T.R.N.C.
NEAR EAST UNIVERSITY
HEALTH SCIENCES INSTITUTE

INVESTIGATIONS OF THE EFFECTS OF FLUID BED GRANULATION PROCESS PARAMETERS ON THE GRANULATION AND TABLETING PROPERTIES OF OXCARBAZEPINE BASED FORMULATIONS

Chem. Melek Sena GEYİK

M.SC. THESIS IN
PHARMACEUTICAL TECHNOLOGY PROGRAM

NICOSIA
2010

T.R.N.C.
NEAR EAST UNIVERSITY
HEALTH SCIENCES INSTITUTE

INVESTIGATIONS OF THE EFFECTS OF FLUID BED GRANULATION PROCESS PARAMETERS ON THE GRANULATION AND TABLETING PROPERTIES OF OXCARBAZEPINE BASED FORMULATIONS

Chem. Melek Sena GEYİK

M.SC. THESIS IN
PHARMACEUTICAL TECHNOLOGY PROGRAM

THESIS ADVISOR
Ass. Prof. Dr. Metin ÇELİK

ASSOCIATE THESIS ADVISOR
Ass. Prof. Dr. Yıldız ÖZALP

NICOSIA
2010

To Institute of Medical Sciences,

This study was accepted by our jury as a M.Sc. Thesis in Pharmaceutical Technology Department.

Foreman: Prof. Dr. Yılmaz ÇAPAN
(Hacettepe University)

Advisor: Ass. Prof. Dr. Metin ÇELİK
(Near East University)

Member: Ass. Prof. Dr. Yıldız ÖZALP
(Near East University)

APPROVAL:
This thesis was approved by above mentioned jurors in accordance with respective articles of Near East University Postgraduate Education and Test Regulation and was accepted by the Institute Board decision.

Prof. Dr. İhsan ÇALIŞ
Institute Manager

ACKNOWLEDGEMENT

I would like to thank my thesis advisor Assistant Prof. Dr. Metin Çelik and my associate thesis advisor Assistant Prof. Dr. Yıldız ÖZALP who shared their knowledge and experience with me and who always supported me throughout every step of this thesis.

I would like to thank Biofarma Pharmaceutical Ind. Co. Inc. for providing convenience and support in usage of all devices and equipments, supplying active ingredient and excipients, especially Yıldız ÖZALP, department coordinator, my formulation process development department colleagues Bikem ÇETİN, Mahmut Ali ERMEYDAN, Servet ÖNCÜ and Hasan TAŞKIRAN, Filiz YAŞMUT who provided support in analytical parts of my studies, my friends in method development department Selim Yavuz ENGİN and Esme YILMAZ who helped me with my analysis throughout my thesis studies, and my valuable directors Hatice ÖNCEL and Figen ÖZGEL who supported me to join Master Program and provide continuity throughout my thesis studies.

Lastly, I offer my regards and blessings to my family who supported me in any respect during the completion of the project.

ÖZET

Geyik, M. S. Akışkan Yataklı Kurutucu Sistem (Fluid Bed) Proses Parametrelerinin Okskarbazepin İçeren Granül Ve Tabletlerin Özellikleri Üzerine Etkisinin İncelenmesi. Yakın Doğu Üniversitesi Sağlık Bilimleri Enstitüsü Farmasötik Teknoloji Programı, Yüksek Lisans Tezi, Lefkoşa, 2010.

Bu çalışmanın amacı düşük çözünürlüğe sahip bir etkin madde bazlı formülasyonun akışkan yatak proses granülasyon parametrelerinin ilaç salım karakterleri ve diğer fiziksel özellikleri üzerine etkisini incelemektir.
Bu çalışmada düşük çözünürlüklü model etkin madde olarak Okskarbazepin seçilmiştir ve bu etkin maddenin 3 farkı partikül büyüklüğü (3 µm, 45 µm, 70 µm) içeren formülasyonu Hüttlin alttan püskürtmeli akışkan yatak granülatör kullanılarak granül edilmiştir.
Değişken proses parametreleri, giriş hava sıcaklığı, giriş hava debisi, spreyleme oranı ve spreyleme basıncıdır. Granülasyonunda sadece 45µm ve 70 µm ortalama partikül büyüklüğü içeren Okskarbazepin formülasyonları Manesty XSpress kullanılarak tabletlenmiştir. Tabletler, ortalama tablet ağırlığı, dağılma zamanı, nem, sertlik, aşıma, miktar tayini ve çözünmenı içeren çeşitli fiziksel ve analitik kontrollere tabii tutulmuştur.
Çözünme testleri, saf su ve yüzey aktif madde içeren saf su ortamlarında gerçekleştirilmiştir. Bu testler değişken akışkan yatak proses parametrelerinin en yüksek etkisinin 45 µm ortalama partikül büyüklüğünde Okskarbazepin içeren formülasyonun ilaç salınım özelliklerini üzerinde olduğunu göstermiştir.
Okskarbazepin bazlı formülasyona yüzey aktif madde ilavesinin etkisini göstermek amacı ile baz formülasyona %1 sodyum dodesil sülfat eklendiğine saf suda 2 saat sonunda %99.7 etkin madde açığa çıkmıştır.

Anahtar Kelimeler: Akışkan yatak granülasyonu, okskarbazepin, proses parametreleri, partikül büyüklüğü, düşük çözünürlüğe sahip etkin madde

ABSTRACT

Geyik, M. S. Investigations of the effects of fluid bed granulation process parameters on the granulation and tableting properties of oxcarbazepine based formulations. Near East University Health Sciences Institute M.Sc. Thesis in Pharmaceutical Technology Program, Nicosia, 2010.

The goal of this study was to investigate the effects of fluid bed granulation processing parameters on the drug release characteristics and other physical properties of a poorly soluble drug based formulation.
In this study, Oxcarbazepine was selected as the model poorly soluble drug and the formulations containing three different particle sizes (d(0,5): 3 µm, 45 µm, 70 µm) of this drug were granulated using a Hüttlin bottom spray fluid bed granulator. The variable process parameters were inlet air temperature, airflow, spray rate and air pressure. Only formulations containing Oxcarbazepine with 45µm, 70µm mean particle size were resulted in granulations which were then compressed using a Manesty Xspress. Tablets were subjected to various physical and analytical post compaction tests including average tablet weight, disintegration time, hardness, friability, assay and dissolution.
The dissolution tests were performed in both distilled water alone and distilled water containing surfactant. These tests showed, that varying the fluid bed process parameters showed its highest impacted the drug release properties of the formulations containing Oxcarbazepine with a mean particle size of 45 µm.
When 1% sodium dodesil sulphate was added to the base formulation in an attempt to show the effects of adding a surfactant to the Oxcarbazepine based formulation, 99,7% drug dissolved in distilled water in two hours.

Key Words: Fluid bed granulation, oxcarbazepine, process parameters, particle size, poorly soluble drugs

TABLE OF CONTENTS **Page**

LIST OF SYMBOLS AND ABBREVIATIONS

ACN	Acetonitrile
API	Active Pharmaceutical Ingredient
BD	Bulk Density
C	Concentration
CI	Carr's Index
DMF	Drug Master File
DSC	Differential Scanning Calorimeter
EP	European Pharmacopeia
F	Friability
FB	Fluidized Bed
FDA	Food and Drug Administration
H	Hausner ratio
HPLC	High Pressure Liquid Chromatography
HSM	High Shear Mixer
ICH	International Conference on Harmonization
IR	Infrared
KH_2PO_4	Potassium Dihydrogen Phosphate
KOH	Potassium Hydroxide
LM	Lactose Monohydrate
MeOH	Methanol
MCC	Microcrystalline Cellulose
OX	Oxcarbazepine
PDR	Physicians' Desk Reference
PVP	Polyvinyl Pyrrolidone
rpm	Revolutions per minute
SDS	Sodium Dodecyl Sulfate
TD	Tapped Density
UV	Ultraviolet

LIST OF FIGURES

LIST OF TABLES

1. INTRODUCTION

Pharmaceutical Technology developed widely on the subject of drug formulation design especially on the development of drug formulation designs with high industrial viability intended for the increasing of solubility of low soluble active ingredients in immediate release solid dosage forms.

Since it is known to increase the solubility with the choice of different equipment and technology in addition to the excipients used and formulation changes, there is a great concern on this subject in industrial drug development.

It is possible to increase the solubility of low soluble active ingredients in a certain ratio with the solid drug production technologies and the controls of critical process stages of these technologies.

In the mean time, it is well known that particle size, particle shape and specific surface area of an active ingredient have an influence on the solubility. Capan (2004)

In addition to the active ingredient, the influence of physicomechanical properties of the granule on the dissolution of drug product is in the scope of this thesis. Baykara (2004)

For that purpose, the usage of low soluble Oxcarbazepine active ingredient with different particle sizes, changes in the process parameters of production technology and the demonstration of formulation changes on the degree of influence on dissolution are the objective of this thesis study.

2. GENERAL INFORMATION

2.1. Theory and Technology of Granulation

Granulation, being an industrial terminology according to Ennis (2007), in general terms, is regarded as procedure of stirring of powder mixture with foreign intervention, agglomeration and later on, size change or size extension of that powder.

In our study, tableting technology is explained in separate headings, by knowing granulation techniques and the granulation as an intermediate step in tablet production.

According to Fonner et al. (1981), characteristics of granule should be understood well since tablets are obtained with the granules. These characteristics are summarized as follows:

- Particle size measurement and interpretation
- Particle shape
- Surface area
- Density
- Robustness and friability
- Electrostatic properties
- Flow properties
- Consolidation and ease of handling

According to Birudaraj et al. (2007), although the granule properties have an influence on dosage form, chemical and physical properties directly affect the compression of tablet.

Purpose of granulation according to Khatry (2010) is summarized below:

- Enhance flowability
- Enhance dispersion
- Enhance dissolution or reduce the activation energy of highly soluble drug substances
- Enhance stability
- Avoid segregation
- Enhance compressibility
- Reduce formation of dust

2.1.1. Granulation Procedures and Equipments

According to Kristensen (1988), Kristensen et al. (1985), granulation process, to adjust the particle size of powder mixture by agglomeration, is a required process for dosage forms, especially for tableting technology in pharmaceutical industry.

According to Parikh (2008), it is expected from the material that is compressed into tablets, to have sufficient humidity, density and compressibility. According to Çelik (2008), the properties of the powder to be compressed are very crucial for production at rotary type tableting machines.

As a conclusion, general purpose of granulation is to enhance the flowability and compressibility of a powder mixture. Rupp (1977)

In addition to these, according to Brittain et al. (1991) followings are required;

- A powder mixture with specific density and reduction of powder formation
- A powder with narrow particle size distribution
- Improved dissolution property of finished product, tablet

According to Parikh (2008), granulation properties depend on the surface area and size of the components in the formulation.

According to Strahl (2004), at pharmaceutical industry, in order to disperse drug substance in a formulation homogenously, to mix, adjusted the density and to fill by gaining good flowability properties or to compress, there are two granulation processes for classic solid dosage forms. These are wet and dry granulation processes. However, hot-melt granulation is another process used according to the goal.

Each process in principle has differences in terms of granulation equipment and excipients used.

2.1.1.1. Hot-Melt Granulation

According to Wong et al. (2007), product following the process is called hot-melt agglomerate while process is named as hot-melt granulation or hot-melt pelletization. The basic principle of this process is similar to wet granulation.

At this process, which has applications in industries other than pharmaceutical, the most important topic is to have a uniform final shape by melting materials with binding properties (PEG 2000 – 10000, paraffin etc) and without using solvent. Several studies stated the findings that by using this technology, dissolution and density of drugs products in forms of granule, capsule and tablet are enhanced.

The advantages and disadvantages of this process are summarized below:

as binder, process steps are short, particles are mechanically stabile, particles with narrow size distributions are achieved, used for taste masking and allow developing controlled release dosage forms.

Requires high energy input, not being appropriate for materials sensitive to heat, not being able to use the substances with low melting point and process optimization for substances with variable temperature to be hard are acknowledged as disadvantages.

Commonly high-shear type mixers are used for this process, however usage of fluid bed granulators and coating pans are also stated.

2.1.1.2. Granulation

First approach of granulation is to agglomerate the powder, to provide pellets by compression or compaction.

According to Parikh (2008), agglomeration of powder mixture is provided by means of pressure-power (tableting machine or compactor). Thus, powder mixture is obtained as compacts forms like layers or slugs or tablets.

According to Baykara (2004), examples with this granulation technique are as follows;

- To compress slug tablets, then to sift through dry sieves after crushing them
- To get compact powder by a compactor and then to sift through dry sieves within the same system

With the equipment shown in figure 2, powder is fed from the top, compacted between the disks rotate reversely and the compacted powder is sieved from a specified size sieve that provides a specified flow property is collected from the bottom.

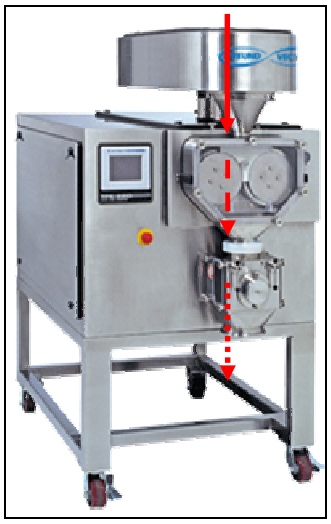


Figure 2.1. Compactor for dry granulation

Van der Waals power that holds the powder mass together and compressibility of powder are essential for this process where different equipments used (for compaction and sieving). With this design, if a binder should be used, this is known as dry binder.

