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Application of Solid Dispersion Method for Increasing Solubility of Remeron as an Antidepression Drug

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Abstract

Since the solubility behavior of drugs is one of the challenging aspects in the development of their formulations, various techniques have been proposed to improve their dissolution rates, including using solvents, solid dispersions and surfactants. Remeron (Mirtazapine, **I**) is a drug that widely used in the treatment of depressive disorders. This drug has a weak dissolution rate in water, which causes decreasing in absorption, therapeutic benefit and its excretion without effectiveness. Therefore, the aim of this study is increasing the solubility of this drug using solid dispersion method, in which the hydrophobic drug is dispersed inside a hydrophilic matrix. In this research, solid dispersions of **I** using different carriers including mannitol and polyethylene glycols (PEGs) in different ratios with solvent evaporation and physical mixing methods were prepared. Then, the solubility of the prepared formulations was investigated by determining the saturation solubility. The results showed that the saturation solubility of all formulations increased compared to pure Mirtazapine and the superior formulation was selected. It can be concluded that solid dispersion method with PEGs (as carriers) has been a suitable technique to improve the dissolution rate of **I**.

Key words: Depressive disorders, Drugs' solubility, Remeron (Mirtazapine), Solid Dispersion Method, Carriers.

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Introduction

Antidepressants are classified as: Tricyclic Antidepressant (TCA) and Mono Amine Oxidase Inhibitors (MAOI) due to their effects on the neuro-adrenergic and serotonin systems and with different mechanisms and effects on different receptors [1].

Remeron (Mirtazapine, Methyl-1,2,3,4,10,14b-hexahydropyrazino-2-(+_)[2,1-a]pyrido [2,3-c][2]benzazepine, **I**), is a relatively new antidepressant drug from the category of Noradrenergic and Specific Serotonergic Antidepressants (NaSSAs). This category of drugs are used in the treatment of anxiety and depression disorders [2], which have more specific effect on receptors and do not affect unwanted receptors such as histamine and acetylcholine, causing less side effects such as dry mouth and constipation [1].

Mirtazapine has dual (increasing neuroadrenergic and serotonergic) activities and its therapeutic effect is due to the antagonistic effect of central presynaptic alpha-2 receptors and the antagonistic activity of serotonin 5HT2 and 5HT3 receptors [3, 4].

According to the mechanism of action of this drug, various therapeutic uses of it have been observed, including the treatment of depression, anxiety disorders, Post-Traumatic Stress Disorder (PTSD) and in low doses, in the treatment of Obstructive Sleep Apnea (OSA) insomnia [5, 6].

This drug is insoluble in water and according to the drug classification system, it is placed in the second category because it has low solubility and good absorption, and this means that the absorption of this drug is a function of its solubility [7, 8].

Increasing the solubility of this drug in water can be a good way to increase the efficiency, effectiveness and lack of common side effects of older drugs. Currently, several methods are used to increase the rate of dissolution in the digestive system and thus increase the bioavailability of poorly soluble drugs, and the use of solid dispersion system is one of these methods [9].

Solid dispersion refers to the uniform dispersion of the active ingredient in a neutral carrier or matrix in the form of a solid phase using solvent evaporation or melting methods [21]. Since the non-dissolution of the drug means its elimination without effectiveness, the solubility factor is considered as a very important factor [10].

By increasing the solubility, it is possible to achieve a suitable blood concentration and then an acceptable effectiveness while reducing the dose and side effects. Most drugs that are poorly soluble in water are facing problems in terms of bioavailability, so the most practical and best way to increase the bioavailability of these drugs is to increase their solubility or dissolution rate [11].

The most important way to correct dissolution is to increase the accessible surface. To increase this level, the particle size of solid compounds should be reduced or the level of surface wetness should be increased [12].

It is possible to reduce the particle size of compounds by grinding drug powder, but in most cases mechanized powders tend to stick together. One of the ways that can increase drug solubility is the use of water-soluble carriers in the form of solid dispersion. In these systems, drugs with increased solubility can be obtained by placing the drug on the base of a polymer substrate with a favorable characteristic [13].

Although various reports on the use of solid dispersion systems have been published, unfortunately, they have been used in the development of a few commercial products. The reason for this problem is probably due to the physical instability of the drug surrounded in the polymer bed. Phase separation and crystal growth lead to a decrease in solubility and dissolution rate. The presence of a polymer carrier is a factor that may prevent the recrystallization of the drug. Creating an amorphous state in solid dispersion formulations is an important factor for increasing its dissolution rate and preventing its crystallization and it is very important to maintain and stabilize the drug release process from the powder bed [36].

In this research, it has been tried to increase the dissolution rate by preparing a solid dispersion of the poorly soluble of **I** by using different carriers and drug-to-carrier ratios in order to find the most appropriate system that is able to improve the solubility of the drug in addition to improving other physicochemical properties of mirtazapine.

