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Research Article

# Evaluation of Operation Times in The Burn Center Operating Room and The Importance of Surgical Nursing with Its Versatile Contribution to Treatment; An Observational Retrospective Study

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**ABSTRACT:** Operating room nurses take an active and complementary role in the entrance to the operating room, surgical intervention and post-surgical procedures. In our study, it was aimed to emphasize the importance of burn nurses in the burn operating room and the contribution of burn nurses to the process by evaluating the operation times. The operations performed in the burn operating room between 01.11.2020 and 01.11.2021 were examined. The durations of the procedures performed before, during and after the surgery were evaluated. The mean duration of 432 operations was 66 minutes. It was determined that in 9.72% (N=42) of the operations, debridement was applied to the intubated patients in the hydrotherapy room before the operation, and the debridement time was 16 minutes on average. The average postoperative dressing time of all surgeries was 21 minutes, and it was determined that the operating room nurses played an active role in this process. Since burn center operating room nursing will be studied in more than one area, care and attention will undoubtedly play an active role in infection control and treatment success. In this study, it was observed that the burn operating room nurses contributed positively to the success of the patient's treatment in many areas, from the preparation of the operation in a burn center.

**Keywords** : Burn center, operating room nursing, operating time

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## 1. INTRODUCTION

Purpose: Nurses are healthcare professionals with professional values who provide health care services and receive training [1]. Nursing values are based on certain principles by the American Nurses Association and the International Nurses Association. These; Benefit, sacrifice, equality, freedom, human dignity, justice and truth are gathered under 7 main headings. Benefit has been stated as the most basic value [2,3].

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Operating room nurses take a broad active role and responsibility before, during and after the operation. Operating room nurses are responsible and active duty during the entrance of the patients to the operating room, premedication stage, operation period, awakening of the patient and transfer to the clinic or intensive care unit [4-6].

While providing medical services, success can be achieved with all the components of physical and spiritual activation, teamwork, experience and training. Operating room nursing, as a work area that requires stress and high attention, is a work area where sacrifice is added to all these. Operating room nurses are health workers who are responsible for all areas of the operating room and ensure that the system works well, quickly and safely. Success can be achieved with all of the components of teamwork, experience and being educated. Operating rooms are work areas that include attention, sacrifice and difficult working conditions, and they are places where the fastest results can be obtained in patient treatment and do not accept mistakes. Operating room nurses take responsibility for the patient when the patient is anxious, has no consciousness under anesthesia, and has limited physical functions [6-9].

Operating room nurses play an active role in providing the necessary environment for the operation, preparing the equipment, following the postoperative tools and equipment, cleaning and sterilizing them [10- 12].

Burn center is a multidisciplinary nursing branch that includes operating room nursing, operating room, intensive care, debridement and dressing of burn patients. Burn Center Nursing trainings, which have been intensified in our country in recent years, continue in accordance with this purpose. It is an important factor that the nurses working in the Burn Center operating rooms have both training and experience in burn treatment and operating room nursing. Burn surgeries are specific surgeries. They are areas with their own protocols before entering the operating room. Nursing service plays the main role in this area. Collaboration between burn care team members plays an active role in the treatment of the patient. In this team, coordination is arranged with the burn nurse.

Burn centers are inclusive areas established in tertiary hospitals with polyclinics, clinics, intensive care and operating rooms. Burns operating rooms are special areas, and they are directly connected to the hydrotherapy room, dressing room and intensive care unit in the center. It is one of the rare areas that can start in a sterile state before entering the operating room. Operating room nurses take an active and complementary role in the entrance to the operating room, surgical intervention and post-surgical procedures. Burn surgeries are specific surgeries. They are areas with their own protocols before entering the operating room. Nursing service plays the main role in this area. Collaboration between burn care team members is important in the follow-up and treatment of burn patients. This team coordinates with the burn nurse. The process is long and tedious. In our study, we aimed to emphasize the importance of the contribution of burn operating room nurses to the process by evaluating the operation times in the operating room of the burn center.

## 2. MATERIALS AND METHODS

The operations performed in the burn operating room of Eskişehir City Hospital Burn Center between 01.11.2020 - 2021 were examined. General surgery specialist, 3 burn operating room nurses, anesthesiologist, technician and operating room personnel participated in the operations. The recorded operation times were evaluated retrospectively from the patient file; the durations of the procedures performed before, during and after the surgery were evaluated.

## 3. RESULTS

The mean duration of 432 operations was 66 minutes. In 42 of the operations, it was determined that the patients who were intubated were debrided in the hydrotherapy room before the operation, and the debridement time was 16 minutes on average. The average postoperative dressing time of all surgeries was 21 minutes, and it was determined that the operating room nurses took an active role in all of these processes (table 1).

**Table 1:** Number of transactions and average duration of transactions

| | Counts (%) | Operation time (average) |
|---|---|---|
| Operation Counts | 432 (100%) | 66 minutes (42-94) |
| Debridement in the Hydrotherapy Room | 42 (9,72 %) | 16 minutes (7-28) |
| Postoperative Dressing | 432 (100%) | 21 minutes (18-24) |

## 4. DISCUSSION AND CONCLUSION

The good quality of nursing care increases the discipline in the operating room, the success of the patient's surgical intervention and provides the comfort of the employees [6]. Burn operating room nursing is one of the nursing services with high physical and mental fatigue, which requires a lot of self-sacrifice and extensive knowledge in professional nursing.

Areas where nurses play an active role in burns; evaluation of the deterioration of the patient's skin integrity, infection risk and follow-up, fluid volume deficiency, monitoring of physical movements, recognizing the anxiety in the patient, and informing the patient after discharge [13]. The applications in hydrotherapy performed under general anesthesia before the operation should be considered as a guide and facilitator for the surgical intervention to be performed during the operation of the patient. Damaged skin can be evaluated more easily, foreign harmful substances and dead tissues that may cause the patient's infection can be partially removed.

Burn operating room nursing requires absolute multidisciplinary training. Experience, physical and mental strength are important parameters. In a study conducted with operating room nurses, 69.7% of the nurses were women, 48.4% were between the ages of 36-40, 59.3% were at the undergraduate level, 71.3% had 11-15 years of professional experience, and 82% liked the profession. it was observed that he did it voluntarily [1,14]. In burn nursing, education, counseling and informing the patient about the post-treatment period contribute positively to the treatment in the course of the disease so that the patient's physical and mental quality of life is not adversely affected [13,15].

Nursing services progress holistically in the treatment of patients in the burn center. The burn center operating room nurse is an important element of the team that requires active work in the burn intensive care unit, patient room, hydrotherapy area and operating room, located in a wide area, with the knowledge of burn treatment and operating room nursing. Nurses undoubtedly play an active role in infection control and treatment success, with careful attention and care, as more than one field will be studied one after the other. In this respect, studies on regulating working conditions and workload are as valuable as training qualified burn center operating room nurses. This retrospective observational study has shown that burn operating room nurses make a positive contribution to the success of the patient's treatment in many areas, from the operation preparation of the operations in a burn center to the procedures in the postoperative process. In this respect, we think that the arrangements to be made regarding the working conditions and workload are important.