2.1.1.3. Wet Granulation

According to Kristensen and Hansen (2006), wet granulation occupies an important place in the pharmaceutical.

According to Kristensen and Schaefer (1987) wet granulation is a process where small particles are agglomerated as partially stable bigger particles or aggregated.

With this granulation process, the need of a liquid substance (water, alcohol), binder, equipments with different properties (mixer, sift, dryer) and may be other excipients, is essential.

According to Fonner et al. (1981), binding of particles to each other during wet granulation is formation of liquid bonds in the agglomerates getting bigger with humidity during wetting process.

It is possible to classify binding materials under three groups; According to Hamed et al. (2007)

- Natural polymers: Starch, pregelatinized starch, gelatin, acacia, alginic acid, sodium alginate
- Synthetic polymers: Polyvinylpyrrolidone (PVP), Methyl cellulose (MC), Hydroxymethyl cellulose (HPMC), Sodium carboxymethyl cellulose (Sodium-CMC), Ethyl cellulose (EC).
- Sugar based: Glucose, Sucrose, Sorbitol

The factors determine the efficiency of the binders can be classified under two main groups.

- Properties of drug substance and excipient
    - Particle size
    - Solubility

- Properties of binder and solvent system
    - Mechanical properties of binder
    - Interaction between binder and surface
    - Viscosity and surface tension of binder solution
    - Properties of binder

2.1.1.3.1. Wet Granulation with Shear Type Equipments

According to Parikh (2008), the equipments with mechanical mixers used for wet granulation are divided into 3 main groups per shearing strengths; Low-shear, high-shear and medium-share or continuous granulators.

For continues granulator many names are used in the literature; rotary processor Holm et al. (1996), rotary fluidized bed Turkoğlu et al. (1995), Rotary fluidized bed granulator Jaeger and Bauer (1982), Rotor fluidized bed granulator Leuenberger et al. (1990), Fluid bed roto granulator Vuppala et al.

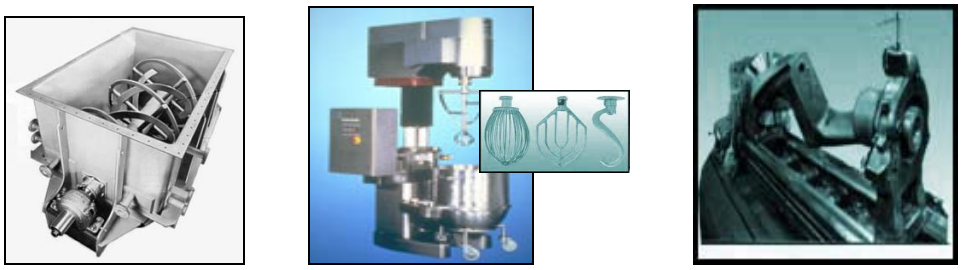
Table 2.1. Mechanical mixer systems and equipment models

Shear tip mixer/granulator group	**Examples of different granulator**
Low-shear granulator	Twin shell or double cone, planetary mixer, ribbon blenders, sigma blade.
High-shear granulator	Loedige type system with bottom mixer, GRAL type system with top mixer
Medium-shear / Continuous granulator	Roto type system with top mixer (Fluid-bed) system

Low-shear mixer; Chirkot and Propst (2007), is the general name given for those generally having agitation speed applied to powder, sweep volume of powder or pressure in the bed are less than high shear.

When the detailed literatures Hausman (2004), Parikh (2007), Lieberman et al. (1990) are reviewed, it is said that low-shear granulators produces granules with different properties than others.

High-shear mixers; Scahaefer et al. (1987), Schaefer et al. (1986), Giry et al. (2009), shape of mixer binder is generally cylinderic or conic. In the mixer there is an impeller with 3 blades and a chopper other than the mixer. Depending on the mixer position, upper or lower, the copper location in the binder can differ. The figures of known low-shear and high shear type mixers are shown below.



(a) **(b)** **(c)**

Figure 2.2. Low-shear equipment models
Ribbon blender (a), planetary mixer (b) sigma knife edge mixer (c).

(a) **(b)**

Figure 2.3. High shear equipment models
Bottom mixer and vertical shear equipment (a)
Top mixer and top shear equipment (b)

Different process techniques affect the physical properties of the granule, Faure et al. (2001). A granule property in the end affects that of finished product.

Giry et al. (2009), though these granulators can perform the same application, the final products may be very different from each other. The differences are caused by the different process requirements of each granulator.

Gokhale and Sun (2007), after pouring the powder mixture into the mixer, at the mixing step homogenous mixture should be obtained. Time to reach homogenous mixture depends on the unit mass and the amount of movement property of the unit. At the same time, different homogeneity level changes from one to the other mixer.

The mixing step is followed by the addition of binder solution and type and amount of binder depend on the type of mixer chosen for wet granulation. This was

shown by Nouh (1986), the differences of particle size and the density granule at the study using different binders in sulfadiazine formulation by means of fluid bed and classical procedure. Sheskey and Williams (1996) performed niacin amide formulation by using low-shear and high-shear granulators and no significant difference was report for the apparent density.

Generally it is known that; the bulk density values obtained by the processes using low-shear tumbling granulator are in between that of using fluid bed ve high-shear granulator. When a similar evaluation is considered for morphology of the granule, it is known that more porous granules are obtained with low-shear granulator than with a high –shear granulator, Hausman (2004).

To understand the granulation process is important since after all it affects the behavior of the tablet or capsule. If we summarize the factors affect the granulation according to Leuenberger (1982), Badawy and Hussain (2004), Knight et al. (2000), Badawy et al. (2010), Holm et al. (2001), Knight (1993), Kristenen (1988):

- Equipment type
- Mixture type and position
- Chopper blades and speed
- Type of binder
- Amount of binder
- Time of binder addition
- End point of granulation
- Mixing speed
- Mixing time

Other than these, there are also API, formulation and environmental factors.

Sherif and other (2000), after these steps, there are the sieving of the wet mass, drying, determination of flowability and density of dried mass by sieving steps.

After granulator, type of drier, properties of sieving/grinding equipment are the other critical equipments that influence the properties of powder.

2.1.1.3.2. Wet Granulation with Fluidized Bed Dryer System (Fluid Bed)

Fluidization theory and technology was taken part in the literature years ago, Othmer (1956), Zenz and Othmer (1960), Scott others (1963). Fluid bed technique is used for drying Vanecek et al. (1966), for coating Robinson et al. (1968) and lately for granulation in the pharmaceutical. The first use of fluid beds for the production of granules of tablet was mention by Scott et al. (1964).

Fluid bed granulation is a complex process that granule properties may affect both product and process parameters. Product parameters include parameters of excipients, physicochemical properties (particle size, surface area, solubility in water etc), type of binder and concentration of binder. According to Scahaefer and Worts (1977), Scahaefer and Worts (1978), process parameters are inlet air temperature, inlet air pressure, spraying pressure, binder addition rate, and nozzle height and spraying angle.

Powder mixture is exposed to a pressured air from the bottom to the up of the granulator at fluid bed granulation. Binder is sprayed to the bottom of the powder bed in reverse direction. Granules are formed by sticking of liquid particles on the solid particles. Partial drying process is continued constantly. Process is continued till the powder agglomerates under a humidity balance. Balance may not be constant, therefore attention should be paid. The last drying step is started after the end of binder spraying by hot air flow.

If we explain the development of fluid bed granulation theory; fluid bed process was used to coat tablets first by Wurster (1960) by means of air suspension technique, and the tablets that were compressed by air suspension technique prepared with the appropriate granules and drying was reported.

Scott et al. (1964) by using a fundamental engineering approach reported the theory and design factors of the process by applying mass and thermal energy

balances. They widen this application to a pilot production model of 30 kg capacity for a mass and continuous process. Process variables like air flow rate, process temperature and fluid flow rate were studied. Later on, Contini and Atasoy (1966) reported the process details and the advantages of fluid bed process at continuous stage.

Wolf (1968), discussed the main structural properties of fluid bed components, Liske and Mobus (1968) compared fluidized bed and conventional granulation process.

All results show that the material processed with fluid bed granulator has finer and more flowable homogenous granules than that of with conventional wet granulation procedure and thus tablets, compressed by using granules having these properties, having with more strong and fast disintegration were obtained.

One of the most common unit process used at Pharmaceutical industry is fluid bed process. To upscale by using fluid bed granulation, functionality of equipment, theoretical approach of fluidization, interaction of excipients and all supplementary variables affects the granulation process should be understood well.

2.1.1.3.2.1. Equipment Properties

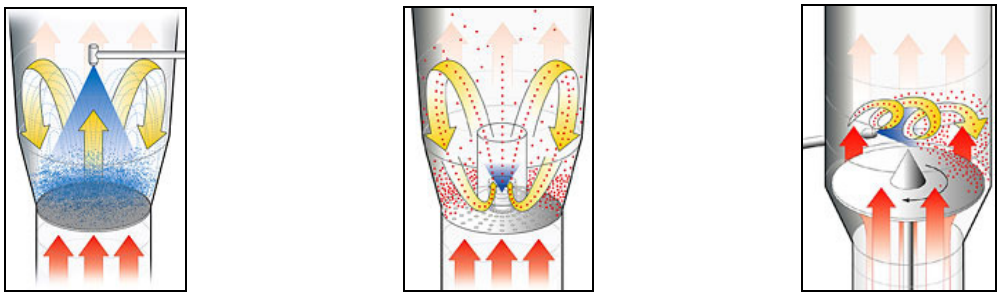
As with any granulating system, in fluid bed granulation processing, the goal is to form agglomerated particles through the use of binder bridges between the particles.

According to Parikh (2007), to achieve a good granulation, the particles must be uniformly mixed, and the liquid bridges between the particles must be strong and easy to dry. Therefore, this system is sensitive to the particle movement of the product in the unit, the addition of the liquid binder, and the drying capacity of the air.

The components that build up a fluidized bed system are presented below.

- Air handling unit and air inlet
- Pre-filter and heater fan
- Product container and dust collector filter
- Spray nozzle
- Disengagement area and process filters
- Exhaust blower or fan
- Control system

FB systems have different types with respect to the location of spray nozzle where binding solution is sprayed over the powder mass suspended in the air. These FB systems are known as top spray, bottom spray, and tangential spray Diedrich et al. (2009). Schematic representation is presented below.



(Top spray) Bottom Spray (Wurster coating) (Tangential Spray)

Figure 2.4. Schematic drawing of 3 different fluidized bed granulation systems considering spraying point location.

The FB system used in this study is a system, known as discjet technology, where spraying system is localized in the bottom air distribution filter. In this bottom spray system, spraying nozzle is located in the disc shaped metal table in a tangential way, Erdil et al. (2009). In addition, this metal disc had such characteristics which provided air filter flow with laser-cut line-shaped thin grooves. Air flowing through these grooves does not move from bottom to top inside the product container, yet it moves producing a cyclone inside the container. Thus, dust mass spirals in the container with this air movement and at the same time, is wetted by the spray system from the bottom and rapidly dried. Patented components which differ the system used from other known systems are shown in Figure 2.5.

(a) **(b)** **(c)**

Figure 2.5. Laser etched perforated metal disc of fluidized bed system with discjet technology and spraying nozzles that can be fixed on (a), long dust collector filter system (b), spraying system with micro climate system (b)

2.1.1.3.2.2. Significant Factors That Affect the Process

Each phase of the granulation process must be controlled carefully to achieve process reproducibility.

Knöll (2010) is especially affected from mixing phase, air flow rate, and air volume. When the binder liquid is sprayed into a fluidized bed, the primary particles are wetted and form together with the binder, relatively lose and very porous agglomerates.

The liquid binder sprayed into the bed should be relatively large in quantity, compared with that used in high or low shear granulation processes. During spraying, a portion of the liquid is immediately lost by evaporation, so the system has little tendency to pass beyond the liquid bridge phase.

According to Schaefer and Woerts (1978b), Gao et al. (2002), particle size of obtained granules can be controlled to a certain extent by adjusting atomization air pressure, inlet airflow, inlet air temperature, the amount of binder, and spray rate. The mechanical strength of the particles depends principally on the composition of the primary product being granulated and the type of the binder used.

Critical variables for fluid bed granulation system can be classified as process, formulation and equipment.

- **Process related variables**

There are a number of process variables that control the granulation. These process parameters are related to each other and the desired product can only be prepared by well understanding the relationship between these interdependent parameters.

If these parameters are summarized:

- Process inlet air temperature
- Atomization air pressure
- Fluidization air velocity and volume
- Liquid spray rate
- Nozzle position and number of spray heads
- Product and exhaust air temperature
- Filter porosity and cleaning frequency
- Bowl capacity

Significant variables of process parameters and their impact on the fluid bed granulation process are summarized in Table 2.2.