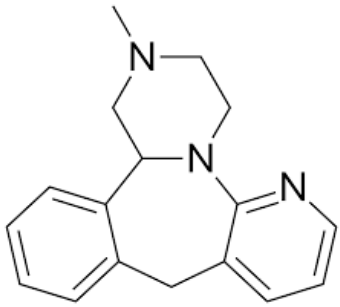

Figure 1. Structure formula of Remeron (Mirtazapine, **I**).

Experimental

Chemicals

Polyethylene glycol (PEG), Ethanol, Primellose, Magnesium stearate, Mannitol, Lactose monohydrate, Corn starch, Silicon dioxide and other chemicals and reagents were prepared from Cargill, DFE, Evonik, Meggle, Merck (Germany) and Anhui Sunhere (China) companies.

Procedure

In this research, using the mentioned method to increase the solubility of mirtazapine, polyethylene glycols with molecular weight of 400, 1000 and 4000 and mannitol with ratios of 1:0.25, 0.5:1, 1:1, 1:2 and 1:3 were used by solvent evaporation method. The solubility of the prepared formulations was compared by determining the saturation solubility. In addition, dissolution rate, flow ability and compressibility studies were performed on the selected samples. FTIR spectrophotometry and thermal analysis (DSC) of the superior formulation were also performed in order to investigate the possible interaction between drug and polymer.

Apparatus and instruments

FTIR spectrophotometer and thermal analyzer (Shimadzu, Japan), Magnetic stirrer (Heidolph), Analytical balance (Satorious, Geramany) and DT-800 dissolution (Erweka, Germany) instrument were used in this research.

Standard graph of mirtazapine in distilled water

30 mg of mirtazapine powder was weighed with an analytical balance and reached a volume of 900 ml and stirred on the stirrer until it was completely dissolved. The concentration of the resulting solution was 32 µg/ml. Then, using this stock solution, 4, 8, and 16 µg/ml solutions were prepared. The absorption of these drugs from dilute to concentrate was read by a spectrophotometer at a wavelength of 316 nm (λ_{max}) against distilled water as a control.

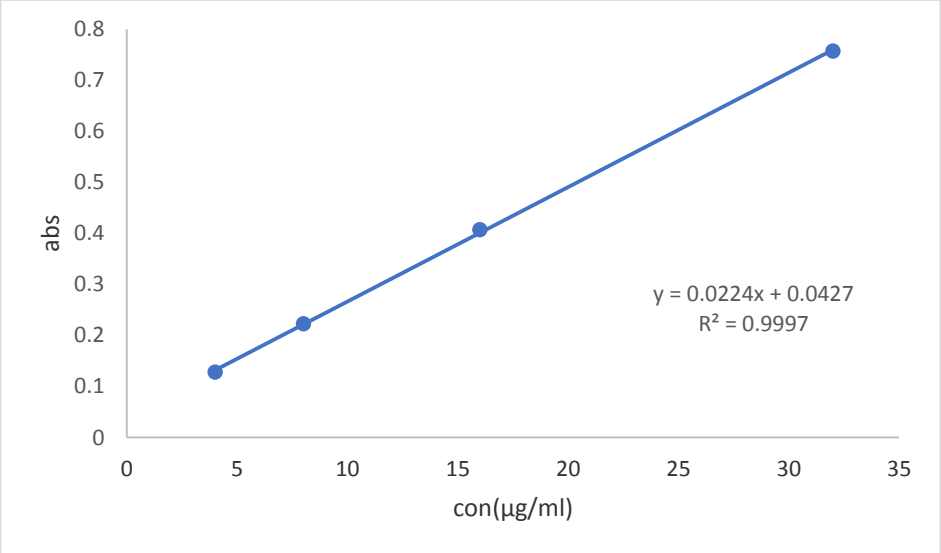

Figure 1. Standard graph of mirtazapine in distilled water at 316 nm wavelength.

Then the absorption graph was drawn against the original mirtazapine solution and its line equation was calculated. This work was repeated three times and the average was taken. Using the obtained data, the standard diagram of mirtazapine was drawn and its regression coefficient was obtained (R^2 = 0.9997) (Figure 1).

Methods of making Mirtazapine solid dispersion formulations

Using polyethylene glycols (group A formulation)

In this group, polyethylene glycols with molecular weight of 400, 1000 and 4000 were used. Except for polyethylene glycol with a molecular weight of 400, which is liquid and a simple physical mixing method was used to make it, the others were prepared by solvent evaporation method and first mixed with ethanol until they were completely dissolved in ethanol. Then the drug was slowly added to them and stirred. This mixing continues for 24 hours until the ethanol evaporates. Then the solid dispersion formed from the bottom of the plate was scraped and passed through a sieve and mixed with other additives**.**

Table 1. Components of mirtazapine solid dispersion system prepared with polyethylene glycol (group A formulation).