**Conflict of Interest**

Author has no personal financial or non-financial interests.
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Research Article

# Chemometric Determination of Valsartan in The Presence of Its Carboxylic Acid-Induced Triiodide Ion Product by Spectrophotometric Method

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**ABSTRACT**

A new spectrophotometric method optimized with central composite design (CCD) for quantitative estimation of valsartan (VL) in pharmaceutical preparations was developed. The developed method is based on the oxidation of VL with potassium iodate ($KIO_3$) to form a carboxylic acid derivative. In the presence of the -COOH group, iodide (KI) is oxidized by iodate, leading to the formation of a yellow-colored triiodide ion with an absorption maximum at 352 nm. The CCD, one of the chemometric methods were applied for the determination of the experimental conditions and then Kinetic studies were used for the stability period. The equilibration time was determined as 10 min. The volumes of 0.05 M KI and 0.003 M $KIO_3$ were calculated as 1.92 mL (0.0192 M) and 2.96 mL (0.000177 M), respectively, and the temperature was measured as 27°C. The method was linear in the concentration range of 6-34 µg/mL (R2: 0.996). The LOD and LOQ were obtained as 0.81 and 2.46 µg/mL, respectively. The pharmaceutical dosage forms were analyzed with developed method, and the obtained results ranged from 98.3% to 102.9%. The developed method was a simple, rapid and inexpensive method for routine analysis of VL in pharmaceutical dosage form.

**Keywords:** Central composite design, UV-Vis Spectrophotometry, Valsartan.

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## 1. INTRODUCTION

Hypertension is a common disease in which the force exerted on the arterial walls by the blood carried from the heart to the body is quite high, and is an important risk factor for cardiovascular diseases. It is managed by maintaining blood pressure above 140/90 mmHg [1]. Angiotensin II (AII) receptor antagonists are the newest class of drugs to be introduced in clinical practice for the treatment of hypertension [2]. Valsartan (VL), is an orally active, potent and specific competitive angiotensin II

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antagonist acting at the ATI receptor, which mediates all known effects of angiotensin II on the cardiovascular system, and it is dilates blood vessels and reduces blood pressure by blocking the action of angiotensin [3]. Since VL is one of the important drugs used in the treatment of hypertension, it is desirable to develop a simple, rapid and reproducible analytical methods for measurement of VL. UV-Visible spectrophotometry one of the most used and most important analytical instruments for most drug quality control analysis, because of its simplicity, speed, versatility, cost-effectiveness, quite high accuracy and precision.

Literature survey reveals that there are UV-Vis spectrophotometric determination of VL in pharmaceuticals. These include direct [4-7] and derivative [8-11] UV measurements, formation of selective ion-pair with acidic dyes, namely, bromophenol blue (BPB) [12, 13] and bromocresol green (BCG) [12], and methyl red [13], the charge transfer complexation reaction between VL as n- electron donor and *p*chloranilic acid (*p*-CA) as π-acceptor [14] and its complexes with calcium(II) and magnesium(II) [15]. Direct spectrophotometric methods have some analytical disadvantages: low sensitivity and low selectivity in ultraviolet region [4-7]. In the literature, a very limited number of methods based on formation of complex have been described for the determination of VL [12-15]. The assay method in our study can be presented as an alternative to existing methods. As far as our knowledge is concerned, no analytical procedure based on the formation of a yellow-colored triiodide ion is reported for the estimation of VL in pharmaceutical preparations Although in other sartan drug groups [16, 17]. There are many specific advantages associated with the kinetic spectrophotometry which is considerably simple and fast method such as high sensitivity, selectivity and low limit of detection. In addition, these advantages, the kinetic study of reaction in our method was executed for avoid the interference of colored and/or turbidity background of samples. In this study, the central composite design (CCD), also called response surface methodology (RSM), was employed for the optimization of the reaction conditions. CCD is a useful method for carrying out a limited number of experiments and save the time and effort by the estimation of the optimum conditions. Thus, the aim of this work was to investigate the validation and application of analytical method based on the oxidation of VL with potassium iodate ($KIO_3$) to form a carboxylic acid derivative, thus in the presence of –COOH group iodide (KI) is oxidized by iodate resulting in the formation of triiodide ion for estimation of VL, using kinetic spectrophotometry and an experimental design known as CCD.

## 2. MATERIAL AND METHODS

### *2.1. Instrumentation and Software*

A Thermo Scientific brand, Multiscan GO UV-Visible spectrophotometer (51119300 model) with 1.0 nm bandwidth and connected to lenovo brand computer was used

for all of spectral run. Samples were placed in the Hellma quartz 96 Well microplate for scanning and absorbance measurements. Experimental design was performed Stat-Ease Inc. Design-Expert8.0 (USA).

### *2.2. Optimization of Maximum Wavelength*

Maximum wavelength was carried out with mixture of KI and $KIO_3$ in the presence of VL. Then, the obtained yellow-colored triiodide ion was scanned from 400-800 nm by UV-Visible Spectrophotometric method.

### *2.3. Chemicals*

VL reference standard was purchased from Sigma-Aldrich (Germany). KI, $KIO_3$, Dimethylsulfoxide (DMSO) and methanol were of analytical grade and again purchased from Sigma-Aldrich (Germany). Deionized water (EASY Milli-Q grade) was used in the all experimental study. Commercial pharmaceutical dosage forms of VL (Cardopan® and Premium®) were purchased from a Pharmacy in Erzurum/Turkey.

### *2.4. Preparation of Stock, Calibration and Quality Control Solutions*

The stock solution of 2 mg/mL VL was prepared in methanol and was stored at 4°C. The 0.05 M KI solution and 0.003 M $KIO_3$ solution were freshly prepared in ultrapure water. Calibration solutions (6-34 µg/mL) and QC samples (8, 20 and 30 µg/mL) were obtained daily by dilution of respective stock solution with DMSO. 1.92 mL 0.05 M KI and 2.96 mL 0.003 M $KIO_3$ were added in the obtained solutions and then the volume was completed with deionized water at 27°C. Prepared respective solutions were taken in quartz microplate and kept for 10 min with shaking. In these solutions absorbance values at 352 nm were measured against the blank reagent. In this study, the method previously developed was used by revising it [16, 17].

### *2.5. Preparation Pharmaceutical Dosage Form*

Ten tablets of each formulation were accurately weighed and crushed to fine powder. The approximately 80 mg VL, that is the amount of 1 tablet, was transferred into the flask and 40 mL of methanol was added. Obtained solutions were dissolved by aid of ultrasonication for 15 min and cooled to room temperature. Then the volume was completed to 50 mL with methanol, and then stock solution diluted at 12 µg/mL concentrations with DMSO and 1.92 mL 0.05 M KI and 2.96 mL 0.003 M $KIO_3$ were added in the obtained solutions and then the volume was completed with deionized water at 27°C, and the obtained solutions were analyzed at 352 nm as mentioned above.

