12.59	20.78	44.37	62.67	77.63	88.13	92.89	95.98
Similarity factor (f_2)					***76.31***				

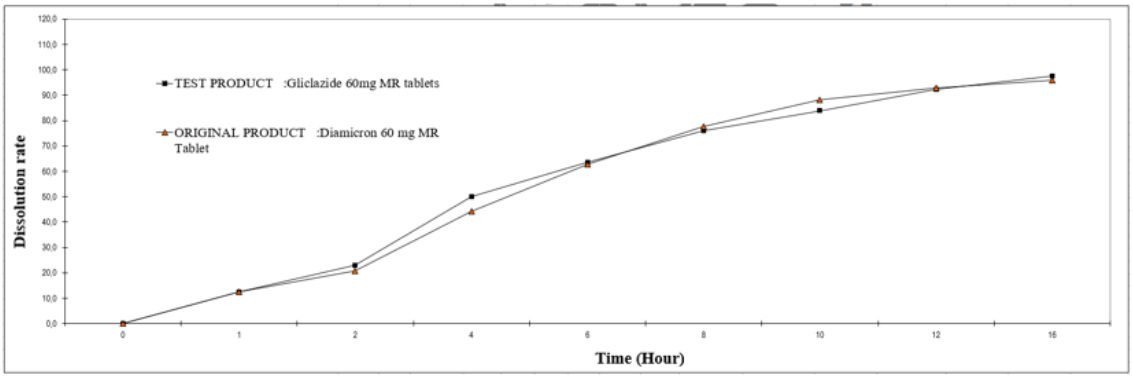


Figure 6: Dissolution rate profile.

As a result of the trial productions, when the physical and chemical analysis results of Trial 5 were evaluated, it was decided to carry out a scale-up study with the formulation and production parameters of Trial 5, on the grounds that it provided the specifications. Based on the production parameters of Trial 5, calculations were made on the following High Shear Mixer and Fluid Bed Dryer formulas according to the batch size to be enlarged, and the studies were completed.

Theoretical Formulas To Be Used During The Transition Of Laboratory-Scale Studies To Large-Scale Studies

High Shear Mixer Parameter Conversions

Determining the High Shear Mixer Spray Speed

In order to capture the quality of the granule captured in the small scale study in the same way; The spray rate of the granulation solution to the powder mix mass during small scale operation should be equal to the powder mix mass/spray rate during large scale operation.

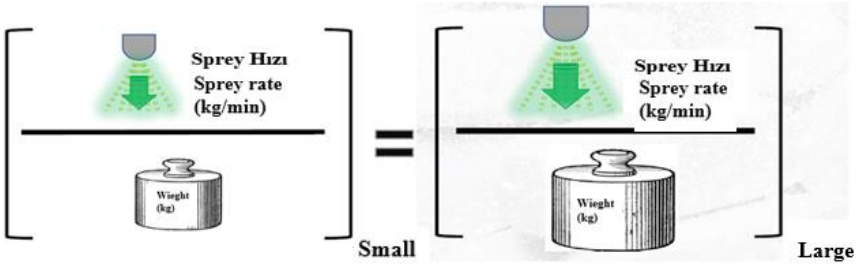


Figure 7: Determination of spray rate according to weight.

During small-scale studies, 1000 tablets were produced. In Trial 5, 3 kg of internal phase mixture was given 1.8 kg of granulation solution at 25 rpm within 3 minutes. Considering these parameters, the Spray Speed should be as follows during large scale operation.

$$\text{Sprey Speed} = \frac{\text{25 rpm (1,8 kg/3 dk)}}{\text{3 kg}} = \frac{\text{x rpm (18 kg/3 dk)}}{\text{30 kg}} = \text{The spraying speed should be 250 rpm.}$$

Determining High Shear Mixer Propeller Rotation Speed

In order to capture the quality of the granule captured in the small scale study in the same way; During small-scale operation, the power of the mixer speed should be in parallel with that of large-scale operation.