Drug to polymer ratio	**Formulation name**	**Carrier type**
1: 0.125	A1	**PEG-400**
1: 0.25	A2	
1:0.5	A3	
1: 0.125	A4	**PEG-1000**
1: 0.25	A5	
1:0.5	A6	
1:1	A7	
1: 0.25	A8	**PEG-4000**
1:0.5	A9	
1:1	A10	
1:2	A11	
1:3	A12	

Using mannitol (group B formulation)

In this group, mannitol was used and solvent evaporation method was used. First, mannitol was dissolved in alcohol, and then the drug was slowly added and stirred for 24 hours to evaporate the

ethanol. Then the solid dispersion formed from the bottom of the plate was scraped and passed through a sieve and mixed with other additives.

Table 2. Components of mirtazapine solid dispersion system prepared with mannitol (group B formulation).

Drug to carbohydrate ratio	Formulation name	Carrier type
1:0.5	B1	**Mannitol**
1:1	B2	
1:2	B3	
1:3	B4	

Results

Saturated solubility of mirtazapine in distilled water at ambient temperature (25°C)

The results of the saturation solubility of mirtazapine in distilled water at ambient temperature can be seen in Table 3.

Table 3. Saturated solubility of mirtazapine in distilled water at ambient temperature (25°C).

%CV	Standard Deviation	Mean	Saturated solubility (µg/ml)			Formulation type
			Sample 3	Sample 2	Sample 1	
0.667	0.024	3.601	3.572	3.602	3.631	Mirtazapine

As the results from table 3, mirtazapine has a very low saturated solubility (Practically insoluble).

Control experiments on prepared mirtazapine solid dispersion systems

Saturation solubility of the samples

After preparing the solid dispersion formulations and in order to calculate the saturation solubility, the equivalent of 50 mg of drug from the solid dispersion powder of each formulation was weighed and mixed for 24 hours, and the amount of absorption of the resulting solution after centrifugation and passing through filter paper was obtained. Then, using the standard chart, the saturation solubility concentration was obtained (Tables 4 and 5).

Table 4. Saturation solubility of mirtazapine in distilled water and ambient temperature (group A formulas).

%CV	Standard Deviation	Mean	Saturated solubility (µg/ml)			Formulation type
			Sample 3	Sample 3	Sample 3	
5.698	1.5	26.3221	28.2964	24.5464	26.1235	**A1**
2.104	0.8	38.0115	37.8568	39.1235	37.0542	**A2**
6.642	2.2	33.1205	36.1212	30.6981	32.5422	**A3**
2.282	0.9	38.4301	38.0816	38.9823	39.2264	**A4**
7.719	3.1	40.1603	41.5489	43.0213	35.9107	**A5**
2.124	0.91	42.8267	42.5234	41.8902	44.0665	**A6**
8.657	2.8	32.3416	31.2904	29.5231	36.2113	**A7**
1.016	0.38	37.7461	37.2154	38.4389	37.5873	**A8**
7.080	2.7	38.1346	37.5204	35.1213	41.7603	**A9**
1.556	0.74	47.5503	47.8175	48.3017	46.5317	**A10**
3.696	1.6	43.2805	43.3805	41.2458	45.2152	**A11**
3.515	1.5	42.6702	43.1205	44.3162	40.5739	**A12**

Table 5. Saturation solubility of mirtazapine in distilled water and ambient temperature (group B formulas).

%CV	Standard Deviation	Mean	Saturated solubility (µg/ml)			Formulation type
			Sample 3	Sample 3	Sample 3	
1.702	0.6	35.2341	36.0326	35.1276	34.5421	**B1**
2.101	0.9	42.8534	43.6380	43.3401	41.5821	**B2**
8.570	3.3	38.5043	42.9672	34.8345	37.7112	**B3**
9.770	3.4	34.7981	35.7634	32.6541	35.9768	**B4**

Statistical study of saturation solubility in order to select superior formulations

SPSS 21 program with T-test method was used to select the best formulations from each group. First, the saturated solubility of the prepared formulations was compared with the saturated solubility of the pure drug. The main goal is to choose the best formulations from each group. These

comparisons in each group were first made between different proportions of each polymer of that group. After choosing the best formula of each polymer, a comparison was made between the best ratios of polymers in a group to determine the best polymer with a certain ratio in that group.

Using polyethylene glycols (group A formulation)

Table 6. The results of the investigation of saturation solubility in PEG-400 to choose the best formula.

***P*-value**	**Concentration (µg/ml)**	**Compared formula**	**Target Formula**		
			Concentration (µg/ml)	**Formula name**	**Carrier type**
0.003	38.0115	**A2**	26.3221	**A1**	**PEG-400**
0.051	33.1205	**A3**			
0.092	33.1205	**A3**	38.0115	**A2**	

Table 7. The results of the investigation of saturation solubility in PEG-1000 to choose the best formula.