## 3. RESULTS AND DISCUSSION

### *3.1. Optimization of UV-Vis Spectrophotometric Method*

A few of Angiotensin II (AII) receptor antagonists, known as sartans, include the methyl group of the butyl side chain: Losartan, Irbesartan and Valsartan. As suggested in the literature, the oxidation reaction of irbesartan and losartan can be

monitored spectrophotometrically [16, 17]. A schematic representation of the reactions is shown in **Fig 1.**

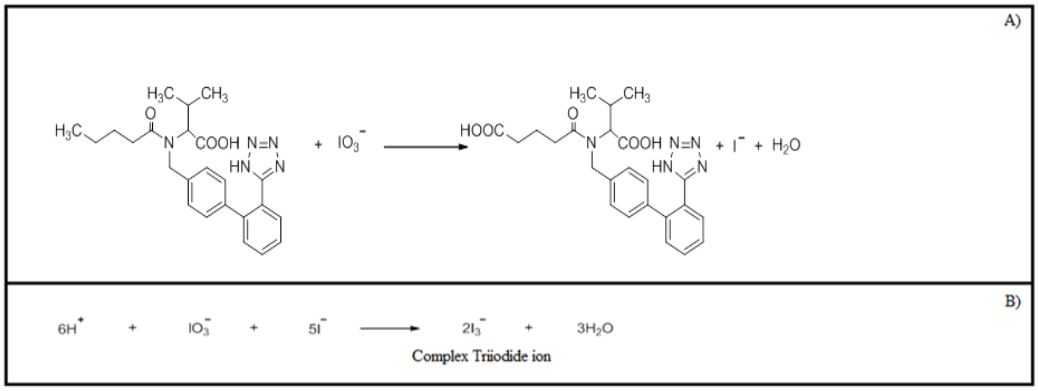


**Figure 1. A)** The oxidation reaction of VL with $KIO_3$ to form a carboxylic acid derivative. **B)** The oxidation reaction of KI by $KIO_3$ in the presence of carboxylic acid form of VL, leading to the formation of a yellow-colored triiodide ion.

Initially, VL was oxidized with iodate and the carboxylic acid form of VL was obtained as a result of this reaction. The production of triiodide ion, which is yellow in color, occurred by oxidation of iodide with iodate in the presence of carboxylic acid form of VL similar to other sartan group drugs found in the literature [16, 17]. The triiodide ion showed the maximum absorbance at 286 nm and 352 nm (**Fig. 2**). The measurements were found to be higher at 352 nm according to the 286 nm as a result of the calculations of molar absorptivity. Therefore, the 352 nm was selected for absorbance measurements in determining of VL.

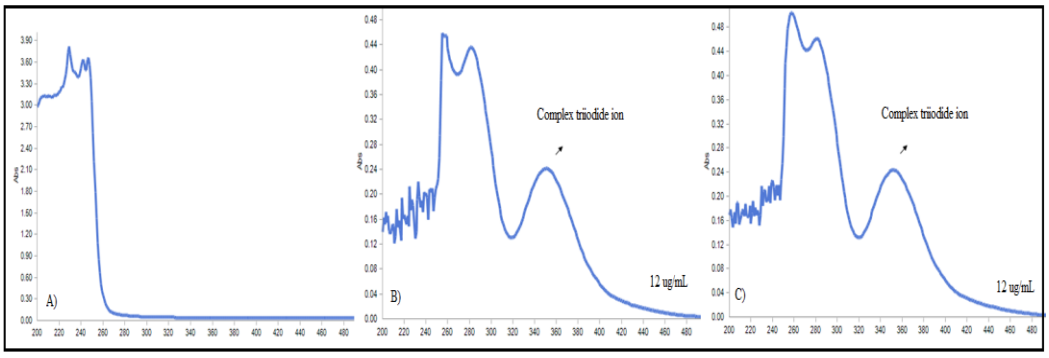


**Figure 2.** A) Absorption spectra of blank B) Absorption spectra of triiodide complex formed with 12 µg/mL VL standard solution C) Absorption spectra of triiodide complex formed with 12 µg/mL VL drug solution.

Central Composite Design (CCD) is applied in designing the experiments to evaluate the interactive effects of selected factors. For determination of VL, the CCD in three most significant independent factors; 0.05 M KI volume (A), 0.003 M $KIO_3$ volume (B) and temperature (C) was employed for experimental design and

optimization of results. The choice of these three parameters was realized the result of some preliminary experiments with the help of the prior knowledge of literature [16, 17]. The specified ranges of each parameters were: 0.05 M KI volume (0.6 mL ($6.10^{-3}$ M) - 2 mL ($2.10^{-2}$ M)), 0.003 M $KIO_3$ volume (0.8 mL ($4.8.10^{-4}$ M) - 2.6 mL ($1.56.10^{-2}$ M)) and temperature (30°C-40°C). The response variables for this experimental design was the absorbance of VL. A set of 20 experiments consisting of 6 axials and 8 factorial runs along with 6 replicates at central point was performed to employ a CCD. The α value was 1.689 ($\alpha = (2^3)^{1/4} \sim 1.689$) as rotational. The absorbance values from each experiment were obtained in the CCD experiments and the three-dimensional RSM plots were made for the estimated absorbances as responses of CCD experiments (**Fig. 3**). The RSM was applied to gain a better understanding of the results and it was concluded that the experimentally obtained actual values were fitted to the response surface. In developing quadratic regression model, the response of tested variables in coded units was given by:

$$Y=0.023A+0.052B-0.00689C-0.040A^2-0.006155B^2-0.012C^2+0,011AB+0.00375AC+0.00125BC+0.25$$

where, Y is the measured response (absorbance). A, B and C are coded values of the above-mentioned independent variables. The statistical significance of the quadratic regression equation demonstrated that the regression is statistically significant with P-value of 0.0455 ($P<0.05$) obtained from the ANOVA for response surface quadratic model. In this case A, B, and C are significant model terms and significantly affects the absorbance of VL. From CCD, the most optimum values of the parameter were found as 0.05 M KI volume: 1.92 mL, 0.003 M $KIO_3$ volume: 2.96 mL and temperature: 27°C. The predicted absorbance was found as 0.82 with model. Repeated experiments (n=10) were performed by using the optimized conditions to compare the experimentally obtained actual values with the predicted values and the results from ten replications confirmed that the measured mean value was very close to the predicted value with 0.794 ± 0.029.