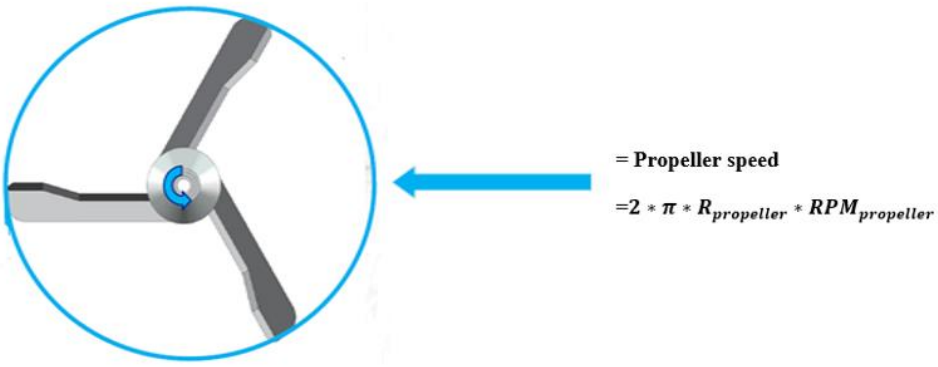


Figure 8: High Shear Mixer Propeller Speed.

Lab Scale High Shear Mixer Propeller Diameter	:15 cm
Large Scale High Shear Mixer Propeller Diameter	:120 cm

Table 3.2: Hihg Shear Mixer pervane hızı hesaplama tablosu.

Lab Scale High Shear Mixer Speed Parameter	Large Scale High Shear Mixer Speed Parameter **
Propeller Speed= 2x3,14x15x25 =2355 rpm/dk	Propeller Speed =2x3,14x120xX = 2355 rpm/dk X = 3,125
3 kg internal phase was mixed with 15 impeller diameters at 25 rpm for 3 minutes.	It should mix 30 kg of internal phase with 120 impeller diameter at 78,125 rpm for 3 minutes.

** Since 80 rpm is the closest mixing speed to 78,125 rpm mixing speed in a large scale High Shear Mixer, the mixing speed will be set to 80 rpm during the optimization studies.

Determining High Shear Mixer Chopper Speed

The chopper speed parameter should be applied in laboratory and large-scale studies without changing the High Shear Mixer equipment if the same parameters are available.

** Since there is a minimum (1500 rpm) and a maximum 3000 rpm Chopper speed in the laboratory scale and large scale High Shear Mixer, the parameters will be set without changing.

As a result of all these calculations, the process parameters to be applied during scale-up in the Wet Granulation process are as follows.

Table 39: Comparative High Shear Mixer production parameters.

Laboratory Scale Study High Shear Mixer		Large-Scale Study High Shear Mixer	
Mixer speed	25 rpm	**Mixer speed**	80 rpm
Mixer time	3 dk	**Mixer time**	3 dk
Sprey speed	25 rpm	**Sprey speed**	250 rpm
Chopper speed	1500 rpm	**Chopper speed**	1500 rpm

Scale-Up Production Method

Series Size: 10000 Tablets

- Raw materials are weighed in accordance with the production formula.
- 16.67% of Gliclazide, Maltodextrin, Calcium Hydrogen Phosphate Dihydrate Povidone K-90 and Povidone K-30 is loaded into High Shear Mixer and premix process is applied with the following parameters.

Table 39: Scale-Up Premix Parameters.

Premix Parameters		Process Steps
Mixer Speed	25rpm	Premix Stage
Chopper Speed	Closed	
Mixing Time	10 min	

- By adding 96% Ethanol to the mixture, granulation is done with the following parameters.

Table 40: Scale-Up Wet Granulation Parameters.

Wet Granulation Parameters		Process Steps
Mixer Speed	25rpm	Wet Granulation
Duration	3 min	
Pump Speed	25rpm	
Chopper Speed	1500rpm	
Mixer Speed	25rpm	After Wet Granulation

Duration	1 min	
Chopper Speed	1500rpm	
Compression force	5-10 kW	

- In order to ensure a homogeneous drying of the granules obtained , the Wet Sieving process is applied with the following parameters.

Table 41: Scale-Up Wet Sieving Parameters.

Wet Sieving Parameters		**Process Steps**
Sieve Size	9525µ	Wet Sieving Stage
Sieve Speed	1000RPM	

- The wet granules obtained are dried in a fluid bed dryer with the humidity in the range of 1%-3% with the following parameters.

Table 42: Scale-Up Drying Parameters.

Drying Parameters		**Process Steps**
Inlet Air Temperature	50°C	Drying Stage
Inlet Air Amount	60 CFM	
Shaking Period	5 seconds	
Product Temperature	35-40°C	
Outlet Air Temperature	30-35°C	

- The dry granules obtained are sieved through an oscillator type sieve.