Table 2.2. Significant variables and their impact on fluid bed granulation process

Process parameter	Impact on process
Inlet air temperature	Higher inlet temperature produces finer granules and lower temperature produces larger stronger granules
Humidity	Increase in air humidity causes larger granule size, longer drying times
Fluidizing air flow	Proper airflow should fluidize the bed without clogging the filters. Higher airflow will cause attrition and rapid evaporation, generating smaller granules and fines.
Nozzle and position	A binary nozzle produces the finest droplets and is preferred. The size of the orifice has an insignificant effect, except when binder suspensions are to be sprayed. Optimum nozzle height should cover the bed surface. Too close to the bed will wet the bed faster producing larger granules, while too high a position will spray dry the binder, create finer granules, and increase granulation time.
Atomization air volume and pressure	Liquid is atomized by the compressed air. This mass-to-liquid ratio must be kept constant to control the droplet size and hence the granule size. Higher liquid flow rate will produce larger droplet and larger granule and reverse will produce smaller granules. At a given pressure an increase in orifice size will increase droplet size.
Binder spray rate	Droplet size is affected by liquid flow rate, and binder viscosity and atomizing air pressure and volume. The finer the droplet, the smaller the resulting average granules.

- **Formulation related variables**

  - Properties of primary material

Ideally, the article size properties desired in the starting material can be described as a low particle density, a small particle size, a narrow particle size range, the particle shape approaching spherical, a lack of particle cohesiveness, and a lack of stickiness during the processing.

Properties such as cohesiveness, static charge, particle size distribution, crystalline and amorphous nature, and wettability are some of the properties which have an impact on the properties of the granules formed.

The cohesiveness and static charges on particles present fluidization difficulty.

The same difficulties were observed when the formulation contained hydrophobic material and a mixture of hydrophilic and hydrophobic materials.

  - Low-dose drug content

Wan et al. (1992) studied formulations of low-dose drug content. They concluded that the randomized movement of particles in the fluid bed might cause segregation of the active ingredient and that uniform drug distribution was best achieved by dissolving the active ingredient in the granulating solution.

  - Binder

Different binders have different binding properties, and the concentration of the individual binder may have to change to obtain similar binding of primary particles in the inner phase. Thus, the type of binder, binder content in the

formulation, and concentration of the binder have a major influence on granule properties. These properties affect friability, flow, bulk density, porosity, and size distribution.

- Binder solvent

In most instances, water is used as the solvent. The selection of solvent, such as aqueous or organic, depends on the solubility of the binder and the compatibility of the product being granulated. Different solvents have different heats of vaporization. Generally, organic solvents, due to their rapid vaporization from the process, produce smaller granules than the aqueous solution.

- **Equipment related variables**

- Process air

To fluidize, and thus granulate and dry the product, a certain quantity of process air is required. The volume of the air required will vary based on the amount of material that needs to be processed.

- Air distributor plate

Perforated air distributor plate covered with the fine stainless steel screen provides an appropriate means of supplying air to the product.

- Pressure drop

A blower with appropriate pressure drop will fluidize the process material adequately. However, a blower without enough pressure drops will not allow proper fluidization of the product, resulting longer process time and improper granulation.

- Process filters

To retain entrained particles of a process material, process filters are used. These filters are cleaned during the granulation process. To avoid process interruptions, a multishaking filter bag arrangement is desired, where the granulation process is continuous. Generally, filters should be cleaned frequently during the granulation step, to incorporate the fines back in the granulation.

- Other miscellaneous equipment factors

Granulator bowl geometry is considered to be a factor that may have an impact on the agglomeration process.

2.1.2. General Properties of Granule

The choice of granulation technique depends on physical and chemical stability of the final dosage form, intended biopharmaceutical performance, and is occasionally limited due to available equipment.

It is not so easy to compare the granules obtained from the usage o FB and granulators. The reason behind this is the difficulty of successful application of the same formulation with every equipment.

However, it is seen that two properties are widely reported when an overall evaluation is made. These properties are bulk density and particle size. Thereby, comparisons are in progress for these properties.

Physical property characterization of pharmaceutical granulations has been extensively reported in literature.

Physical characterization can be performed at molecular, particulate, and bulk (macroscopic) levels.

From the terminology cited by Brittain et al. (1991), molecular properties are associated with individual molecules, particulate properties are considered as properties that pertain to individual solid particles, and bulk properties are those that are associated with an assembly of particulate species.

Most reports in pharmaceutical literature cover characterization of bulk properties.

In addition to that, chemical properties are equally important to physical properties due to their impact on specifications of a dosage form such as content uniformity, chemical purity, and in vitro performance.

Dosage form performance is assessed through a characterization program in which drug dissolution, bioavailability, chemical stability, and manufacturing ruggedness is taken into account.

The effect of granule size on the dissolution performance could affect the outcome of such a bioequivalence study.

Particle size and its dependence on granulation process parameters can influence dissolution and ultimately in vivo performance.

2.1.2.1. Tests Performed on Granules

Dosage form performance is strongly dependent to the properties of granule mass. Since physical properties of bulk mass contain results that will be evaluated in tablet technology, the most important tests for investigators are summarized.

- Particle morphology

Particle morphology can be assessed using optical microscopy. Samples of granulation can be evaluated directly under a microscope. Another technique is scanning electron microscope (SEM).

Particle shape can be quantified by different methods. One popular method is Heywood coefficient. The effect of particle shape on bulk powder properties has been illustrated by Rupp (1977). Packing of powder in the bulk becomes more efficient as the shape factor or loss in sphericity increases. The flow rate becomes worse wit loss in sphericity.

- Particle size distribution

Particle size distribution can be measured by sieve analysis, laser light scattering, or optical microscopy. Light-scattering techniques are generally not applied to granulations due to the large size distribution of granules. Dry-sieve analysis and microscopy are generally the most popular methods for determining size distribution of granules. Microscopy provides a more exact measurement of size.

Dry-sieve analysis is the easiest and the most convenient method. The granulation is placed on top of a stack of five to six sieves which have smaller-sized openings from top to bottom. The stack is vibrated, and the particles collect on top of the sieves. The data are obtained by calculating the amount of particles retained on the sieves.

- Surface area

Granulation properties are mainly dependent on the size and surface area of particles and granules. The surface area of a granule or particle can also affect the dissolution rate of a solid. Gas adsorption is the most common method to determine the surface area, although liquid penetration methods have also been proposed. In one of the methods developed by Brunauer, Emmet and Teller, called the BET

method, an inert gas is adsorbed onto the surface of a solid at low temperature and then desorbed at room temperature.

Another method that has been proposed for measuring the surface area of powders is known as air permeability.

- Granule porosity

Mercury intrusion methods are routinely applied in the determination of pore size and distribution to both granulations ad tablet compacts.

Farber et al. (2003) studied the porosity and morphology of granules by two different techniques, x-ray computed tomography (XRCT) and mercury porosimetry. These authors concluded that XRCT is less accurate in the determination of total porosity when compared to mercury porosimetry. However, XRCT provided detailed morphological information such as pore shape, spatial distribution, and connectivity.

- Granule flowability and density

According to Davies and Gloor (1971), Menon et al. (1996), flow behavior of granules is affected by multiple variables such as physical properties of granulation and the equipment design used for handling during a given process.

Specific volume is one of the properties of a powder that is believed to affect powder flowability. Specific volume is determined by pouring a known mass of blend into a graduated cylinder. The volume is read off the cylinder and the specific volume is calculated by dividing the volume by mass of the blend. Bulk density is calculated by dividing the mass to volume. The compressibility of a blend can also be determined at this time. The graduated cylinder is vibrated on a shaker for a time period. This vibration reduces the volume that the blend occupies in the graduated cylinder and the percentage compressibility is calculated. The percentage compressibility is known as Carr’s index. According to this index; when the compressibility is higher, flowability is poorer.

- Moisture control in granulations

Control of moisture content in granulations is very important and it could affect the physical and chemical performance of final dosage form. Moisture could affect flow of granules, tablet compression, tablet disintegration, crystal habit, capsule brittleness, chemical stability, and many other properties. Moisture content is generally measured using moisture analyzer during product development. A thin layer of samples is heated at a set temperature until it reaches a constant weight and the results are expressed as LOD.

Some polymorphic transitions in granulations are moisture mediated. Minimizing moisture exposure during process and storage was recommended.

It is ideal to develop equilibrium moisture isotherms for granulations to understand the moisture content at different humidity. To develop moisture isotherms granulations are exposed to different relative humidity at a set temperature and the equilibrium moisture content is determined. This information could be used to develop specifications for the moisture content of the granulation and would help device ideal processing and packaging conditions. One application of moisture isotherms data could be applied to the formulation development of capsules. Capsules show brittleness at low relative humidity and a tendency to cross-link at humidity and high temperature.

A common application in characterization of granulations is based on thermogravimetry and is known as loss on drying. In a LOD analysis, a sample of the granulation is heated at a temperature near the boiling point of solvent or water. The weight loss, recorded directly on an analytical balance, is due to the evaporation of water or solvent and is considered as residual moisture content of a granulation. This technique is extensively used to establish both granulation and drying parameters for wet granulation unit operations.

X-ray diffraction which provides determination of polymorph changes resultant to production, DSC analysis for determination of crystal and amorphous structure of formulation and friabilator use in order to measure granule resistance are the additional tests used when necessary in this matter**.**

2.2. Tablet Technology

According to Türkoğlu (2004), tablets are pharmaceutical forms which constitute the largest group amongst solid dosage forms obtained by compressing one or more active ingredients with excipients or without any excipient use under pressure.

Tablets are usually taken via oral route; oral administrations are also possible through effervescent or sublingual routes depending on active ingredient properties or treatment objective.

Besides the known advantages of industrial productivity of solid active ingredients in this dosage form such as economy, easy use by the patient, and possible technological masking of bitter and bad scents of active ingredients, the hardest part for the person who designs a formulation is achieving bioavailability-bioequivalence.

In order for the active ingredient to be released in desired amounts in a desired time, it has to be disintegrated first and then has to be absorbed inside the gastro-intestinal tract in desired intervals.

That’s why excipients, granule properties and formulations of tablets to be prepared according to local or systemic effects required from active ingredients show differences.

Various granulation techniques are used for the preparation of solid dosage forms. The methods used for the tabletting of granules or powder mixture are explained below in detail.

- **Tablet preparation by direct compression**

It is the easiest and fast procedure. However, in order to use this procedure, the granule or powder mass should be flowable, should have a uniform particle size distribution, and should be compressible. The stability of active ingredient is improved due to the absence of temperature and moisture in the process.

Tablet compression by this method depends on the flowability of direct compressible excipients and the compressibility. First compressible excipient is spray dried lactose. Thereafter, Avicel and Sta-Rx 1500, Emcompress and direct compressible sugars are used in this compression method.

According to Çelik (1996), the most important factor is the proper selection of excipients.

Physicochemical and mechanical properties of pharmaceutical powders directly affect the quality of tabletting process. Çelik and Driscoll (1993)

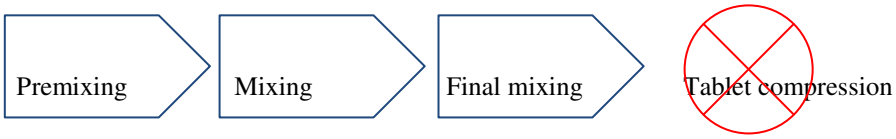


Figure 2.6. Work flow diagram of tablet preparation by direct compression procedure.

This procedure is not applicable when the drug content is too low and flowability and compressibility of the granule is poor.

- **Tablet preparation by dry granulation**

Dry granulation method is basically performed without using heat and solvent. In this method, granulation is achieved by performing mechanical mixing. Compression is ensured by briquette tablet compression and crashing or passing the powder from a rotating steel cylinder at high pressure.

It is least preferred method among 3 tablet compression methods. Requiring separate and expensive equipment for pre-compression and briquette tablets, high amount of powder generated compared to wet granulation, the decrease in solubility by crashing of pre-compressed powder that contains low water soluble substances are the known disadvantages of dry granulation.

The granulation of active ingredient and excipients without any wetting and drying and preference for heat sensitive drugs are the advantages. This method is suitable for high-dose drugs in order to obtain high density granules.

Figure 2.7. Work flow diagram of tablet preparation by dry granulation procedure

- **Tablet preparation by wet granulation**

Tablet compression by wet granulation is the oldest but most common method. This is an expensive compression method due to the needed material variety, number of procedures performed, time, and place.

Achieving active ingredient content uniformity in tablet formulations best by wet granulation method, and direct compression method use in high dose active ingredient containing low-compressible tablet formulations are still known as common reasons why the industry has used its experience and investments in this oldest method known.