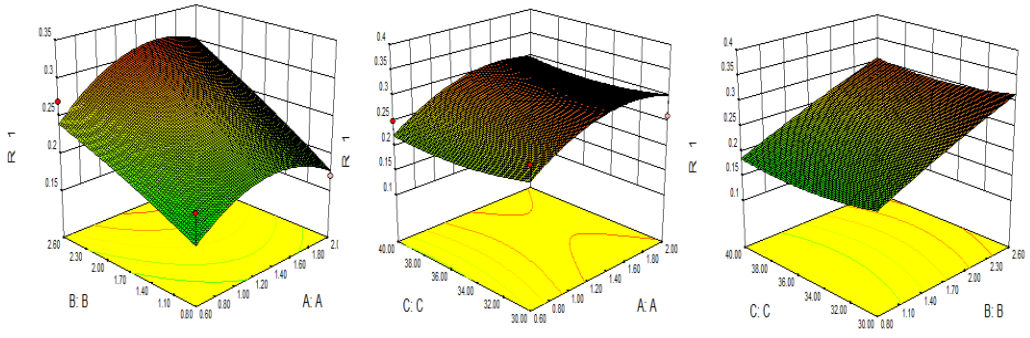


**Figure 3.** Response-surface plots (Three-dimensional) Y: VL absorbance, X: A) A and B; fixed factor: C, B) A and C; fixed factor: B, C) B and C; fixed factor: A (A:0.05M KI volume, B:0.003M $KIO_3$ volume, C: Tempereture)

### *3.2. Kinetic Study*

Under the optimized conditions, the absorbance-time curves for the reaction of VL concentration were observed. The calculation of the log IRR (initial reaction rates) as a function of logVL was carried out by utilizing the slope of the curve. According to the data, a straight line whose slope value was found as 1.041 (~1, first order). But the concentrations of KI and $KIO_3$ concentration were very less than VL. So, the reaction was considered to be a pseudo first order reaction, and triiodide ion formation was determined as the rate-limiting step of the reaction. The reaction time was set as 10 minutes according to absorbance-time curve.

### *3.3. Validation of UV-Vis Spectrophotometric Method*

The new UV-Vis Spectrophotometric method for determination of VL was validated in accordance with ICH Q2B guidance [18].

Linearity was established for the method described above by plotting calibration curves between absorbance and various concentrations of VL (6-34 µg/mL). The mean linear regression equation was calculated based on six calibration curves formed by measuring the absorbance. The related equation was found as $A_{286nm}$= 0.0335C-0.1722 (C: VL concentration (µg/mL), and $A_{286nm}$: the absorbance measured at 286 nm) with 0.9996 mean correlation coefficient. The method is linear with very high mean correlation coefficient.

The limit of detection (LOD: 3.3 σ/S) and the limit of quantitation (LOQ: 10 σ/S) were calculated by using the standard deviation of the intercepts (σ) and the slopes (S) of regression lines of the calibration curves. LOD and LOQ obtained from UV-Vis Spectrophotometric method for VL were found as 0.81 µg/mL and 2.46 µg/mL, respectively.

The accuracy and precision of UV-Vis Spectrophotometric method were calculated with intra-day and inter-day measurement for QC concentrations of standard solutions of VL (6, 12 and 24 µg/mL). The results were presented in terms of the percent relative standard deviation (RSD%) for intra-day and inter-day precision of methods and the RSD % values were found to be ≤ 4.28 %. The results were presented in terms of percent relative error (RE%) for intra-day and inter-day accuracy of methods and the RE % values were found to be between -4.11 and 3.25. Recoveries (R%) were carried out by spiking known quantities of standard in pharmaceutical tablets (Cardopan® and Premium®). The obtained results had good accuracy with≤ 99.27 % mean recovery. Also, as we mentioned in our previous study [16], triiodide formation is not affected by pharmaceutical excipients.

### *3.4. Application of UV-Vis Spectrophotometric Method*

The new UV-Vis Spectrophotometric Method was applied the determination of VL in the pharmaceutical dosage forms (Cardopan® and Premium®). Absorption spectra obtained from tablet dosage form (12 µg/mL) was shown in **Figure 2C.** The

estimation of level of VL in the pharmaceutical dosage forms, which was prepared as described in the procedure, was performed and analyses was replicated ten times for the samples. Determinations of VL in pharmaceutical dosage form were successfully achieved with good accuracy results of 98.3%-102.9 % (**Table 1**). The obtained good recovery indicated that the developed UV-Vis Spectrophotometric Method was accuracy enough for the analysis of the drug.

**Table 1.** Determination of VL in pharmaceutical dosage forms by UV-Vis spectrophotometric method

| Drug | Label claim (mg VL per tablet) | Found[a]±SD (mg) | Mean Recovery (%) | RSD (%) | Confidence Interval |
|---|---|---|---|---|---|
| Cardopan | 80 | 80.57±2.012 | 100.72 | 2.49 | 98.3-101.5 |
| Premium | 80 | 80.81±1.430 | 101.01 | 1.77 | 99.5-102.9 |

SD: standard deviation, [a]: Average of twenty-four determinations

## 4. CONCLUSION

A new UV-Vis spectrophotometric method which is rapid, simple and cheap has been developed with good sensitivity and selectivity. In this study, the CCD was employed as an experimental design for this new analytical method based on oxidation of VL to form triiodide ion. The developed method has an advantage in terms of saving the time and effort by carrying out a limited number of experiments to determine the optimum assay conditions. The kinetic study which is used for determining of the order of reaction and time required for the reaction is another advantage for the method in terms of avoiding the interference of colored and/or turbidity background of samples. The simple reaction conditions were supported with the validation studies. It can be concluded from the results that developed UV-Vis spectrophotometric method is sensitive, specific, accurate and precise. Under the optimum conditions which were selected easily by using CCD, assay results obtained by this method confirmed that the UV-Vis spectrophotometric method is applicable usefully for routine analyses of VL in pharmaceutical dosage forms.

### Conflict of Interest

Author has no personal financial or non-financial interests.

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Review

# Fixed-Dose Combination-Orally Disintegrating Tablet (FDC-ODT) Studies for the Treatment of Type 2 Diabetes or Cardiovascular Diseases -A Mini Review

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**ABSTRACT:**
The orally disintegrating tablet (ODT) is a dosage form that stands out for its organoleptic elegancy, better patient compliance, rapid disintegration, and rapid onset of action in geriatric, psychiatric, pediatric, paralyzed, and bedridden patients. Drug combination therapy refers to the concomitant use of two or more drugs used separately or the use of two or more active pharmaceutical ingredients (APIs) in fixed-dose combinations (FDCs) in a single dosage form. FDC drug products have been developed to target a single disease or multiple diseases/conditions. There have been studies showing that taking FDC drug products may be more effective than using dosage forms containing individual APIs. However, the safety, efficacy, and rationality of many FDCs still remain questionable. Furthermore, FDC-ODTs combine the advantages such as better compliance and efficacy of both FDC and ODTs, especially in dysphagic patients and the patients on multiple drug therapy. FDC-ODTs have been prepared for the treatment of different diseases such as Type 2 diabetes, epilepsy, cardiovascular disease, Parkinson's disease. In this mini-review, I aimed to provide an overview with some studies on FDC-ODTs prepared for cardiovascular diseases and Type 2 diabetes treatments in the literature.