***P*-value**	**Concentration (µg/ml)**	**Compared formula**	**Target Formula**		
			Concentration (µg/ml)	**Formula name**	**Carrier type**
0.091	40.1603	**A5**	38.4301	**A4**	**PEG-1000**
0.065	42.8267	**A6**			
0.071	32.3416	**A7**			
0.089	42.8267	**A6**	40.1603	**A5**	
0.048	32.3416	**A7**			
0.010	32.3416	**A7**	42.8267	**A6**	

Table 8. The results of the investigation of saturation solubility in PEG-4000 to choose the best formula.

***P*-value**	**Concentration (µg/ml)**	**Compared formula**	**Target Formula**		
			Concentration (µg/ml)	**Formula name**	**Carrier type**
0.862	38.1346	**A9**	37.7461	**A8**	**PEG-4000**
0.003	47.5503	**A10**			
0.040	43.2805	**A11**			
0.047	42.6702	**A12**			
0.001	47.5503	**A10**	38.1346	**A9**	
0.046	43.2805	**A11**			
0.055	42.6702	**A12**			
0065	43.2805	**A11**	47.5503	**A10**	
0.048	42.6702	**A12**			
0.637	42.6702	**A12**	43.2805	**A11**	

According to the results of the Tables, the best formulations in group A were selected, which are: A2, A5, A10 (Table 9).

Table 9. Selection of the best formulation of group A.

***P*-value**	**Concentration (µg/ml)**	**Compared polymer**		**Target Formula**		
				Concentration (µg/ml)	**Formula name**	**Carrier type**
		Formula name	**Carrier type**			
0.426	40.1603	**A5**	**PEG-1000**	38.0115	**A2**	**PEG-400**
0.003	47.5503	**A10**	**PEG-4000**			
0.005	47.5503	**A10**	**PEG-4000**	40.1603	**A5**	**PEG-1000**

Based on the results of Table 9, it was found that the best formulation of this group is A10.

Using mannitol (group B formulation)

Table 10. The results of the investigation of saturation solubility in mannitol to choose the best formula.

***P*-value**	**Concentration (µg/ml)**	**Compared formula**	**Target Formula**		
			Concentration (µg/ml)	**Formula name**	**Carrier type**
0.007	42.8534	**B2**	35.2341	**B1**	**Mannitol**
0.304	38.5043	**B3**			
0.724	34.7981	**B4**			
0.209	38.5043	**B3**	42.8534	**B2**	
0.017	34.7981	**B4**			
0.075	34.7981	**B4**	38.5043	**B3**	

Based on the results of Table 10, it was found that formula B2 is the best formula in this group.

Additional tests on selected formulations

According to the results of statistical studies, formulations A10 and B2 were selected as the best formulations and the following tests were performed on them.

Determination of mirtazapine active ingredient in tablets prepared from the selected formulation

The effective ingredients in the best formulations are quantified and can be seen in Table 11.

Table 11. Determining the amount of active ingredient in superior formulations**.**

%CV	**Standard Deviation**	**Mean**	**Amount of active ingredient (%)**			**Superior formulations**
			Sample 3	**Sample 2**	**Sample 1**	
0.485	0.48	98.84	99.43	98.84	98.25	**A10**
0.889	0.89	100.01	99.29	99.45	101.26	**B2**

Saturated solubility of selected formulations mixing

The results of the saturation solubility of the selected formulations when prepared by physical mixing method are shown in Table 12.

Table 12. Saturated solubility of superior formulations made by physical mixing method in distilled water (25°C).

%CV	Standard Deviation	Mean	Saturated solubility (µg/ml)			Superior formulations
			Sample 3	Sample 2	Sample 1	
1.362	0.35	25.6813	25.2710	25.6381	26.1348	A10
2.224	0.62	27.8751	28.1227	27.0247	28.4779	B2

FTIR spectra and DSC diagrams of superior formulation (A10)

Possible drug-carrier interaction, formulation with the highest solubility, physical mixture of drug-carrier, pure drug and carrier were investigated through FTIR spectra and DSC diagrams. These analyzes were done in order to investigate whether the use of solid dispersion technique changes the chemical structure of mirtazapine or not**.**

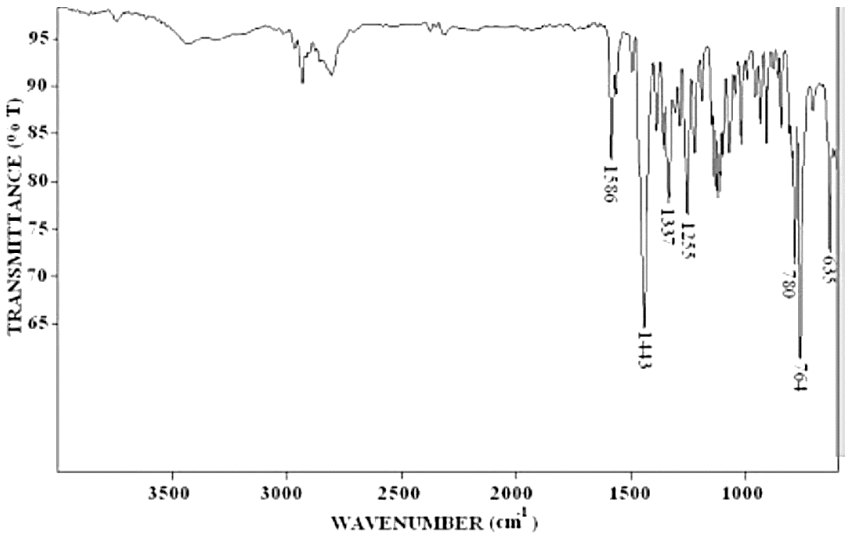

Figure 2. FTIR of mirtazapine.