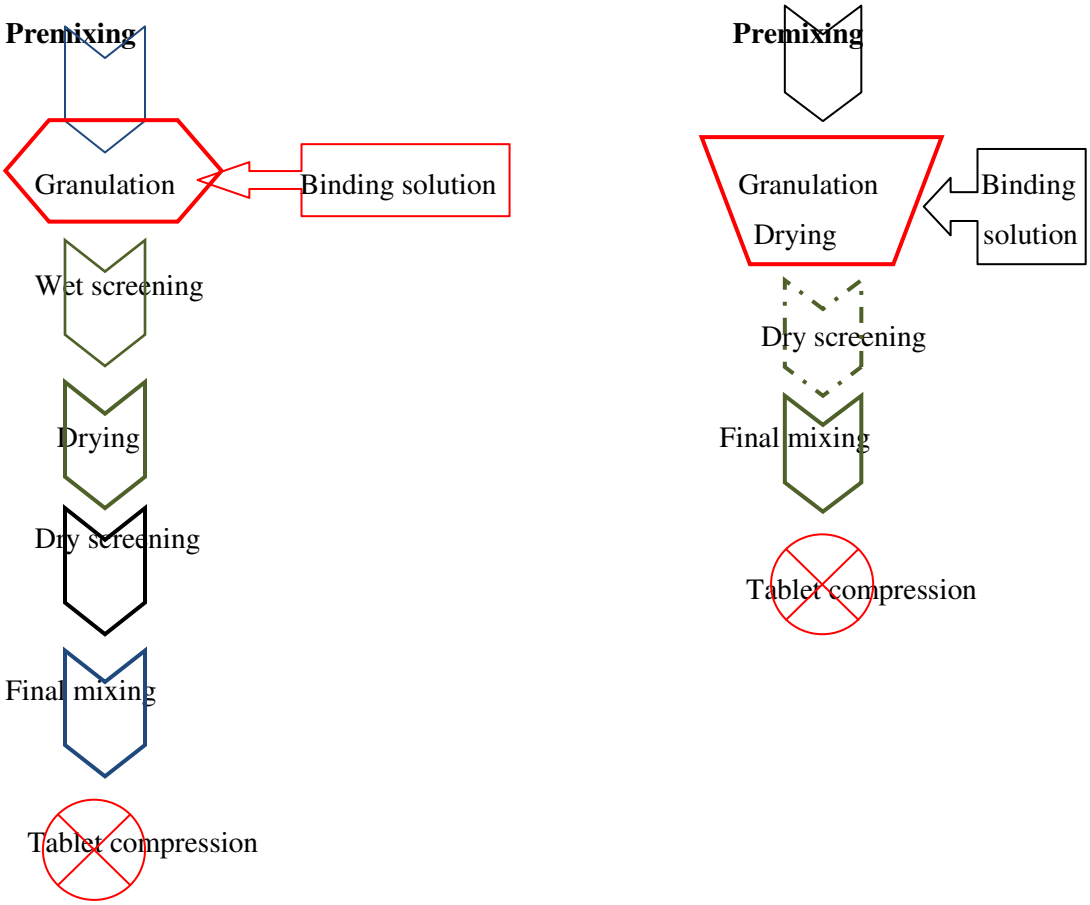


Figure 2.8. Work flow diagram of tablet preparation by shear type granulation and FB wet granulation procedure

2.2.1. Importance of Powder Properties and Granule in Tablet Technology

According to Banker et al. (1980), Hıncal and Bilensoy (2004), Türkoğlu (2004), the properties of powder that will be mixed in tablet technology are presented below.

- Particle size and distribution
- Particle shape
- Surface area
- Density
- Granule hardness and friability

- Electrostatic properties
- Flow properties

Until 1950's, tablet compression has been generally performed by granulation methods in pharmaceutical technology. After new excipients, in which physical properties has been recovered, came into the market in following years, it was possible to use direct compression method in tablet preparation.

2.2.2. Excipients Used in Immediate Release Tablet Formulations

Generally, excipient/excipients are added into a tablet formulation according to desired powder/granule properties and tablet properties.
If an active ingredient itself has a suitable crystal structure, it can be directly compressed into tablets without addition of any excipient. Cubical crystals are the optimal structures for this kind of compression technology.

The compressibility of active ingredients with crystal structure is dependent on the followings:

- Particle size distribution
- Crystal shape
- Apparent density
- Moisture content

In tablet formulations with expected systemic effect, the main objectives are sufficient level of solubility and the most rapid disintegration possible in order to provide desired absorption in the first place.

Factors that affect these are;

- The type and amount of granulation excipients used,
- Formulation and process methods

- The amount of disintegrant and lubricant materials and their addition methods to the formula

According to Parrott (1981), Sheth et al. (1980), Wadke and Jacobson (1980), Gil et al. (2010), Powder mixture or granule that will be compressed into tablets should primarily have desired mechanical and physical properties. Additionally, this powder or granule should have a flowability that could be filled completely and fast into burnisher/matrix. Excipients are certainly used in the formulations in which they contain active ingredients that are not suitable for direct compression.

When tablet excipients are known, determinations must definitely be made by knowing tabletting process. For example, in a formulation with direct tablet compression method use, particularity-given (good viscosity, known particle shape, density and moisture value) special powders (direct tabletting agent) are used as excipients, in this context, if a tablet is to be compressed after improving powder properties of active ingredient, granulation processes must be recalled and excipients to be used will have to be selected appropriate to equipments and process. For preference, attention has to be paid regarding water soluble or non-soluble chemical properties of all excipients.

Tablet excipients can be classified as major components, minor components, and other excipients in terms of their function.

- Major components; diluents/fillers, binders, disintegrants,
- Minor components; lubricants, glidants,
- Other excipients; coloring agents, buffer substances, taste and odour regulators, wetting agents.

Major components;

- **Diluents/Fillers**

Inert materials affect physical, chemical, and biopharmaceutical properties of the obtained tablet. The moisture content of these materials is important for the stability of active ingredient. Generally, they are used in the formulations in order to improve the flowability of the active ingredient. When we divide fillers into water soluble and insoluble groups, Lactose group matters are water-soluble fillers where microcrystalline cellulose and dibasic calcium phosphate are main material examples to water-insoluble fillers. In formulations which require direct compression and granulation, fillers with different type and properties are used. Use ratios range between 20 to 80% in formulas.

- **Binders**

Binders are substances needed to produce granules from powder and tablets from granules. In short, it is possible to bind particles which do not form bounds under pressure with these substances. Presence of these substances decreases compression force in the formulation. Binders can be added dry or solved in a solvent like water or alcohol depending on the process. The robustness and integrity of a tablet is successful by means of binders. The most preferred binders are cellulose derivatives and PVP. Their share in formulations alters in 1 to 5%. For substances to be used in granulation as binders with melting in heat, solutions cannot be prepared, so melting property is of importance.

- **Disintegrants**

Disintegrants are substances which provide tablets to disintegrate to granules and powders which form granules in the GI tract in order to contribute on the nature of local effects or dissolving of a drug and join to bloodstream. Disintegrants are substances which rapidly swell in contact with water and cause tablets to break into

pieces. Disintegrants divide into two groups as water-insoluble but swelling and chemically CO_2 releasing substances. Including granulation process, addition step in processes affect effect-presenting capacities. A group of substances called super disintegrants can disintegrate tablets in a water medium in maximum 5 minutes when they are added in a formulation with 1 to 10%. There is a positive relation between tablet disintegrants and drug release and bioavailability.

Minor Components;

- **Lubricants**

These are materials that make the tablet compression easier. They have mainly three types of functions.

- They are easily ejected out by the lower mould. They decrease the friction of tablet between burnisher and the mould surface (anti friction). The most commonly used lubricant is magnesium stearate. It directs to the surface of the particles under pressure and forms an antistatic film layer. This film layer weakens the bonds between the particles and decreases the cohesion.

- By this way, it decreases the friction between the granule and the mould. It also maintains the homogeneous distribution of pressure in the tablet, and as a consequence it prevents the tablet from sticking onto the mould surface (anti-adherent effect). İe. Cab-O-Sil

- It also has slight flow regulating (glidant) properties. İe. Talk.

- **Glidants**

Materials that decrease the friction force between the powder and the granule mixture regulate the flowability and preventing sticking are called glidant. They fill into the cavities on the particles and cover the surface as film layer by decreasing the friction force between the particles. Silisium dioxide is the most common material having highest glidant properties.

Others;

- **Coloring agents**

These are materials that are added into the granulation or the powder mixture appropriately in order to form a homogeneous distribution, and mainly targeting to differentiate the tablets having similar shape and weight but comprising different active ingredient from each other. Especially for chewable tablets, they are used together with taste and odour regulators. The coloring agents that can be used for pharmaceuticals and food are defined by FDA.

- **Buffering agents**

In order to maintain the stability of a pharmaceutical product, materials with acidic or basic characteristics can be included into the formulation, by the help of these materials the pH values of the formulations can be buffered in a range and the degradation of the product can be prevented.

- **Taste and odour regulators**

These are very important materials especially for effervescent and chewable tablets in order to hide the undesired tastes and odours. Artificial sweeteners and fruit aromas are commonly used with this purpose

- **Wetting agents (surfactants)**

In cases where the water solubility of the active ingredient is low, in order to increase the solubility materials that increase the contact with water (wetting agents) are used. They are present in the formulation at low concentrations and generally they are anionic materials like sodium lauryl sulphate or non ionic surfactants like polysorbate.

2.2.3. Equipments Used in Tabletting Technology and Tablet Compression Physics

Tablet compression in pharmaceutical technologies is performed by eccentric and rotary type machines.

After learning about the granulation and tablet excipients, it is very important to know about the mechanism of the tablet compression in order to overcome the potential problems that may occur during the formulation phase.

Tablet compression physics comprises compression physics, transfer of forces during compression, distribution of forces in the tablet, effect of the applied force over relative volume of the powder, adhesion and cohesion forces between the particles, tablet compression energies, mechanical resistance of tablets issues.

Working principles of the eccentric and rotary tabletting machines that differ from each other because of their yields are summarized below.

- **Eccentric Machine**

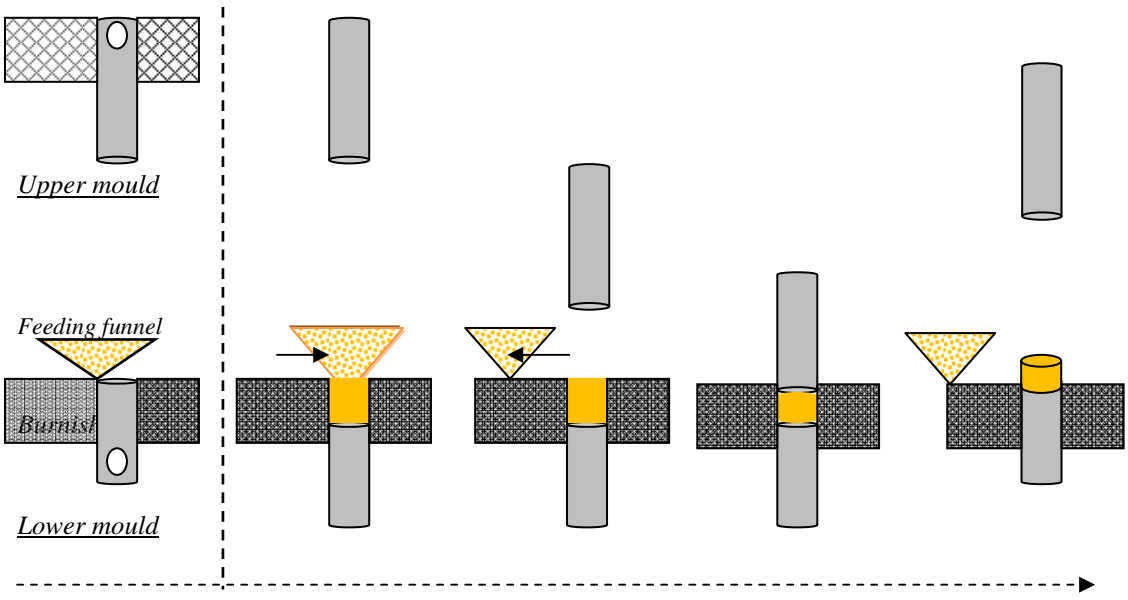


Figure 2.9. Schematic demonstration of the working principle of eccentric type machine

Most important parts of this type of machine;

- Matrix/compression unit
- 1 upper and 1 lower mould
- Feeding unit and feeding funnel

When the lower mould is at the top position, the upper mould is also at the top position. At this point the powder passes from the feeding funnel and fills into the burnisher. Feeding unit is mobile over the matrix. Lower mould is as its first position without movement, and then upper mould applies the force to compress the powder in the matrix. After the compression, upper mould goes back to its initial position and the lower mould takes out the tablet out of the matrix.

Tablet weight is adjusted by the movement of lower mould in matrix and tablet hardness is adjusted by the force applied by the upper mould.

- **Rotary type machine**

In these types of machines feeding unit is immobile. The moulds are mobile. Each compression unit has one upper and one lower mould and they rotate together. Weight control is performed by the unit (kam) carrying the lower moulds.

In contradiction with the eccentric machine, force is applied onto the powder by both lower and upper moulds.

According to Marshall (1989), the parameters that must be controlled on a tabletting machine during the compression process are applied compression force, force applied to the lower mould, movement and ejection force of both moulds.

- Pre compression force

It is the first force applied to the powder before the main compression. It makes preparation to the tabletting process and causes 2 compressions in the same period of time. It takes out the air and prevents breaking and capping problems. It is average 0,2 – 0,9 kN.

- Main compression force

Power of the main compression applied to the tablets. Generally shown as kN.

- Ejection force

It is the indication of the friction force between tablet and the mould during main compression of tablets when tablets are ejecting. Generally it is shown as N. Lubricants must be used to decrease this force.

2.2.4. Controls on Tablets

There are tests performed on finished products during process and (in-process) and after the process for conventional tablets.

Hardness and weight control are important tests during tabletting process. Physical tests for the finished product are weight variation, diameter and thickness, friability, disintegration and dissolution.