**Keywords***:* Cardiovascular diseases, fixed-dose combination, orally disintegrating tablet, type 2 diabetes

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## 1. INTRODUCTION

The ODT is a dosage form that stands out for its organoleptic elegancy, better patient compliance than conventional tablets and capsules, rapid disintegration, and rapid onset of action in geriatric, psychiatric, pediatric, paralyzed and bedridden patients [1–3]. ODT is also called as fast/rapid-dissolving, orodispersible, mouth-dissolving, or fast-disintegrating tablet. Pharmacopeias and Center for Drug Evaluation and Research (CDER) at Food and Drug Administration (FDA) have made some definitions for ODT. The following definition, developed by CDER for ODT, is given in the "Guidance for Industry Orally Disintegrating Tablets": "A solid dosage form containing medicinal

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substances which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue" [4]. Besides, European Pharmacopoeia defines ODT as "uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed. ODTs disintegrate within 3 min" [2,5]. Japanese Pharmacopoeia also defines ODT as follows: "Orally Disintegrating Tablets are tablets which are quickly dissolved or disintegrated in the oral cavity. ODTs show an appropriate disintegration" [6]. ODTs have the advantages of both liquid dosage forms and conventional tablets [2]. APIs with relatively higher doses are difficult to formulate as ODTs. However, some technologies such as Orasolv® technology, and Flashdose technology allow high API loading. APIs' bioavailability can be increased with the use of ODT because some APIs are absorbed from the mouth, pharynx, and esophagus and go down to the stomach in a dissolved form. Also, first-pass metabolism, the dose and side effects of APIs can be reduced. Besides these advantages, there are some limitations for ODTs. For example, ODTs have low mechanical strength compared to conventional tablets, so they need special packaging. Also, it is not easy to formulate bitter APIs as ODTs, so taste masking excipients must be used to develop ODT formulations of such APIs. Again, some excipients, such as surfactants, are needed to formulate poorly water-soluble APIs as ODTs [1,3,7,8].

Drug combination therapy refers to the concomitant use of two or more drugs used separately or the use of two or more APIs in FDCs in a single dosage form [9]. Drug combination therapy can be beneficial for lowering the concentrations of individual APIs, reducing their undesirable side effects, improving patient compliance, increasing therapeutic efficacy, and overcoming drug resistance compared to the use of a single pharmacological agent [10–12]. This approach has become a promising strategy for the treatment of various complex diseases such as diabetes, cancer, and bacterial infections [9,11]. The pharmaceutical industry has been studying the potential to improve the currently used medicinal products, including increasing the efficacy and safety of medicinal products or reducing the side effects of treatment. In this direction, studies aiming to increase patients' access to modern treatments and improve patient compliance have been carried out [13]. The FDA's "combination rule" (21CFR 300.50) states that "(1) each component must make a contribution to the claimed effects; and (2) the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for the intended patient population" [14]. FDC drug products have been developed to target a single disease or multiple diseases/conditions [9]. There have been studies showing that taking FDC drug products may be more effective than using dosage forms containing individual APIs. The importance of FDCs is increasing due to the synergistic effect, lower doses of individual APIs, reduction of side effects, simple treatment plan/reduction in drug (tablet, capsule, etc.) burden, reduced cost and increased patient compliance [13]. On the other hand, there are some concerns about the use of the FDC drug product. These: 1.

Limiting the ability of clinicians to customize dosing regimens (less dosage flexibility), 2. There are difficulties in developing FDC formulations (compatibility issues among APIs and excipients, solubility, etc.), 3. If an adverse reaction occurs, it may be hard to identify the API causing the reaction 4. May cause significant problems in patients using FDC drug products containing broad-spectrum antibiotics, such as antibiotic-associated diarrhea and increased risk of developing resistance to antibiotic/s [9,13]. Despite the positive aspects associated with prescribing FDCs [15], the safety, efficacy, and rationality of many FDCs still remain questionable [15,16]. Various FDCs were even banned due to reasons such as potential safety concern, lack of efficacy, and pharmacodynamic and pharmacokinetic mismatch [13,16–18].

The pharmaceutical industry prepared different dosage forms of FDC, such as tablets [e.g., Synjardy® tablet contains a combination of empagliflozin and metformin hydrochloride (MET)], extended-release tablets (e.g., Synjardy® XR tablet contains a combination of empagliflozin and MET), delayed-release tablets (e.g., Diclegis® delayed-release tablet contains a combination of doxylamine succinate and pyridoxine hydrochloride), ODTs (e.g., Carbidopa and Levodopa ODT contains a combination of carbidopa and levodopa), and capsules (e.g., Lotrel® capsule contains a combination of amlodipine besylate and benazepril hydrochloride), extended-release capsules (e.g., Adderall® XR capsule contains a combination of dextroamphetamine and amphetamine salts) and delayed-release capsules (e.g., Talicia® delayed-release capsule contains a combination of omeprazole magnesium, amoxicillin and rifabutin) [13,19].

FDC-ODTs (two or more APIs-containing ODTs) combine the advantages such as better compliance and efficacy of both FDC and ODTs, especially in dysphagic patients [20] and the patients on multiple drug therapy [2]. However, in the Orange Book ("Approved Drug Products with Therapeutic Equivalence Evaluations"), only FDC-ODTs containing carbidopa and levodopa (strength: 10 mg+100 mg or 25 mg+100 mg or 25 mg+250 mg) for the treatment of the symptoms of Parkinson's disease appear to have been approved by the FDA [19]. FDC-ODT is a suitable dosage form to help patients with Parkinson's who have difficulty taking their medications for various reasons (forgetting to take the drugs, leaving home without the drugs, etc.) overcome these difficulties and facilitate drug use. Poor medication adherence causes inadequate symptom control and undesirable side effects in Parkinson's patients. It has been reported that FDC-ODTs containing carbidopa and levodopa may provide improved patient compliance, ease of use, and rapid access to medication for patients with Parkinson's [21]. Furthermore, in the literature, FDC-ODTs have been prepared for the treatment of different diseases such as Type 2 diabetes [22–24], cardiovascular diseases [25,26], epilepsy [27], Parkinson's disease [21], and Tuberculosis [28].

Therefore, in this mini-review, I aimed to provide an overview with some studies on FDC-ODTs prepared for cardiovascular diseases and Type 2 diabetes treatments in the literature.

## 2. THE STUDIES ON FDC-ODTS PREPARED FOR THE TREATMENT OF CARDIOVASCULAR DISEASES AND TYPE 2 DIABETES IN THE LITERATURE

Cardiovascular diseases (coronary heart disease, peripheral arterial disease, rheumatic heart disease, cerebrovascular disease, congenital heart disease, deep vein thrombosis, and pulmonary embolism) refers to a group of disorders/diseases of blood vessels and the heart [29]. The incidence of cardiovascular diseases, the leading cause of disability in humans and premature death, is increasing globally [26]. These diseases cause a heavy burden on the economies of low- and middle-income countries, where more than three-quarters of cardiovascular disease deaths occur. Hypertension, hyperlipidemia, obesity, diabetes, unhealthy diet, physical inactivity, and smoking are the risk factors leading to the onset of cardiovascular diseases. Primary approaches for the prevention and treatment of cardiovascular disease include lifestyle modifications (such as improvement in diet, increase in physical activity, and smoking cessation), use of antihypertensives, anticoagulants, lipid-lowering drugs, and antiplatelet therapy. Despite their effectiveness, new treatment approaches are still needed for cardiovascular diseases [26].