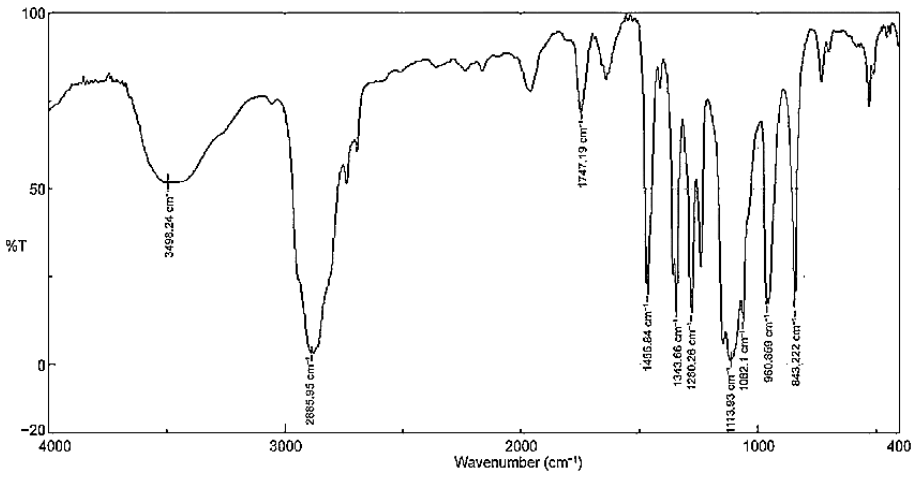

Figure 3. FTIR **spectrum** of mirtazapine and PEG-4000 (pure drug and carrier).

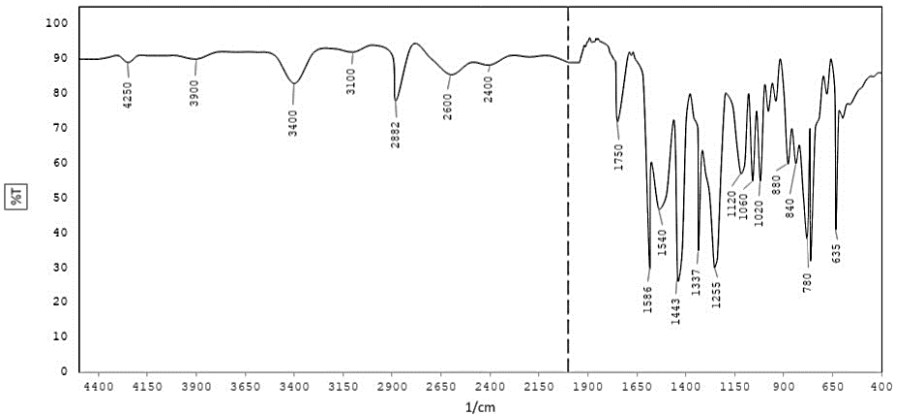

Figure 4. FTIR spectrum resulting from physical mixing of mirtazapine and PEG4000.

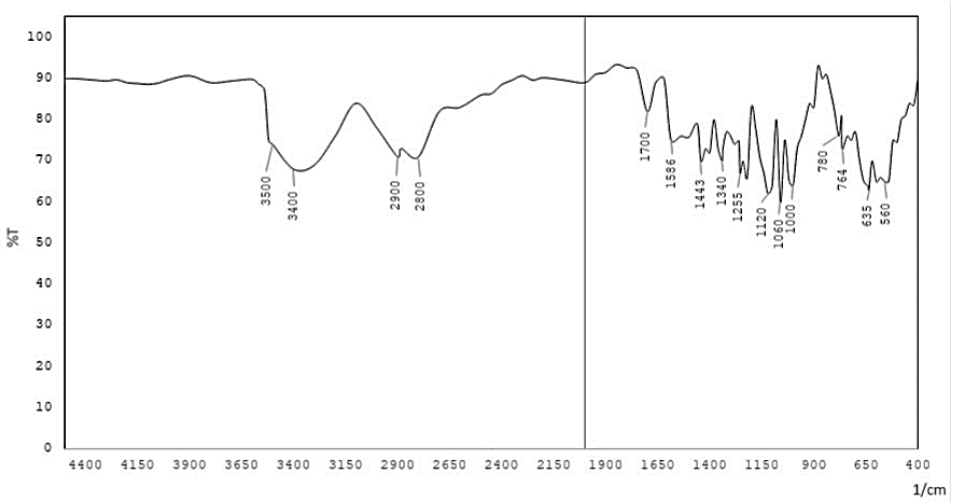

Figure 5. FTIR spectrum obtained from formulation A10.