2.3. Solubility and Dissolution

2.3.1. Solubility

According to Çapan (2004), for many dosage forms, especially solid dosage forms like tablets, capsules, the absorption of the active ingredient, is dependent on the solubility and the diffusion throughout the digestion system is dependent on its solubility in gastrointestinal liquids.

Solubility can be defined in different ways. USP 32, defines solubility as, volume of solvent in which 1g of material dissolves in milliliters.

Solubility is defined as the maximum amount of material dissolved in 100 ml at a certain temperature.

The maximum amount of dissolved material in a certain amount of solvent is called the solubility of the material in that solvent and generally it is defined as the maximum concentration of the saturated solution.

2.3.1.1. Factors That Affect the Solubility between Solid–Liquid

- **Regarding Solvent;**

    - **Type of Solvent and Dissolved Material**

Solvents are chemically classified as; polar, semi polar, a polar.

Solubility of an active ingredient is dependent on the polarity and dipole moment of the solvent. Polar solvents are good in dissolving material with ionic structure and polar material. And thus, water well dissolves sugars, compounds with polyhydroxy structure and mixed with alcohol at each proportion.

Semi polar solvents can partially be polarized. They can mix with polar and non-polar solvents. As an example acetone increases the water solubility of ether, propylene glycol increased the water solubility of mint oil with this method.

Apolar solvents like hydrocarbons, do not decrease the attraction between ions of the weak or strong electrolyte materials. Furthermore, apolar solvents cannot break the covalent bonds. Thus, ionic or polar materials do not dissolve in apolar solvents.

Factors effecting solubility can be summarized as follows;

- Temperature,
- Shared ion concentration,
- pH effect on weak electrolytes solubility,
- Effect of surfactants

Solubility of the active ingredient can be increased by several different methods during formulation studies. Generally water is used as the solvent in the formulation. Water dissolves the active ingredients mainly having weak acid or basic characteristics by either ionizing or without separating into its ions.

The portion of the active ingredient that dissolves without ionisation is not affected by pH. On the other hand, the portion that is dissolved by separating into ions is affected by the changes in the pH changes. This way it is possible to change the solubility of some excipients by increasing or decreasing the pH.

Solubility of the part that is dissolved without ionization can be increased by using supportive solvents or materials, misels can be increased by solubility or creating weak complexes in the medium.

- **Regarding Dissolved (Active Ingredient)**

  - **Particle Size and Shape**

It is effective on solubility and dissolution. Decrease of particle size results in the increase of the particle surface area and consequently increase of dissolution.

Effect of particle size on solubility has been investigated by Higuchi and Smolen. As the particle size decreases solubility increases due to the increase in the free energy of the particle. Below equation is used to calculate this energy.

$$\text{Ln } Sr / S = 2\,\gamma\, M / Pr \,.\, R.T \qquad (2.1.)$$

Table 2.3. Explanations related to the formula used in the solubility calculation

Sr	Solubility of grinded particles
S	Solubility of bigger particles at the beginning
γ	Surface tension of particles (energy)
M	Molecular weight
Pr	Radius of particles at final stage
R	Molar gas constant (8.314 x 107 erg/K mol)
T	Absolute temperature

2.3.2. Dissolution

After a plain tablet is taken via oral route, the active ingredient starts to get into the solution first with disintegration followed by disintegration.

Dissolution; can be defined as the amount of solid material dissolved in a certain period of time.

According to the equation of Noyes-Whitney , one of the first researchers of the topic in 1897, dissolution can be calculated mathematically as follows:

$$\frac{dM}{dt} = K.S(Cs - Ct) \qquad (2.2.)$$

Table 2.4. Explanations related to the formula of dissolution calculation

dM/dt	Dissolution
S	Surface area of active ingredient
K (D/h)	Diffusion coefficient (constant)
Cs	Saturation concentration of active ingredient
Ct	Active ingredient concentration in solution at time point t

2.3.2.1. Dissolution Test Apparatus

The most important control and comparison test of solid dosage forms, dissolution test is performed with equipment defined in the pharmacopoeias.

USP I and USP II dissolution test equipment known as basket and paddle, are equipments that are most widely used and accepted by authorities to determine the dissolved material amount at a defined time periods in solid dosage forms.

There are other dissolution test equipment and methods defined in pharmacopoeias. Properties of each of them are present in the literature Banakar (1992).

Figure 2.10. Basket and Paddle Dissolution test equipment known as USP I (basket) and USP II (paddle) apparatus

Dissolution comparisons of the formulations are calculated according to the similarity factor called f2, where detailed Formula is given below.

$$f_2 = 50 \log \{[1+(1/n)\sum n\ t=1\ (Rt-Tt)^2\ ]^{-0.5}\ x\ 100\} \quad (2.3)$$

Table 2.5: Explanations related to the f_2 calculation formula

f_2	Similarity factor
Rt	% dissolved material at the time of each sampling for reference sample
Tt	% dissolved material at the time of each sampling for test sample
n	Number of study points

2.3.2.2. Factors That Affect Dissolution

According to Banakar (1992), the main factors effecting the dissolution can be summarized as; dissolution test parameters, physicochemical factors, formulation, manufacturing methods and their process parameters.

According to Çapan (2005), the dissolution test parameter that affects the dissolution is;

- Stirring rate,
- pH of media,
- existence of active ingredient
- solvent viscosity,
- medium temperature, medium volume

Physicochemical factor affecting the dissolution;

- solubility of the API,
- salt formation,
- crystal structure,
- polymorphism
- particle size

Dissolution increases with the increase in the surface area of the active ingredient in other words, when the particle size decreases. Dissolution of the active ingredient with limited solubility can be increased by decreasing the particle size. The correlation between the particle size and the specific surface area (Sw) is shown with the following equation. Increase of Sw, increases the dissolution.

$$Sw = 6 / \rho.d \qquad (2.4.)$$

Table 2.6. Explanations related to the formula between particle size and specific surface area

Sw	Specific surface area
ρ	Real densities of particles
d	Particle diameter

The water soluble or insoluble states of the excipients, the ratios and the types of fillers, disintegrators, binders, granulation agents, and lubricatns, surfactants and coating agents are important factors effecting the dissolution.

Production method as direct compression or granulation methods, process parameters of these methods and the compression power of tabletting are also the factors affecting the dissolution directly. Our findings during our study have been presented in the relevant sections.

2.4. Instrumental Analysis Equipments

According to Stout and Dorsey (2002), they are known as the equipment having frontier technology to perform the chemical analysis of the materials. These equipments are used in the pharma industry for the assay analysis of finished product, intermediate product, impurity analysis compatibility determination tests. The most common ones are; UV spectrophotometers, high pressure liquid chromatographies having different detectors (HPLC, LC-MS), gas chromatography (GC).

2.4.1. Chemical Analysis with High Pressure Liquid Chromatography (HPLC)

HPLC; is an instrumental equipment widely used in the pharma industry for quantitative determination of the assay.

The principle of the equipment is to separate the materials chromatographically by using the differences between their solubility, disintegration and polarity.

The main parts of the equipment can be summarized as; high pressure pomp, sampling unit and the detector (UV, PDA, FLR, RI).

Assay analysis of granules and the tablets was performed with HPLC, where dissolution assay analysis was also performed with the same method.

2.4.2. Analytical Method Validation

Repeatability of the analytical methods is expected to be according to ICH. Method validation is an indication showing the repeatability of the methods, and the validation is performed by showing the repeatability by statistical evaluation. The parameters that should be present in the validation study are listed below:

- Specificity
- Linearity
- Recovery
- Precision
- Robustness
- Stability

2.5. Active ingredient

2.5.1. Oxcarbazepine

2.5.1.1. Physical and Chemical Properties

Oxcarbazepine, the API chosen as the model active ingredient in our study is a cream to yellow colored crystal powder. Molecular formula is $C_{15}H_{12}N_2O_2$, molecular weight is 252,27. pKa value is 10.7 ± 0.2, pH of the 0,004% aqueous solution at 25°C is 7.0. Oxcarbazepine is practically insoluble; the solubility at 25°C, pH 7.0 is 0,04g/L.

Oxcarbazepine whose molecule structure is given below is a strong and effective anticonvulsant.

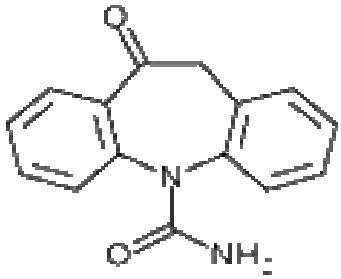


Figure 2.11. Oxcarbazepine molecule.

OX does not exhibit isomerism and stereochemistry, whereas exhibit polymorphism. We used Form-A polymorph during our studies. OX is a Class IV molecule with low solubility and low permeability.

2.5.1.2. Pharmacological and Pharmacokinetic Properties

Oxcarbazepine is in the group of antiepilectics with its general properties and the ATC code is N03AF02. According to Gerald (2004), pharmacological activity shows itself mainly with monohydroxy metabolite (MHD). Oxcarbazepine is used for the treatment of simple, complicated and widely seen tonic-clonic attacks

including subtypes of partial attacks followed by secondary widely seen attacks. It is used for adults and children as the first step antiepileptic monotherapy and supportive treatment (RxMedia Pharm 2010).

3. EQUIPMENTS and PROCEDURE

3.1. Equipments

3.1.1. The Chemical Substances Used

Acetonitrile (HPLC grade)	Panreac-0000222594
Lactose Monohydrate	Domo-635515
Methanol (HPLC grade)	JT Backer-1006729004
Oxcarbazepine (d0.5:3µm)	Jubilant Organosys Limited-0XC/0808156
Oxcarbazepine (d0.5:45µm)	Jubilant Organosys Limited-OXC/1002025
Oxcarbazepine (d0.5:70µm)	Jubilant Organosys Limited-OXC/1002024
Oxcarbazepine Working Standard	Jubilant Organosys Limited-0XC/1002020WS
Potasssium Dihydrgen Phosphate (KH_2PO_4)	Merck-A00473 73923
Potassium Hydroxide (KOH)	JTBaker-09273 01029
PVP K30	BASF-27198809T0
SDS	Merck-K38764534
Starch 1500 (Pregelatinised Starch)	Dow Chemical-DT20002
Stearic Acid	FACI-SA-80017

3.1.2. The Equipments Used

Flow Measurement Device	Copley-BEP2
Fluidized Bed	Hüttlin Unilab-H00464 Erweka-FR1
Friablity Tester	Erweka-ZTX20
Disintegration Apparatus	Erweka- SWM102
Density Measurement Device	Ditsek-EVOLUTION 6100
Dissolution Apparatus	

DSC	Netsch-DSC 204 F1
Analytical Balance	Mettler Toledo-XP1203S
Light microscobe	Olympus BX50-7C07219
Laboratory Type Mixer	Erweka Motor-AR402
Tablet Compression Machine	Manesty-XSpress
Mechanical Mixer Membrane	Heidolph-RZR2021
Filter(0,45µm) Moisture	Chromosil PET-45/25
Analyzer	Mettler Toledo-HR83
Particle Size Measurement	Malvern Mastersizer 2000-MAL100307
Hardenss Tester	Erweka-TBH30
Balance	Metler Toledo-XS3200ILX
Ultrasonic Bath	Maxwell Bandelin-RK1028
High Pressure Liquid Chromatogrphy System (HPLC)	HP Agilent-1100 Series
• Column, HPLC Length: 15 cm Internal Diameter: 4,6 mm Particle Size: 5µm	Inertsil-ODS 3V
• Column Oven	HP Agilent-1100 Series
• Autosampler	HP Agilent-1100 Series
• UV Dedector	HP Agient-1100 Series
• Pump	HP Agilent-1100 Series

3.2. Procedures and Experiments

3.2.1. Studies Performed on Oxcarbazepine Active Ingredient

Particle size measurement, assay, dissolution and DSC analysis which are explained in detail were performed on Oxcarbazepine active ingredient, shapes of the particles were monitored with light microscope by taking pictures.

• Particle Size Measurement

Particle size determination of Oxcarbazepine active ingredient is performed by using a laser diffraction particle size equipment. Dry measurement method was used. Ball-measurement was performed under 2,0 bar vacuum by using 30% vibration between 0,2 – 2 concentration range.

Figure 3.1. Malvern Mastersizer 2000-MAL100307 particle size measurement device

• Assay Analysis of Oxcarbazepine Active Ingredient by HPLC

Chromatographic conditions related to the method used for the HPLC assay analysis of Oxcarbazepine active ingredient were summarized in Table 3.1. Preparation of solutions used in the analysis, procedure and calculation are specified in detail below. Calculation used in the determination of assay result is defined in Formula 3.1 and explanations related to the formula used in the determination of assay result are presented in Table 3.2.

Table 3.1. Chromatographic conditions of the HPLC method used in the assay analysis of Oxcarbazepine active ingredient.

Column	Inertsil ODS 3V 150 X 4.6 mm, ID, 5µm
Mobile Phase	0,02 M KH_2PO_4:MeOH:ACN (50:40:10) pH:7,00±0,05 (with 1 M KOH)
Flow	1,0 ml/min
Injection Time	10 min
Injection Volume	10µl
Wavelength	UV, 286 nm
Column Teperature	40°C
Tray Temperature	10°C

Preparation of Solutions:

Preparation of 0,02 M KH_2PO_4 solution: 2,72 g KH_2PO_4 is dissolved in 1000 ml purified water.