In a study on the preparation of FDC-ODTs for the treatment of cardiovascular diseases, optimum ODT formulations containing amlodipine besylate (AB) and/or atorvastatin calcium (AC) [in single (AB-containing formulation=AB-ODT and AC-containing formulation=AC-ODT) or FDC formulations (AB and AC-containing formulation=FDC-ODT; 6.95 mg AB and/or 10.85 mg of AC per 500 mg ODT)] was prepared using Pearlitol® Flash (mannitol-starch copolymer) as a direct compression agent with diluent and disintegrant properties, Avicel PH-102 (microcrystalline cellulose) as a binder and disintegrant, and sodium stearyl fumarate as a lubricant. The hardness and friability values were approximately 108 N and 0.71% for AB-ODT, about 114 N and 1.02% for AC-ODT, and about 118 N and 0.73% for FDC-ODT, respectively. The disintegration time of AB-ODT, AC-ODT, or FCD-ODT formulations was 25.33 sec, 24 sec, and 21.67 sec, respectively. In vitro dissolution studies performed in dissolution media [fasted-state simulated intestinal fluid (FaSSIF) and fed-state simulated intestinal fluid (FeSSIF)] for single or FDC-ODT formulations showed that there was no difference in AB or AC dissolution between single formulation (AB-ODT or AC-ODT) and FDC-ODT formulation (except for AB dissolution from single and FDC formulations in FeSSIF medium). Besides, Papp values for amlodipine and atorvastatin alone and in combination across Caco-2 monolayers were determined. Physiologically based pharmacokinetic (PBPK) modeling, which is a tool for prediction of API absorption through integration of information such as physicochemical and cell-based

permeability data, makes it possible to simulate clinical trials. The researchers found that there was no difference in bioavailability based on pharmacokinetic parameters between FDC and single doses of AB or AC in simulated clinical trials [25].

Statins are widely used to treat hypercholesterolemia and dyslipidemia and prevent the risk of cardiovascular disease development. One of the side effects of statin therapy is myopathy. A study was conducted in the literature to develop an FDC-ODT formulation containing pitavastatin calcium (PC) and lornoxicam (LX), and determine the pharmacokinetic parameters of PC and LX in FDC-ODT (PC+LX-FDC-ODT) by pharmacokinetic study in male Wistar rats [30]. In the PC+LX-FDC-ODTs, PC, which belongs to the statin drug class, was used for the management and treatment of hyperlipidemia, while LX, a non-steroidal anti-inflammatory drug, was used to help in the management of statin-induced myopathy. In that study, PC+LX-FDC-ODTs was prepared by direct compression method. The mean weight, friability, and in vitro disintegration time of PC+LX-FDC-ODTs were found to be as 98.66 mg, 0.84%, and 7.33 sec, respectively. In-vitro dissolution study for PC+LX-FDC-ODTs and the marketed products [Lipidalon® tablets containing PC (1 mg); Lornoxicam® tablets containing LX (4 mg)] was performed in simulated saliva fluid pH 6.8. The amounts of dissolved PC and LX obtained for PC+LX-FDC-ODTs after 10 min were about 79% and 74%, respectively. These results were higher than the amount of dissolved PC or LX obtained for marketed drugs (dissolved PC after 10 min= about 54% for Lipidalon®; dissolved LX after 10 min= about 46% for Lornoxicam®). As a result of the in vivo pharmacokinetic study, the authors determined that the percent relative bioavailability values of PC+LX-FDC-ODT to the marketed products were 286.7% for PC and 169.73% for LX. They emphasized that PC+LX-FDC-ODT is a promising dosage form for immediate co-delivery of both APIs [30].

In another study, FDC-ODT containing amlodipine (5 mg) and valsartan (40 mg) for the treatment of hypertension was prepared by direct compression method. They used synthetic or natural superdisintegrants (synthetic superdisintegrants: croscarmellose, and crospovidone; natural superdisintegrants: banana powder, and gallen gum) in the formulation. The hardness and disintegration time values of FDC-ODT formulations are in the range of 2.9 to 4.2 kg/cm$^2$ and 23.1-400 sec, respectively. They found that the best disintegration time results were obtained for the formulations containing crosspovidone, and the disintegration time decreased (from 50 sec to 23.1 sec) as the amount of crosspovidone increased (from 45 mg to 135 mg). The formulation containing crosspovidone were quickly disintegrate compared to the formulations containing the other superdisintegrants [31].

Studies in which FDC-ODT formulations were prepared for the treatment of diabetes are also included in the literature. Type 2 diabetes, in which the body's ineffective use of insulin due to peripheral tissue insulin resistance, impaired

insulin production and/or secretion by β cells of pancreatic islets (various degrees of beta-cell dysfunction), is a chronic metabolic disorder that has an increasing prevalence and has become a significant healthcare burden all over the world [32–34]. Type 2 diabetes management includes the use of oral hypoglycemic agents [biguanides (mainly Metformin); sulfonylureas (glyburide, glipizide, glimepiride, gliclazide); meglitinides (nateglinide, repaglinide); thiazolidinediones (pioglitazone, rosiglitazone), alpha glucosidase inhibitors (miglitol, acarbose, voglibose), DPP-4 inhibitors, SGLT2 inhibitors, and bromocriptine] and insulin (it is widely used in combination with oral hypoglycemic agents), as well as lifestyle changes (such as a healthy diet and regular physical activity) and obesity treatment [35,36]. FDC-ODTs can be prepared especially for elderly patients with diabetes and diabetic patients with impaired swallowing function to ensure less tablet intake and ease of use and to improve compliance.