Table 43: Scale-Up Dry Sieving Parameters.

Sieving Parameters		**Process Steps**
Sieve Size	1.2mm	Dry Sieving Stage
Sieving Speed	3m/s	

- 83.33% of Povidone K-30 is added on the sieved dry granules and mixed.
- The final mixing process is applied by adding sieved Magnesium Stearate with the following parameters on the sieved mixture.

Table 44: Scale-Up Final Mixing and Sieving Parameters.

Sieving Parameters		**Process Steps**
Sieve Size	900 micron	Sieving
Final Mixing Parameters		**Process Steps**
Mixing speed	12rpm	Final Mixing
Mixing time	3 min	

- Tablet press process is applied to the final mixture obtained in accordance with the specifications determined in the tablet press machine.

Evaluation: Solubility studies were carried out as a result of the formulation of gliclazide and Povidone K30 and Povidone K90 polymers. The solubility study was made in comparison with the commercially available Diamicron MR 60 mg Film Tablet registered by LES LABORATOIRES. The dissolution rate is determined in the sink condition, and it is done by the method given in section 3.3 in pH 7.4 Phosphate medium. As shown in the table below, the test product (Gliclazide 60 mg Tablet) was compared to the original product (Diamicron MR 60 mg Tablet). As it can be

seen in the comparative dissolution rate profile, the dissolution rate of our test product shows a similar profile with the original product. Based on this result, it was understood that the suitable polymer for the long release of Gliclazide was a mixture of Povidone K30 and Povidone K 90.

Table 45: Scale-Up f_2 Dissolution evaluation table for trial 2.

	Time (hour)								
	0	**1**	**2**	**4**	**6**	**8**	**10**	**12**	**16**
Test Product (%)	0.0	12.37	22.97	50.18	63.68	75.93	83.90	92.44	97.49
Original Product (%)	0.0	12.59	20.78	44.37	62.67	77.63	88.13	92.89	95.98
Similarity factor (f_2)					***76.31***				

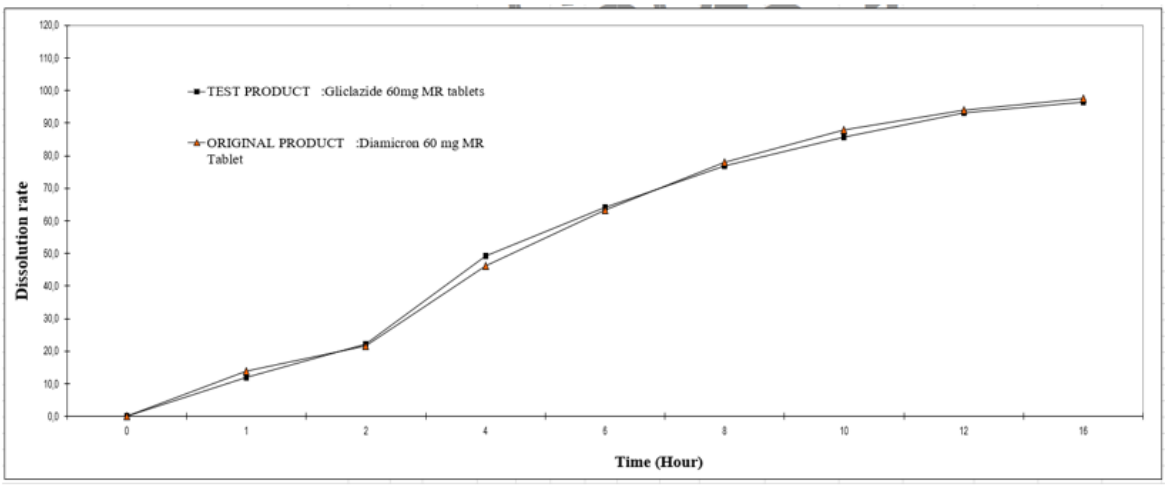


Figure 7: Dissolution rate profile.