Mobile Phase: 500 ml 0,02 M KH_2PO_4 solution, 400ml MeOH and 100 ml ACN are mixed. pH value is adjusted to 7,00 ± 0,05 with 1 M KOH solution. The solution is filtered through 0,45 µm filter and then degassed.

Preparation of Standard Solution: 30 mg Oxcarbazepine working standard is accurately weighed and transferred into a 50 ml volumetric fask. Approximately 40 ml of mobile phase is added and sonicated in an ultrasonic bath for 15 minutes to dissolve. The solution is diluted to volume with mobile phase and mixed. Then, the

solution is filtered through a 0,45 µm membrane filter and is transferred into HPLC vial. (Two paralel samples are prepared) (C: 0,60 mg/ml)

Preparation of test solution: 60 mg Oxcarbazepine active ingredient is weighed in a 100 ml volumetric flask. Approximately 60 ml of mobile phase is added and sonicated in an ultrasonic bath for 15 minutes to dissolve. The solution is diluted to volume with mobile phase and mixed. Then, the solution is filtered through a 0,45 µm membrane filter and is transferred into HPLC vial. (C: 0,60 mg/ml)

Procedure:

Standard solution 1 is injected five times (calibration injection), standard solution 2 and samples are injected twice.

System suitability parameter: %RSD values of the areas obtained from the five injections of standard solution 1 should be not more than 2,0.
The concordance of the average area of Oxcarbazepine peak obtained from Standard solution 1 and the average area of Oxcarbazepine peak obtained from Standard solution 2 should be 100% ± 2,0.

Calculation:

$$\text{Oxcarbazepine} = \frac{Rn}{Rstd} * \frac{Wstd*DF1}{Wnum*DF2} *D*P*1000 \qquad (3.1.)$$

Table 3.2. Explanations related to the formula used in the determination of assay result.

P	**:**	Potency of working standard (as is)
Rstd	**:**	OX peak area in Standard solution
Wstd	**:**	OX working standard weight (mg)
Wsam	**:**	Sample weight (mg)
D	**:**	Density (g/ml)
DF_1	**:**	Dilution factor for standard (=1/50)
DF2	**:**	Dilution factor for sample (= 1/100)

• Dissolution Assay Analysis of Oxcarbazepine Active Ingredient By HPLC

Dissolution and chromatographic conditions related to the method used for the HPLC dissolution assay analysis of Oxcarbazepine active ingredient were summarized in Table 3.3. Preparation of solutions used in the analysis, procedure and calculation are specified in detail below. Calculation used in the determination of dissolution assay result is defined in Formula 3.2 and explanations related to the formula used in the determination of dissolution assay result are presented in Table 3.4.

Table 3.3. Dissolution and chromatographic conditions of the HPLC method used in the dissolution assay of Oxcarbazepine active ingredient

Dissolution conditons	900 ml purified water, 37°C, 60 rpm, 120 min, paddle
Column	Inertsil ODS 3V 150 X 4.6 mm,ID,5µm
Mobile Phase	0,02 M KH2PO$_4$:MeOH:ACN (50:40:10) pH:7,00±0,05 (with 1 M KOH)
Flow	1,0 ml/min
Injection Time	10 min
Injection Volume	10µl
Wavelength	UV, 286 nm
Column Temperature	40°C
Tray Temperature	10°C

Preparation of Solutions:

Preparation of 0,02 M KH_2PO_4 solution: 2,72 g KH_2PO_4 is dissolved in 1000 ml of purified water.

Mobile Phase: 500 ml 0,02 M KH_2PO_4 solution, 400ml MeOH and 100 ml ACN are mixed. pH value is adjusted to 7,00 ± 0,05 with 1 M KOH solution. The solution is filtered through 0,45 µm filter and then degassed.

Preparation of Standard Solution: 3,33 mg Oxcarbazepine working standard is accurately weighed and transferred into a 50 ml volumetric fask. Approximately 40 ml of mobile phase is added and sonicated in an ultrasonic bath for 15 minutes to dissolve. The solution is diluted to volume with mobile phase and mixed. Then, the solution is filtered through a 0,45 µm membrane filter and is transferred into HPLC vial. (Two paralel samples are prepared) (C: 0,0666 mg/ml

Preparation of test solution: 60 mg Oxcarbazepine active ingredent is transferred into a dissolution vessel that contains 900 ml purified water. At the end of the determined time intervals the sampled solution is filtered through a 0,45 µm membrane filter and is transferred into a HPLC vial. (C: 0,0666 mg/ml)

Procedure:

Standard solution 1 is injected five times (calibration injection), standard solution 2 and samples are injected twice.

System suitability parameter: %RSD values of the areas obtained from the five injections of standard solution 1 should be not more than 2,0.
The concordance of the average area of Oxcarbazepine peak obtained from Standard solution 1 and the average area of Oxcarbazepine peak obtained from Standard solution 2 should be 100% ± 2,0.

Calculation:

$$\text{Oxcarbazepine} = \frac{Rn}{Rstd} * \frac{Wstd*DF1}{Wnum*DF2} *D*P*1000 \qquad (3.2.)$$

Table 3.4. Explanations related to the formula used in the determination of assay result

Rn	**:**	Oxcarbazepine peak area in sample solution
Rstd	**:**	Oxcarbazepine peak area in Standard solution
W_{std}	**:**	Oxcarbazepine working standard weight (mg)
Wsam	**:**	Numune tartımı (mg)
D	**:**	Density (g/ml)
DF_1	**:**	Dilution factor for standard (=1/50)
DF2	**:**	Dilution factor for sample (= 1/900)
P	**.**	Potency of working standard (as is)

Figure 3.2. HP Agilent 1100 Series brand HPLC equipment.

Figure 3.3. Ditsek EVOLUTION 6100 brand dissolution apparatus.

• DSC analysis

Oxcarbazepine DSC thermograms were recorded between 50°C - 300°C under nitrogen atmosphere at 20°C / min.

Figure 3.4. Netsch 204 F1 DSC equipment.

3.2.2. Preparation of Oxcarbazepine Tablet Formulation and its Analysis

Studies performed on Oxcarbazepine tablet formulation and its anlysis are explained below.

3.2.2.1. Oxcarbazepine Unit Formula and FB Process Parameters

The unit formula designed for Oxcarbazepine tablet formulation was presented in Table 3.5. In the unit formula, LM and API were used in the inner phase whereas, 3% PVP K30 was used as granulation solution. Starch 1500, MCC PH102 and Stearic acid were ued in the outer phase. No super disintegrant and water soluble excipient was used in the outer phase.

10 different trials were performed by using the process parameters presened in Table3.6.

Table 3.5. Oxcarbazepine tablet formulation.

Name of the ingredient	Unit Formula	
	mg/tb	%
OX	60,00	20,00
LM	183,00	61,00
PVP K30	9,00	3,00
Starch 1500	15,00	5,00
MCC PH102	31,50	10,50
Stearic acid	1,50	0,50
TOTAL	**300 mg**	**100%**

Table 3.6. FB process parameters.

Code	Trial	Inlet temperature °C	Inlet air flow m^3/hr	Spray ratio %	Spray pressure bar
D 1	**45µm_T1**	40	120	60	0,6
D 2	**45µm _T2**	60	120	20	1,3
D 3	**45µm _T3**	40	180	20	1,3
D 4	**45µm _T4**	60	180	20	1,3
D 5	**45µm _T5**	40	120	60	1,3
D 6	**45µm _T6**	60	120	60	0,6
D 7	**45µm _T7**	40	180	60	0,6
D 8	**45µm _T8**	60	180	60	1,3
D 9	**45µm _T9**	50	150	40	0,95
D 10	**45µm _T10**	50	150	40	0,95

Microclimate pressure and drying time were kept constant as 0,2 bar and 10 min respectively.

3.2.2.2. Granule Analysis and Calculations After FB Process

Below mentioned analysis and calculations were performed on the granules obtained from FB wet granulation process. The maximum and minimum process parameters, which can make a difference up to a discrimination on the particle size of the obtained granule, were determined. Shapes of the granules related to the determined maximum and minimum process parameters were monitored with light microscope by taking pictures.

• Particle Size Measurement

Particle size determination of granules is performed by using a laser diffraction particle size equipment. Dry measurement method was used. Ball-measurement was performed under 2,0 bar vacuum by using 30% vibration between 0,2 – 2 concentration range.

• Flow

Flow of granules was measured according to Flow through Orifice as described in EP 2.9.36 Powder Flow section. Flow was measured by using 10 mm - 15 mm and 25 mm nozzles, results were evaluated in terms of time.

Figure 3.5. Copley BEP2 flow measuring device

Bulk volume (vb) and tapped volume (vt) for granules were determined by using 100 g granule samples (m). Granules were filled into a graudated cylinder for density measurement, read volume just after filling and read volume after 750 taps were recorded.

Bulk density (db) and tapped density (dt) were calculated by using Formula 3.3. and Formula 3.4.

$$db = m / vb \qquad (3.3.)$$

$$dt = m / vt \qquad (3.4.)$$

Figure 3.6. Erweka SWM102 density measuring device.

• Carr's Index

Carr's index for garanules is calculated according to Formula 3.5.and evaluated according to Table3.7.

$$CI = 100 * [(dt-db) / dt] \quad (3.5.)$$

Table 3.7. The meaning of Carr's index formula calculation

Result	Flow
< 16%	Good
16-22%	Moderate
23-35%	Poor
> 35%	Bad

• Hausner Ratio

Hausner ratio for garanules is calculated according to Formula 3.6., the flow is considered as poor if the result is greater than 1,25.

$$H = dt / db \quad (3.6.)$$

• Moisture

Moisture of granules was measured by using an IR moisture analyzer. Measurement was performed at 105°C with automatic time.

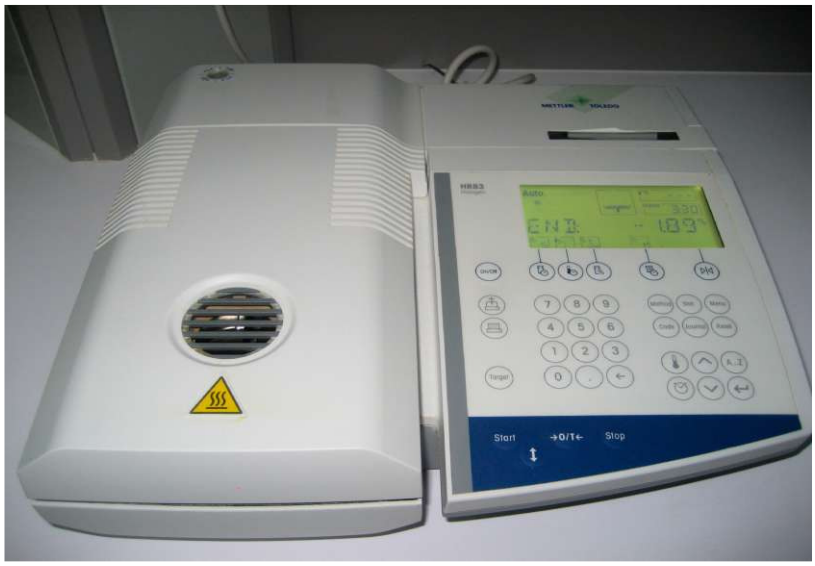


Figure 3.7. Mettler Toledo HR83 moisture analyzer.

Minimum and maximum parameters chosen according to the analysis results presented in Section 3.2.2.2. and the productions that will be repeated for all API's with different particle sizes were presented in Table 3.8.

Table 3.8. New studies planned according to the determined process parameters.

Code	Trial	Aim	Inlet air temperature °C	Inlet air flow m^3/hr	Spray ratio %	Spray pressure bar
F1_3 BG	**3µm_T1**	**Coarse granule**	40	120	0,6	60
F2_3KG	**3µm _T2**	**Small granule**	60	180	1,3	20
F3_45BG	**45µm_T1**	**Coarse granule**	40	120	0,6	60
F4_45KG	**45µm_T2**	**Small granule**	60	180	1,3	20
F5_70BG	**70µm_T1**	**Coarse granule**	40	120	0,6	60
F6_70KG	**70µm_T2**	**Small granule**	60	180	1,3	20

Microclimate pressure and drying time were kept constant as 0,2 bar and 10 min respectively.

Analyses were repeated on the granules obtained from the studies presented in Table 3.8, granules with appropriate results were determined. Granules related to the process which makes a difference were monitored with light microscope by taking pictures.

3.2.2.3. Tablet Compression Process

Tablet compression process for the granules with appropriate results was performed by using Manesty XSpress rotary tablet caompression machine. 8 mm round, biconvex punch and 10 mm mould were used and it was aimed to compress tablets with 300 mg by using turret rpm at 22 rpm, and feeder rpm at 12 rpm.

During tablet compression process, main compression force, pre-compression force and ejection force values were evaluated.

Figure 3.8. Manesty XSPress rotary tablet compression equipment.

3.2.2.4. Physical and Chemical Analysis After Tablet Compression Process

Following physical and chemical analysis were performed on the tablets obtained at the end of the tablet compression process, the results were evaluated and drug release at the final pharmaceutical form and the particle size of the API which was most affected from the process parameters were determined.

The tablet related to the most successul process was monitored with light microscope by taking pictures.

• Average Tablet Weight

Evaluation is performed according to EP 2.9.40. The test is determined over 20 tablets. 20 tablets are individually weighed, the average value should be within the determined limit.