Gulsun et al. [24] prepared MET and Glyburide (GLY)-containing FDC-ODT formulations by two different methods [direct compression (COMP) and lyophilization (L; freeze-drying) methods] using different excipients in these formulations. They performed quality control tests for MET+GLY-FDC-ODTs prepared by COMP or L methods (500 mg MET+ 5 mg GLY-COMP-FDC-ODTs and 250 mg MET+ 2.5 mg GLY-L-FDC-ODTs). In this study, highly porous FDC-ODTs were obtained using L technique, and the hardness, friability, and disintegration time values of MET+GLY-L-FDC-ODTs were 66.54±2.68 N, 0.38%, and 30 sec, respectively. For MET+GLY-COMP-FDC-ODTs, these values were determined as 221.60±40.82 N, 0.24%, and 80 sec, respectively. Although the hardness of MET+GLY-COMP-FDC-ODTs is higher than the preferred hardness value range (30–80 N [37]) for ODTs, these tablets disintegrated in a relatively short time, as expected from ODTs. In addition, MET+GLY-L-FDC-ODTs had a shorter disintegration time than MET+GLY-COMP-FDC-ODTs due to the higher porosity and easier water uptake of L-FDC-ODTs. The authors also determined the water absorption ratio, which is a significant parameter for the water uptake rate and disintegration of ODTs. They reported that the water absorption ratio for MET+GLY-COMP-FDC-ODTs were determined as 1.30±0.05, but this ratio could not determine for MET+GLY-L-FDC-ODTs that disintegrated very quickly without swelling. Moreover, the permeability study across the Caco-2 cell monolayer, which is widely used for drug permeability screening, as well as for the evaluation of the effects of the excipients in the formulation on the drug permeability, was performed. According to Biopharmaceutics Classification System, MET and GLY are classified as Class III (high water solubility and low permeability) and Class II (high permeability and poor water solubility) drugs, respectively. As a result of the permeability study, they reported that unlike COMP-FDC-ODTs, L-FDC-ODTs caused an increase in the permeability of MET and this result may be due to the potential effect of the excipients in the

formulations on Caco-2 permeability. On the other hand, both COMP-FDC-ODTs and L-FDC-ODTs did not affect the permeability of GLY [24].

Mitiglinide, a rapid-acting insulin secretion stimulating agent, and Voglibose, an alpha-glucosidase inhibitor (it lowers postprandial blood glucose levels), are used in the treatment of Type 2 diabetes [22]. Ono et al. [38] showed that an FDC of voglibose (0.2 mg) and mitiglinide (10 mg) significantly reduced postprandial glycemic excursions in Japanese patients with Type 2 diabetes.

Sotoyama et al. [22] prepared FDC-ODT containing mitiglinide and voglibose, ODT containing mitiglinide, ODT containing voglibose, and three corresponding blank-ODTs (without APIs; placebo-ODTs). The hardness and *in vitro* disintegration time values of all prepared ODTs were found to be in the range of 35.7-92.0 N and 18.4-28.7 sec, respectively. Then, they performed two independent clinical trials with healthy subjects to evaluate the clinical pharmaceutics characteristics of ODTs and FDC-ODT (such as disintegration time, the ease of intake of ODTs, the amount of water required for their uptake, palatability of ODTs). In the first trial performed to evaluate the ease of intake of ODT and the amount of water required for their intake, only placebo-ODTs were given to healthy volunteers with 23.0±0.86 years of mean age (8 men and 5 women) to avoid administering APIs. For this purpose, they conducted "a two-phase randomized crossover trial", consisting a phase of taking placebo-ODTs corresponding to ODTs containing single API (two tablets in total) simultaneously and another phase of taking a placebo ODT corresponding to FDC-ODT (only one tablet). As a result of this trial, they found that FDC-ODT, unlike ODTs, could facilitate ODT intake and reduce the water amount required for ODT intake. Furthermore, the second trial was performed on healthy subjects (8 men and 5 women; 23.4±1.6 years of mean age), and the sweetness, bitterness, and general flavor of FDC-ODT or ODTs were evaluated during disintegration and after spitting. For this, "a two-phase randomized crossover trial", consisting a phase of taking an ODT containing mitiglinide and an ODT containing voglibose (two tablets in total) and the other phase of taking an FDC-ODT containing mitiglinide and voglibose (only one tablet). They determined that the disintegration time were 27.9 sec for the phase of taking two ODTs containing single API and 25.3 sec for the other phase of taking an FDC-ODT, respectively. It was found that there was no difference between the FDC-ODT and ODTs in terms of taste assessment (except for the post-spitting sweetness score). It was emphasized that FDC-ODT containing mitiglinide and voglibose can contribute to improving the compliance of patients with Type 2 diabetes [22].

In another study, an FDC-ODT containing MET and glibenclamide was prepared by the melt granulation technique to overcome both the tablet burden, and swallowing problems, occurring at a later stage of diabetes. First of all, the authors prepared eight preliminary FDC-ODTs using two APIs (MET-250 mg/tablet and glibenclamide-2.5 mg/tablet), polyethylene glycol 6000 (PEG 6000; 7 mg or 24.5

mg/tablet), aspartame (1.75 mg/tablet), crospovidone (7 mg or 35 mg/tablet), sodium lauryl sulphate (3.5 mg/tablet), magnesium stearate (3.5 mg/tablet), colloidal silicon dioxide (1 mg/tablet), and microcrystalline cellulose (73.75 mg or 56.25 mg or 45.75 mg or 28.25 mg/tablet). PEG 6000 was used as a binding agent in the FDC-ODTs, and crospovidone was used as a superdisintegrant. Then, the hardness and wetting time values of these preliminary FDC-ODTs were determined in the range of 4.11-10.15 kg/cm$^2$ and 28-96 sec, respectively. In addition, the effects of 3 independent variables [compression force and the amounts of crospovidone and PEG 6000] on response variables [friability, disintegration time and percent APIs release (at 30 min)] was investigated by applying a two-level full factorial experimental design. Increasing the compression force and the amount of PEG 6000 caused a meaningful increase in the disintegration time of the FDC-ODTs while causing a significant decrease in their friability (%) values. Moreover, it was stated that the disintegration time of FDC-ODTs decreased significantly with increasing the amount of crospovidone, but their friability (%) values did not show a significant change. Based on this information obtained from the preliminary study, the authors further studied the effects of crospovidone, PEG 6000, and compression force on the disintegration time and friability of FDC-ODTs and optimized the formulation using a central composite design. Accordingly, the desired optimum conditions were met when the amounts of PEG 6000 and crospovidone were 3.82% and 9.83%, respectively, and the compression force was 10.6 kN. The predicted friability and disintegration time values of the optimum FDC-ODT were 0.302% and 18.7 sec, respectively. Moreover, the experimental values obtained for FDC-ODT prepared using these optimum conditions were within 5% of the predicted values. As a result, it has been reported that ODTs with faster disintegration time and sufficient mechanical strength have been successfully formulated [23].

## 3. CONCLUSION

FDC-ODTs have the advantages of providing better patient compliance and increased efficacy, especially in dysphagic patients and the patients on multiple drug therapy. However, it appears in the Orange Book that only FDC-ODTs containing carbidopa and levodopa have been approved by the FDA. In addition, more studies are needed to demonstrate the safety and efficacy of FDC-ODTs, as many FDCs' safety, efficacy, and rationality are still questionable.

### Conflict of Interest

Author has no personal financial or non-financial interests.