CONCLUSION

Development of a product similar to the reference product (Diamicron MR 60 mg Film Tablet registered by LES LABORATOIRES.) physically and chemically (Dissolution Rate, Permeability and Bioequivalent) with controlled release systems by using 4 different polymers with Gliclazide, which is currently preferred in the treatment of non-insulin-dependent diabetes patients, in trial and scale-up studies targeted. While deciding on 4 different polymer raw materials after literature and resource research, it was prioritized to have different viscosity specifications and properties. As a result, it was decided to use Xanthan Gum and Hydroxypropyl Methyl Cellulose (HPMC) with different properties while choosing Povidone K-30 and Povidone K-90 raw materials with different viscosity specifications. Trial productions were carried out by wet granulation by using Xanthan Gum, Hydroxypropyl Methyl Cellulose, Povidone K-30 and Povidone K-90 polymers in separate formulations, respectively. As a result of the trial productions, it was determined that the suitable polymers were Povidone K30 and Povidone K90 mixtures, and it was proved by the dissolution rate test.

For the gliclazide, dissolution rate analyzes were carried out at 100 rpm using a pH 7.4 phosphate medium in the European Pharmacopoeia. When we analyze the dissolution rate profile analysis of pH 7.4 phosphate in its own medium compared to the reference product (Diamicron MR 60 mg Film Tablet registered by LES LABORATOIRES) of the first 4 trial productions.

The reference product (Diamicron 60 mg Tablet) exhibited a dissolution profile of 45-50%, while Trial 1 exhibited a dissolution profile of over 50% within a 4-hour period. Considering that the tablets with the formulation of Trial 1 are

indicated for diabetics on the grounds that we are trying to develop drugs with controlled release systems, since they will not exhibit an appropriate release due to early dissolution, the bioavailability rate that the patient will receive from the drug will decrease, as a result, the duration of treatment will be prolonged. For this reason, our trial production study number 1 was not found appropriate considering all factors.

After examining the comparative dissolution rate profiles of Trial 1 in detail, Trial 2 and Trial 3 studies were carried out with Hydroxypropyl Methyl Cellulose and Povidone K-90 polymer raw materials instead of Xanthan Gum raw material in order to obtain a dissolution rate profile closer to the reference product; As seen in Figure 37 and Figure 38, the analysis results of the two trials did not show a dissolution profile in their environment at the end of the 16-hour slice.

After examining the dissolution rate profiles of Trial 2 and Trial 3 in detail, trial production was carried out with Povidone K-30 and in order to obtain a dissolution rate profile closer to the reference product. Experiment 4 showed a dissolution profile of over 50% in the first 4 hour period, as in the Xanthan Gum trial, while the reference product (Diamicron MR 60 mg Tablet) exhibited a dissolution profile of 45-50%. For this reason, our trial production study number 4 was not found appropriate considering all factors. The comparative dissolution rate profile of Trial 4 is shown in Figure 5.

When all trial production results are re-evaluated, it is between the other 2 polymers. When Xanthan Gum and Povidone K-30 with low viscosities are used, the products exhibit an early dissolution profile, and when high viscosity Povidone K-90 and Hydroxypropyl Methyl Cellulose polymers are used, the products do not dissolve even in their own environment. Trial 5 production was carried out by mixing low and high viscosity Povidone K-30 and Povidone K-90 polymers, which have the same chemical properties, in appropriate proportions. When the comparative analysis results of the reference product (Diamicron MR 60 mg Tablet) and Trial 5 are evaluated, it shows a dissolution rate profile of 45-50% like the reference product in the first 4 hours, and in the 16-hour period, it is 95%-100% similar to the reference product. It has been observed that it exhibits a dissolution profile in its environment in the range of 100. In parallel with this information, the similarity rate between the Trial-5 and the reference product in the analysis results was as high as 76.31%.

When large-scale production of Trial-5, which was carried out in laboratory conditions, is planned, it is aimed to document the success of our work under the name of process optimization and controlled release drug development with different polymers by carrying out a large-scale study on the assumption that there may be differences in physical and chemical analyzes compared to the product produced in the laboratory environment. A literature review on technology transfer was carried out, and a scale-up study was carried out on theoretical formulas by investigating how the parameters of the laboratory-scale work could be reflected on large-scale productions.

Better dissolution rate results were obtained compared to Trial 5, and a product more similar to the reference product was obtained. Considering all these results; By using 2 different polymers in the form of extended release tablets with gliclazide, drug development with a high similarity rate with the reference product and in accordance with European Pharmacopoeia standards was carried out.

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