Figure 3.9. Mettler Toledo XP1203S analytical balance.

• Hardness

The test is performed over 10 tablets by using automatic hardness tester, results are recorded.

Figure 3.10. Erweka TBH30 hardness tester

• Friability

10 tablets are weighed and average weight is calculated (a), tablets are subjected to rotational turning for 4 minutes by using an automatic friability tester and then the tablets are weighed and average weight is calculated again (b) and friability is calculated according to Formula 3.7.

$$A = [(a-b)/a]*100 \quad (3.7)$$

Figure 3.11. Erweka FR1 Friability tester.

• Disintegration

The test is performed over 6 tablets by using an automatic disintegration apparatus at 37°C purified water without disc. The result is recorded in terms of time, and it should be within the determined limit.

Figure 3.12. Erweka ZTX20 disintegration apparatus.

• Assay Analysis of Oxcarbazepine Tablet Formulation By HPLC

Chromatographic conditions related to the method used for the HPLC assay analysis of Oxcarbazepine tablet formulation were summarized in Table 3.9. Preparation of solutions used in the analysis, procedure and calculation are specified in detail below. Calculation used in the determination of assay result is defined in Formula 3.8 and explanations related to the formula used in the determination of assay result are presented in Table 3.9.

Table 3.9. Chromatographic conditions of the HPLC method used in Oxcarbazepine tablet formulation assay analysis

Column	Inertsil ODS 3V 150 X 4.6 mm,ID,5µm
Mobile Phase	0,02 M KH_2PO_4:MeOH:ACN (50:40:10) pH:7,00±0,05 (with 1 M KOH)
Flow	1,0 ml/min
Injection Time	10 min
Injection Volume	10µl
Wavelength	UV, 286 nm
Column Temperature	40°C
Tray Temperature	10°C

Preparation of Solutions:

Preparatin of 0,02 M KH_2PO_4 solution: 2,72 g KH_2PO_4 is dissolved in 1000 ml purified water.

Mobile Phase: 500 ml 0,02 M KH_2PO_4 solution, 400ml MeOH and 100 ml ACN are mixed. pH value is adjusted to 7,00 ± 0,05 with 1 M KOH solution. The solution is filtered through 0,45 µm filter and then degassed.

Preparation of Standard Solution: 30 mg Oxcarbazepine working standard is accurately weighed and transferred into a 50 ml volumetric fask. Approximately 40 ml of mobile phase is added and sonicated in an ultrasonic bath for 15 minutes to dissolve. The solution is diluted to volume with mobile phase and mixed. Then, the solution is filtered through a 0,45 µm membrane filter and is transferred into HPLC vial. (Two paralel samples are prepared) (C: 0,60 mg/ml)

Preparation of Test Solution: 10 tablets are grinded in a mortar. Approximately 300 mg tablet powder (equivalent to 60 mg Oxcarbazepine) is weighed in a 100 ml volumetric flask. Approximately 60 ml of mobile phase is added and sonicated in an ultrasonic bath for 15 minutes to dissolve. The solution is diluted to volume with mobile phase and mixed. Then, the solution is filtered through a 0,45 µm membrane filter and is transferred into HPLC vial. (C: 0,60 mg/ml)

Procedure:

Standard solution 1 is injected five times (calibration injection), standard solution 2 and samples are injected twice.

System suitability parameter: %RSD values of the areas obtained from the five injections of standard solution 1 should be not more than 2,0.
The concordance of the average area of Oxcarbazepine peak obtained from Standard solution 1 and the average area of Oxcarbazepine peak obtained from Standard solution 2 should be 100% ± 2,0.

Calculation:

$$\text{Oxcarbazepine mg \ tb} = \frac{Rn}{Rstd} * \frac{Wstd*DF1}{Wnum*DF2} * \frac{D}{ED} * ED * P * 1000 \qquad (3.8.)$$

Table 3.10. Explanations related to the formula used in the determination of assay result.

Rn	**:**	Oxcarbazepine peak area in sample solution
Rstd	**:**	Oxcarbazepine peak area in standard solution
Wstd	**:**	Oxcarbazepine working standard weight (mg)
Wsam	**:**	Sample weight (mg)
D	**:**	Density (g/ml)
DF_1	**:**	Dilution factor for standard (=1/50)
DF_2	**:**	Dilution factor for sample (= 1/100)
P	**:**	Potency of working standard (as is)
LA	**:**	Label amount

• Dissolution Assay Analysis of Oxcarbazepine Tablet Formulation By HPLC

Dissolution and chromatographic conditions related to the method used for the HPLC dissolution assay analysis of Oxcarbazepine active ingredient were summarized in Table 3.11. Preparation of solutions used in the analysis, procedure and calculation are specified in detail below. Calculation used in the determination of dissolution assay result is defined in Formula 3.9 and explanations related to the formula used in the determination of dissolution assay result are presented in Table 3.12.

1% SDS was added to purified water medium for the studies of the dissolution analysis performed in a medium containing surfactant, the rest of all parameters and procedures are the same.

Table 3.11. Dissolution and chromatographic conditions of the HPLC method used in the dissolution assay of Oxcarbazepine active ingredient.

Dissolution Conditions	900 ml purified water, 37°C, 60 rpm, 120 dk, paddle
Column	Inertsil ODS 3V 150 X 4.6 mm,ID,5µm
Mobile Phase	0,02 M KH_2PO_4:MeOH:ACN (50:40:10) pH:7,00±0,05 (with 1 M KOH)
Flow	1,0 ml/min
Injection Time	10 min
Injection Volume	10µl
Wavelength	UV, 286 nm
Column Temperature	40°C
Tray Temperature	10°C

Preparation of solutions:

Preparation of 0,02 M KH_2PO_4 solution: 2,72 g KH_2PO_4 is dissolved in 1000 ml purified water.

Mobile Phase: 500 ml 0,02 M KH_2PO_4 solution, 400ml MeOH and 100 ml ACN are mixed. pH value is adjusted to 7,00 ± 0,05 with 1 M KOH solution. The solution is filtered through 0,45 µm filter and then degassed.

Preparation of Standard Solution: 3,33 mg Oxcarbazepine working standard is accurately weighed and transferred into a 50 ml volumetric fask. Approximately 40 ml of mobile phase is added and sonicated in an ultrasonic bath for 15 minutes to dissolve. The solution is diluted to volume with mobile phase and mixed. Then, the solution is filtered through a 0,45 µm membrane filter and is transferred into HPLC vial. (Two paralel samples are prepared) (C: 0,0666 mg/ml)

Preparation of test solution: 1 tablet sample is put in a dissoution vessel tahat contains 900 ml medium. The test is performed at 37°C' de, 60 rpm for 120 minutes. At the end of the determined time intervals the 2 ml sampled solution is filtered through a 0,45 µm membrane filter and is transferred into HPLC vial. (C: 0,0666 mg/ml)

Procedure:

Standard solution 1 is injected five times (calibration injection), standard solution 2 and samples are injected twice.

System suitability parameter: %RSD values of the areas obtained from the five injections of standard solution 1 should be not more than 2,0.
The concordance of the average area of Oxcarbazepine peak obtained from Standard solution 1 and the average area of Oxcarbazepine peak obtained from Standard solution 2 should be 100% ± 2,0.

Calculation:

$$\text{Oxcarbazepine mg \ tb} = \frac{Rn}{Rstd} * \frac{Wstd*DF1}{Wnum*DF2} * \frac{D}{ED} * ED * P * 1000 \qquad (3.9.)$$

Table 3.12. Explanations related to the formula used in the assay determination.

Rn	**:**	Oxcarbazepine peak area in sample solution
Rstd	**:**	Oxcarbazepine peak area in standard solution
Wstd	**:**	Oxcarbazepine working standarweight (mg)
Wsam	**:**	Sample weight (mg)
D	**:**	Density (g/ml)
DF_1	**:**	Dilution factor of standard (=1/50)
DF_2	**:**	Dilution factor for sample (= 1/100)
P	**:**	Potency of working standard (as is)
LA	**:**	Label amount

3.2.2.5. Analytical Method Validation

Analytical method validation is the demonstration of the reliability of the analytical methods used. In the mean time, it is a procedure to confirm that analytical methods are accurate, specific and repeatable at specified conditions. Analysed parameters for the analytical method validations are presented below:

- Specificity
- Linearity
- Recovery
- Precision
- Robustness
- Stability

3.2.2.5.1. Specificty

Specificity of an anlytical method is the ability to assess only the intended component or components. The solutions of the excipients used in the prepared tablet formulation (placebo), known impurities of the active ingredient (carbamazepine, methoxy carbamazepine) and the chemicals used in the analysis (mobile phase, medium) were prepared at the analysis concentrations and HPLC chromatograms were recorded in order to analyse whether or not they give any peaks in the elution region of the active ingredient.

3.2.2.5.2. Linearity

In order to analyse linearity parameter of the analytical method validation of assay method, a stock solution at a concentration of 2.4 mg/ml was prepared in the mobil phase and this stock solution was diluted with mobile phase in order to obtain solutions containing Oxcarbazepine at the concentrations of 0.15, 0.30, 0.45, 0.60, 0.75 and 0.90 mg/ml. These prepared solutions were filtered through a 0.45µm membrane filter, then vialed and injected into the HPLC column. Oxcarbazepine peak area was calculated from the chromatograms and calibration line was plotted by using average area value of six studies calculated for each concentration against solution concentrations.

In order to analyse linearity parameter of the analytical method validation of dissolution assay method, a stock solution at a concentration of 0.264 mg/ml was prepared in the mobil phase and this stock solution was diluted with purified water in order to obtain solutions containing Oxcarbazepine at the concentrations of 0.0066, 0.0165, 0.0330, 0.0495, 0.0660 and 0.0825 mg/ml. These prepared solutions were filtered through a 0.45µm membrane filter, then vialed and injected into the HPLC column. Oxcarbazepine peak area was calculated from the chromatograms and calibration line was plotted by using average area value of six studies calculated for each concentration against solution concentrations.

3.2.2.5.3.Recovery

In order to study recovery parameter for the analytical method validation of assay method, three each samples (placebo+oxcarbazepine) containing 75%, 100% and 125% active ingredient were prepared. These samples were transferred into 100 ml volumetric flask, 60 ml mobile phase was added and the solution was sonicated in the ultrasonic bath. The samples diluted to volume with mobile phase were filtered through a 0.45µm membrane filter and injected into the HPLC column. Oxcarbazepine peak area was calculated from the chromatograms and recovery amount was calculated by using the formula given below:

$$\%\text{Recovery} = \frac{\text{Weighed Active Ingredient}}{\text{Assayed Active Ingredient}} \times 100 \qquad (3.10)$$

In order to study recovery parameter for the analytical method validation of dissolution assay method, three each samples (placebo+oxcarbazepine) containing 80%, 100% and 120% active ingredient were prepared. Dissolution study of these samples was performed in dissolution vessels operating at 60 rpm for 120 minutes containing 900ml purified water heated up to 37°C. At the end of the analysis, 10 ml of solution was sampled from each dissolution vessel, filtered through a 0.45µm membrane filter and injected into the HPLC column. Oxcarbazepine peak area was calculated from the chromatograms and recovery amount was calculated by using the formula given below.

$$\%\text{Recovery} = \frac{\text{Weighed Active Ingredient}}{\text{Assayed Active Ingredient}} \times 100 \qquad (3.11)$$

3.2.2.5.4. Precision

In order to study precision parameter for the analytical method validation of assay method, six samples (placebo+oxcarbazepine) containing 100% active ingredient were prepared. These samples were transferred into 100 ml volumetric

flask, 60 ml mobile phase was added and the solution was sonicated in the ultrasonic bath. The samples diluted to volume with mobile phase were filtered through a 0.45µm membrane filter and injected into the HPLC column. Oxcarbazepine peak area was calculated from the chromatograms and precision ratio for the calculated recovery amount of 6 samples was calculated by using the formula given below:

$$\%\text{Precision} = \frac{\text{Weighed Active Ingredient}}{\text{Assayed Active Ingredient}} \times 100 \qquad (3.12)$$

In order to study intermediate precision parameter for the analytical method validation of assay method, a different analyst was repated the precision analysis at the end of the validation study.

In order to study system precision parameter for the analytical method validation of assay method, five injections of prepared standard solution was performed and %RSD was calculated.

In order to study precision parameter for the analytical method validation of dissolution assay method, six samples (placebo+oxcarbazepine) containing 100% active ingredient were prepared. Dissolution study of these samples was performed in dissolution vessels operating at 60 rpm for 120 minutes containing 900ml purified water heated up to 37°C. At the end of the analysis, 10 ml of solution was sampled from each dissolution vessel, filtered through a 0.45µm membrane filter and injected into the HPLC column. Oxcarbazepine peak area was calculated from the chromatograms and precision ratio for the calculated recovery amount of 6 samples was calculated by using the formula given below:

$$\%\text{Precision} = \frac{\text{Weighed Active Ingredient}}{\text{Assayed Active Ingredient}} \times 100 \qquad (3.13)$$

In order to study intermediate precision parameter for the analytical method validation of dissolution assay method, a different analyst was repated the precision analysis at the end of the validation study.

In order to study system precision parameter for the analytical method validation of dissolution assay method, five injections of prepared standard solution was performed and %RSD was calculated.