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Review

# Type II DM Candidate Biomarkers in the Framework of Obesity, Exercise, and Diet

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**ABSTRACT:**
Biomarkers used in the early diagnosis and treatment of prediabetes and diabetes, which are based on obesity and metabolic syndrome, are inadequate due to the complexity of the etiology of diabetes, and studies for developing new biomarkers for diabetes and/or determining an early diagnosis biomarker are ongoing in the scientific world. Since obesity can be prevented to a certain extent by long-term diet and exercise, it can be considered that the long-term and periodic investigation of a group of cytokines related to exercise and body fat mass may be meaningful. For example, the cytokines irisin (a myokine released from the muscle by exercise) and adiponectin (adipokine, an indicator of decreased body fat mass have similar effects in terms of antiobesity and antidiabetic effects. Therefore, high levels of adiponectin and irisin can be considered in diabetic patients, and delayed micro and macrovascular complications of diabetes due to obesity and metabolic syndrome can be considered. On the other hand, adiponectin levels are low in diabetes and obesity, and these patients generally have low irisin levels due to being sedentary. It is a common belief that for overweight individuals, other than morbid obese people, and prediabetic and diabetic individuals, candidate biomarker (s) from cytokines to monitor the effectiveness of diet and exercise can generally be detected. It is known that adipokines are involved in the pathogenesis of obesity and Type 2 diabetes mellitus together with pro-inflammatory cytokines and can be used as prognostic markers and may be involved in the therapeutic approaches to obesity-related Type 2 DM. During the long-term latent course of diabetes at the prediabetic stage, it is important to identify an early diagnostic biomarker.

**Keywords :** Adiponectin, biomarker, diet, exercise, irisin, obesity, type II DM.

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## 1.INTRODUCTION

Overweight status and obesity are defined using body mass index (BMI). A BMI of 25 to 29.9 is considered overweight, and a BMI ≥ 30 is considered obese [1] . Obesity is an important risk factor for the development of Type II DM, hypertension, obstructive sleep apnea and heart disease. It is known that Type II DM develops in approximately

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80% of all obese people. In adults, elevated BMI due to increased adiposity is known to lead to adiposity (ectopic adiposity in liver and muscle), which leads to various health risks such as diabetes and cardiovascular diseases [2] .

Diabetes is a current health problem in developed and developing countries. The World Health Organization (WHO) report on diabetes states that the number of adults living with diabetes has almost quadrupled since 1980, reaching more than 400 million people. The prevalence of diabetes has reached epidemic proportions and is expected to reach approximately 629 million by 2045 [3]. In 2012 alone, 1.5 million people died worldwide due to diabetes, which can lead to complications such as heart attack, stroke, blindness, kidney failure and lower extremity amputation. WHO estimated that the number of diabetics in Turkey, which was approximately 3 million in 2000, will reach 6.5 million in 2030, but this value estimated for 2030 was reached in 2013 in our country [4]. Today, this figure is over 7 million. According to the data of the Ministry of Health in 2017, the prevalence of diabetes in our country is 9.1%. It is noteworthy that this rate is considerably higher than the 5.1% prevalence of European Union countries. Diabetes-related death rate in our country increased by 11% from 2002 to 2017 and ranked 9th among the causes of death in our country [5]. Years of life lost due to diabetes increased by 29.2% between 2002 and 2017 in our country, ranking 10th among diseases.

During the obesity-insulin resistance-metabolic syndrome connection process, normal functions of adipocytes are impaired, and an increase in the synthesis of proinflammatory cytokines secreted from adipocytes and a decrease in the synthesis of anti-inflammatory cytokines occur. This increase in inflammation contributes to the formation of diabetes. Studies on metabolic changes in diabetes, understanding the mechanisms by which various hormones and neurotransmitters affect energy balance, and studies on developing new biomarkers and new treatment approaches for diabetes are carried out with interest by researchers all over the World [6]. As a result of these studies, a number of biomarkers that can be an indicator for the estimation of DM risk have been proposed to date. In addition to blood glucose and glucose tolerance test, the most prominent ones are; hemoglobin A1c (HbA1c), parameters showing blood lipid profile, inflammatory markers, adiponectin, liver enzymes and fetuin-A [7]. However, most biomarkers fall short in the face of the complexity of Type 2 DM etiology [8]. The results of some promising studies on the use of adipokines as an early biomarker in the diagnosis of Type II DM can be summarized as follows:

- Serum adiponectin levels can be used as a strong risk marker of new-onset prediabetes in healthy Caucasians and blacks (parents with a history of Type II DM) (a cohort study) [9].

- Adiponectin levels are lower in prediabetic patients than in healthy individuals; shows that circulating adiponectin levels begins to decline before diabetes occurs (a meta-analysis) [10]
- High serum adiponectin levels appear to be associated with a reduced risk of Type II DM in different populations (a meta-analysis) [11]
- Elevated plasma adiponectin levels are associated with a reduced risk of Type II DM and a subsequent reduction in cardiovascular risk [12]

Irisin is secreted mainly from skeletal muscle with the effect of exercise and is a thermogenic protein that converts white adipose tissue to brown adipose tissue and releases energy in the form of heat. Irisin makes significant changes in subcutaneous WAT. As a result, it stimulates the expression of UCP1, provides WAT-BAT conversion and performs thermogenesis in the formed BAT cells. This results in a significant increase in total body energy expenditure and the breakdown of obesity-related insulin resistance. According to the results of many studies revealing the relationship between irisin and glucose metabolism, it has been stated that irisin breaks insulin resistance in obese and Type II DM, and irisin can be considered as an alternative molecule for the treatment of diseases such as obesity and Type II diabetes with exercise [13].

Breaking the cycle between obesity, metabolic syndrome and Type II DM is mainly through diet and exercise. Dietary restriction (and accompanying weight loss), one of the two most important factors, reduces total fatty acids. The lipid composition of the diet stimulates the gene expression of proteins involved in fatty acid oxidation and fat burning via PPARs and other transcription factors [14].

The second important factor, exercise, activates AMPK like adiponectin; AMPK inhibits the synthesis of fatty acids and activates fatty acid degradation. It increases AMP by increasing the use of ATP. This, like adiponectin, provides energy homeostasis [14]. Irisin increases gene expression of the UCP1 protein in white adipose tissue. Irisin also stimulates the conversion of white adipose tissue to brown adipose tissue [13].

The biochemical mediator AMP-activated protein kinase (AMPK) plays a central role in energy metabolism. Although the body's main energy sources are glucose and triacylglycerols, the energy metabolism management of AMPK is based on TAG storage and burning [15]. Adiponectin, an adipokine, is secreted from adipose tissue in response to decreased body fat mass. Adiponectin causes the activation of the AMPK molecule with a mechanism similar to the effect of exercise and is effective in many metabolic events through the AMPK molecule. These metabolic events; It can be summarized as increasing insulin sensitivity, increasing fatty acid oxidation, increasing glucose uptake in muscle, decreasing gluconeogenesis in the liver, increasing cardiac glycolysis and suppressing synthesis reactions in general. It is

known that the level of adiponectin is low in obese and Type 2 DM individuals, and high in patients with anorexia nervosa [16].
Understanding biochemical pathways and connections in the framework of obesity, exercise, diet will enable the development of new biomarkers for Type II diabetes.

**Conflict of Interes**
Author has no personal financial or non-financial interests.

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