As seen in figures, the main peaks of both drug and PEG are seen, indicating no change in their structure**.**

DSC diagrams of formulation (A10)

Thermal analysis of mirtazapine, PEG4000, physical mixture of mirtazapine and PEG4000 and formula A10 were performed. The obtained thermograms are presented in Figures 6-9.

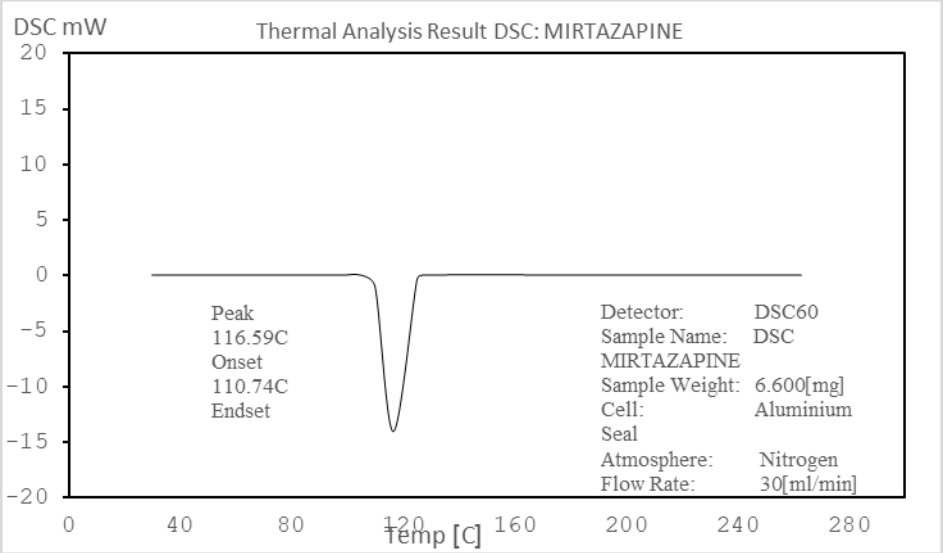

Figure 6. DSC thermogram of mirtazapine powder.

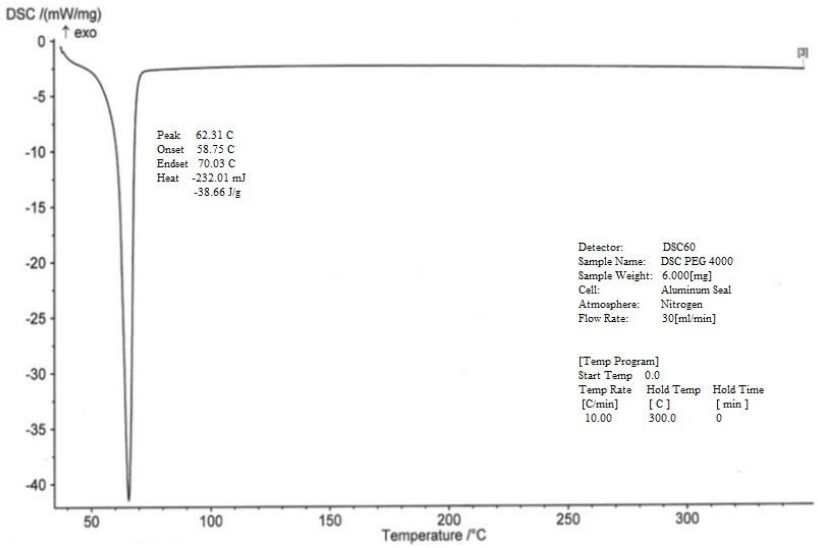

Figure 7. DSC thermogram of PEG-4000.

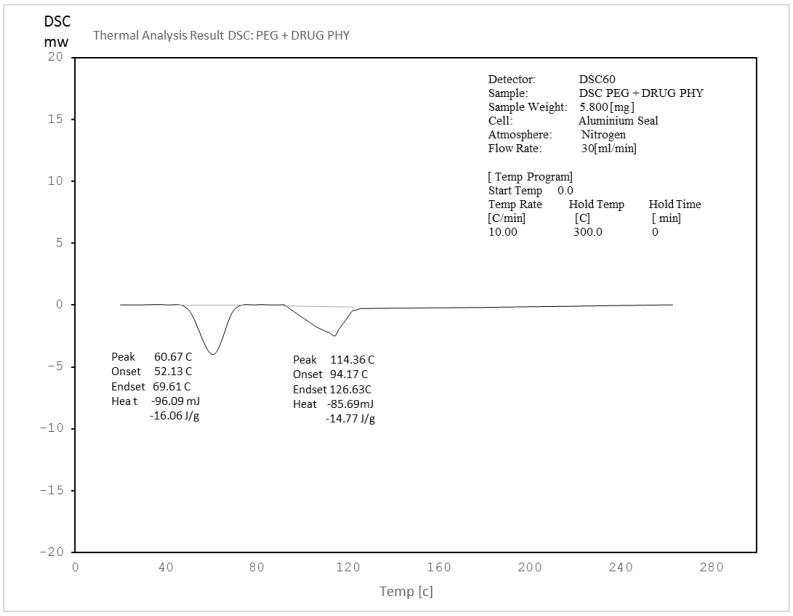

Figure 8. DSC thermogram related to physical mixing of mirtazapine and PEG4000.

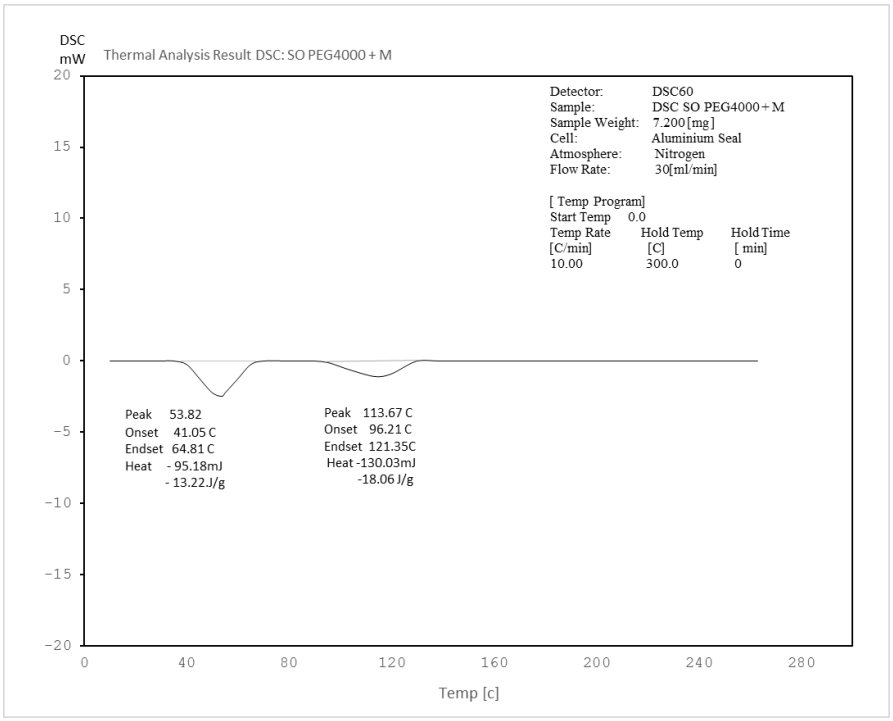

Figure 9. DSC thermogram of formulation A10.

Based on the above figures, the peaks related to the melting point of the drug and the polymer could be seen**.**

Discussion

Based on permeability, drugs are classified into 4 categories: high solubility and permeability, low solubility and high permeability, high solubility and low permeability, and low solubility and permeability [7].

Solubility is one of the important parameters to create the desired blood concentration of the drug and then the desired pharmacological response. One of the main problems associated with the preparation and development of new drug formulations as well as generic drugs is low water solubility. Any drug must first be dissolved in order to be absorbed. There are various methods to increase the solubility of poorly soluble drugs, and the choice of method depends on the characteristics of the drug, pharmaceutical form and absorption site [14].

Solubility enhancement techniques can be done in the form of physical modifications such as reducing particle size through methods such as nanosuspension, micronization, and also dispersing the drug in a carrier through solid dispersion. Of course, chemical modifications including making prodrugs, making salts and changing pH, as well as methods such as using surfactants and co-solvents can also be effective in this regard [15].

Solid dispersion means the dispersion of one or more active substances in an inert carrier. The preparation of solid dispersion of poorly water-soluble drugs using water-soluble carriers increases the dissolution rate of the drug. The technology used to prepare the solid dispersion and the properties and amount of the carrier used in drug dissolution are effective [15].

So far, many studies on solid dispersion have been done [15-20].

This method shows the greatest reduction in particle size and after the carrier is dissolved, the drug is dispersed in molecular form in the dissolution medium and becomes supersaturated. Another way to increase solubility through solid dispersion is to modify the wettability of the drug. Carriers with high surface activation properties such as bile salts and cholesterol esters increase the wetting properties much more than carriers such as urea [20, 21].

In general and comparing the dissolution rate in pure drug, physical mixture and solid dispersion, solid dispersion seems to be more beneficial, which can be prepared by melting and solvent evaporation methods and melting by extruder melting [20-23].

Also, the carrier that is used to increase the dissolution rate in the preparation of solid dispersion should be non-toxic, completely soluble in water, chemically compatible with the drug, pharmacologically ineffective and preferably increase the aqueous solubility of the drug [23].

In this study, it has been tried to improve the solubility of the poorly soluble drug mirtazapine by solid dispersion method and using mannitol and PEGs 400, 1000 and 4000 carriers.

The purpose of this research is to investigate the effect of formulation-related variables in solid dispersion on increasing the solubility of Mirtazapine as a water-insoluble drug. In order to increase solubility, solid dispersion method, solvent evaporation and physical mixing were used. Carriers of mannitol and polyethylene glycols were used in different amounts as agents to increase solubility. The prepared formulations were examined for saturation solubility after manufacturing. The selected formulations were studied in terms of saturation solubility and amount of active ingredient. The selected formulation was analyzed by FTIR and DSC in order to investigate possible drug-carrier interaction.

Based on the results of statistical studies of solid dispersion formulations prepared from PEGs (group A), formulations A1-A12 were prepared by solid dispersion method using fixed ratio of drug and different ratios of PEG. Formulations A1-A3 are related to PEG-400, which increases the solubility of the polymer first and then decreases. This can be considered due to the increase of the thick layer of the drug and creating an obstacle for water permeability. By analyzing the statistics on different ratios, it was found that formula A2 shows a significant difference with A1, but not with A3. In cases where the difference is not significant, it is preferable to use a formula that has less polymer, as a result, the best formula is A2.

Formulations A4-A7 are related to PEG-1000, with increasing amount of polymer, the solubility first increases and then decreases. This factor can again be considered due to the formation of gel in higher concentrations and the lack of access of the dissolution medium to the effective substance. According to the results, A6 had a significant difference only with A7 and no significant difference was seen between other formulas. As a result, formula A5, which uses a smaller amount of polymer, was considered as the selected formulation of this group.

Formulations A8-A12 are related to PEG-4000. To choose the best formula, statistical studies were conducted on different ratios. Formulation A10 increased the solubility more than others and showed a significant difference with other formulations of this group (except for formulation A11) that it is preferable due to the use of less polymer and as the selected formula of this group in considered.

Finally, to choose the best formulation among the three PEGs used, according to the results of the statistical analysis between the superior formulations with PEG carriers (A2, A5, A10), the A10 formulation had a significant difference compared to the other two formulations and is considered the selected superior formulation of PEGs.

Also, for statistical studies of solid dispersion formulations prepared from mannitol (group B), formulations B1-B4 were prepared by solid dispersion method using a constant ratio of drug and different ratios of mannitol. The results of the analysis of the saturated solubility of these

formulations showed that formulation B2 had a higher concentration and a significant difference with other formulations (except B3), which was preferable due to the use of less amount of polymer, and therefore as the selected formulation was considered.

In this study, in order to investigate the saturation solubility results of physical mixing of selected formulations, a statistical study was conducted on the same formulas that were made by physical mixing method.

In formulation A10, by comparing its saturation solubility with the saturation solubility made by physical mixing method, it was found that there is a significant difference and its solubility with the method made (solvent evaporation method) is more than its solubility using physical mixing. Therefore, it can be concluded that in addition to the presence of the polymer, the method used to make the solid dispersion was also effective in increasing the solubility.

In addition, a significant difference was observed in formulation B2, which indicates the preference of the formulation made through the solvent evaporation method. Therefore, in addition to the carrier itself, the method used to make the solid dispersion has also been effective.

To choose the best formula and according to all the results obtained, A10 formulation was considered as the best formula.

Finally, by examining the FTIR spectra of solid dispersion and physical mixture of formulation A10, it was found that the main peaks of the drug and polymer appeared and the difference in the peaks was seen only in their intensity, which is related to the change in the concentration of the substances. This shows that there is no interaction between the drug and the polymer and that the chemical structure of the active substance has been preserved in the investigated formulations.

Also, in the analysis of DSC diagrams of solid dispersion and physical mixture of formulation A10, both drug and polymer peaks are seen. But both of them have slightly shifted towards lower temperatures, which can be considered due to the change in the crystal structure and probably the creation of an amorphous state. Since the shape of the peaks in formulation A10 is preserved and no new peak is seen in the corresponding DSC diagram, it can be concluded that in this formulation, mirtazapine maintains its structure and there is no interference between the drug and the carrier.

Conclusion

It can be concluded that, the prepared formulations had a higher saturated solubility than pure mirtazapine. Also, according to the statistical calculations among the formulations, formulation A10 had the best solubility, which was prepared using PEG-4000 (ratio 1:1). The analysis of this formula by DSC and FTIR showed that in this formulation, there is no interference between the

drug and the carrier and the structure of mirtazapine is preserved. Therefore, A10 formulation can be considered as the best formulation to increase the solubility of mirtazapine.

It is suggested to use natural polymers such as katira or acacia as water-soluble carrier in future works to prepare solid dispersion.

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