3.2.2.5.5. Robustness

Robustness is the ability to assess accurate analysis as a result of the changes (column temperature, flow rate etc.) that may occur due to the errors of the used analytical method. In order to study robustness parameter for the analytical method validation of assay and dissolution assay methods, 100% sample solution and standard solutions prepared for precision analysis were used. The sample and standard injections were performed by changing one parameter of the chromatographic conditions used in the method for each time. Recovery ratio was calculated by using the formula given below:

- Flow rate:0.8 ml/min.
- Flow rate:1.2 ml/min.
- Column temperaure:35°C
- Column temperature:45°C

$$\%\text{Recovery} = \frac{\text{Weighed Active Ingredient}}{\text{Assayed Active Ingredient}} \times 100 \qquad (3.14)$$

% difference between the recovery value of 100% sample solution prepared for the precision analysis of the analytical method validation of assay and dissolution assay methods and the recovery value calculated in the robustness analysis was calculated.

3.2.2.5.6. Stability

In order to demonstrate the stability of Oxcarbazepine during analysis, standard solutions and 100% sample solution prepared for the precision analysis

of assay and dissolution assay methods were re-injected after 48 hours. The stability of the results was evaluated.

3.2.2.5. Surfactant Added Oxcarbezapin Formulation Study

As the final study, surfactant added formulation studies has been performed using the API with same PSD decided upon the results obtained in section 3.2.2.4., with the aim to determine the optimum formulation having 100% drug release. Different levels of surfactant has been added to the unit Formula as tabulated in Table 3.13 and with dissolution studies it was aimed to find the formulation that reaches the 100% drug release.

Table 3.13. Surfactant Added Formulation Studies

Name of Excipient	**F7 45KG 0,25% SDS mg/tb**	**F8 45KG 0,50% SDS mg/tb**	**F9 45KG 1,00% SDS mg/tb**	**F10 45KG 2,00% SDS mg/tb**
OKS	60,00	60,00	60,00	60,00
LM	183,00	183,00	183,00	183,00
PVP K30	9,00	9,00	9,00	9,00
SDS	0,75	1,50	3,00	6,00
Starch 1500	15,00	15,00	15,00	15,00
MCC PH102	30,75	30,00	28,50	25,50
Stearic acid	1,50	1,50	1,50	1,50
Total	300 mg	300 mg	300 mg	300 mg

4. FINDINGS

4.1. Studies Performed on Oxcarbazepine Active Ingredient

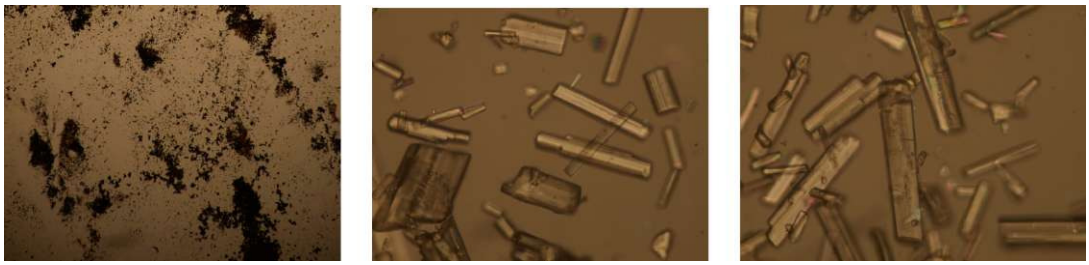
Particle size distribution, assay, dissolution assay and DSC studies as detailed in section 3.2.1 has been performed on Oxcarbazepine active ingredient.

- **Particle Size Distribution**

Particle size distribution results of API with 3µm (a), 45µm (b) and 70µm (c) are presented in Table 4.1 and the particle shapes observed by using light microscope are presented in Figure 4.1.

Table 4.1. Particle Size Distribution Results of Oxcarbazepine API

Batch no	Particle Size	Result
OXC/0808156	d0,5: 3µm	d(0,5): 3.627µm
OXC/1002025	d0,5: 45µm	d(0,5): 52.054µm
OXC/1002024	d0,5: 70µm	d(0,5): 64.066µm



(a) **(b)** **(c)**

Figure 4.1. Particle Photos of the 3µm (a), 45µm (b) and 70µm (c) API under light microscope , (10x20) size

- **HPLC Assay Analysis of Oxcarbazepine Active Ingredient**

HPLC analysis has been performed on API with three different particle size distributions.

Table 4.2 Assay Analysis Results of Oxcarbazepine Active Ingredient by HPLC

Batch no	Particle Size	Result
0X0/0808156	d0,5: 3µm	d(0,5): 100,05
0XC/1002025	d0,5: 45µm	d(0,5): 99,30
OXC/1002024	d0,5: 70µm	d(0,5): 99,30

- **HPLC Solubility Analysis of Oxcarbazepine Active Ingredient**

Active ingredient with three different particle size distributions has been analyzed. Results are summarized in Table 4.3. Comparative solubility graphs are presented in Figure 4.2

Table 4.3 Dissolution Assay Analysis Results of Oxcarbazepine Active Ingredient by HPLC

Purified Water, 900 ml, 60 rpm, Equipment II (paddle), auto sampling			
Time	Oxcarbazepine 3 µm	Oxcarbazepine 45 µm	Oxcarbazepine 70 µm
0	0,0	0,0	0,0
5	8,0	9,7	4,5
10	17,5	14,1	7,9
15	23,6	18,8	11,8
20	26,6	22,7	15,8
30	49,6	28,3	22,8
45	43,6	35,2	32,5
60	48,1	40,7	41,5
75	51,5	44,6	48,2
90	55,2	66,6	54,9
120	61,5	56,3	69,0

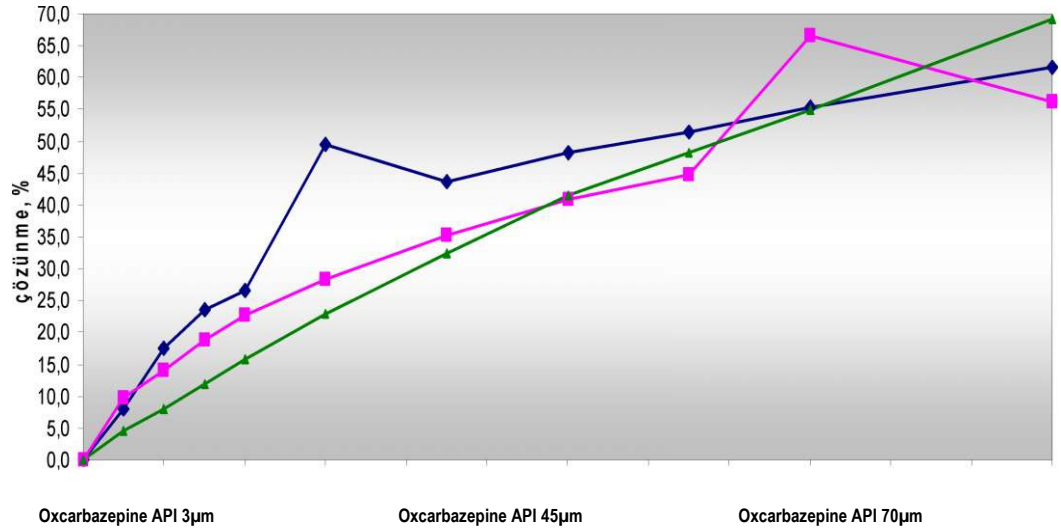


Figure 4.2 Solubility Graph of Oxcarbazepine API

- **DSC Analysis**

Three API with different particle size distribution has been tested. DSC thermograms of each API and the comparative thermogram are presented in Figures 4.3., Figure4.4., Figure4.5., and Figure4.6.

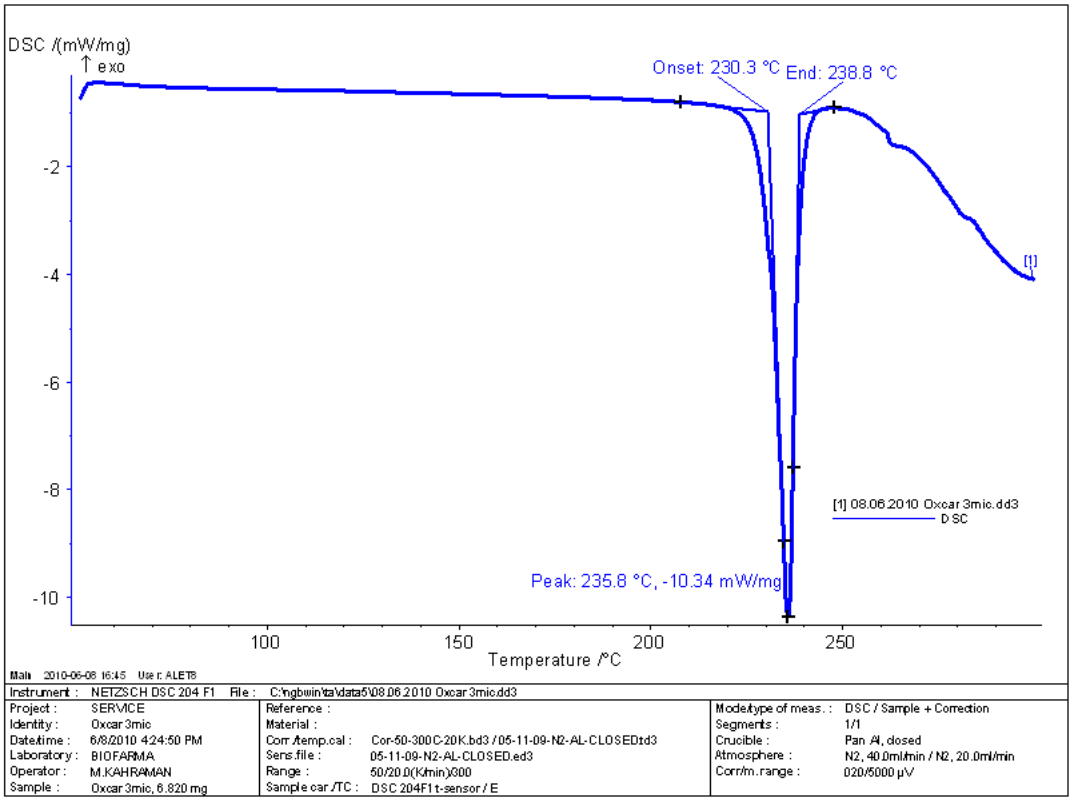


Figure 4.3 Oxcarbazepine API 3µm DSC Thermogram

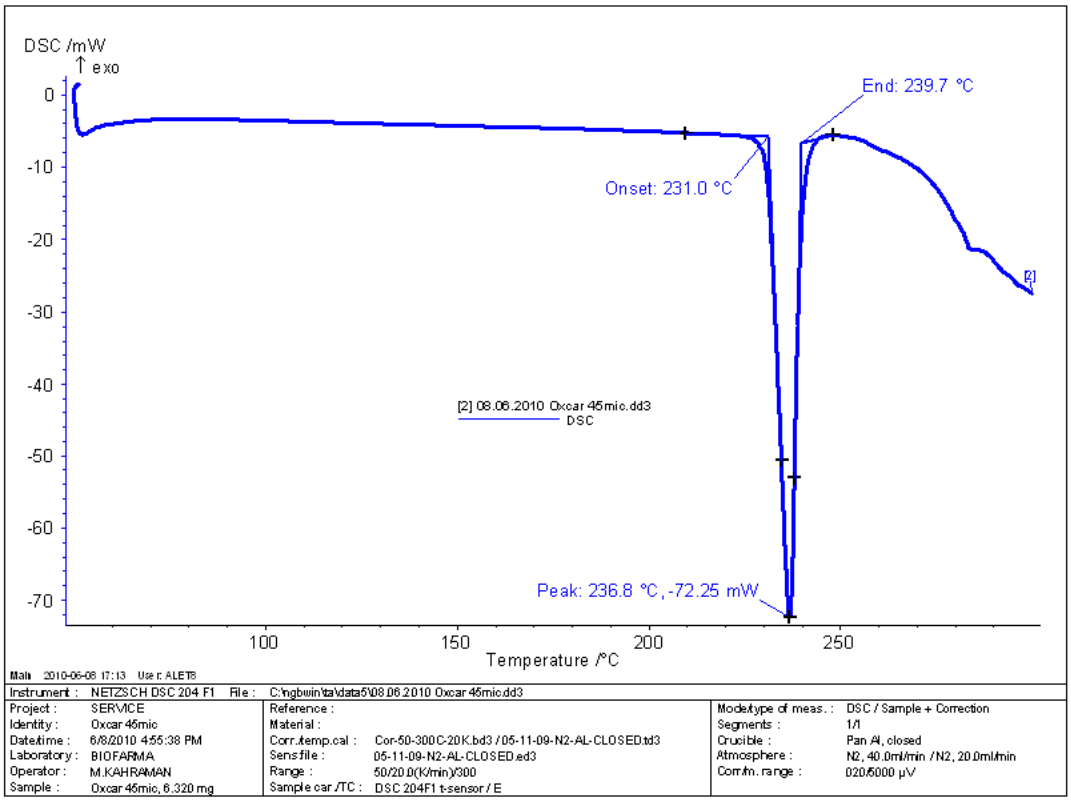


Figure 4.4 Oxcarbazepine API 45µm DSC Thermogram

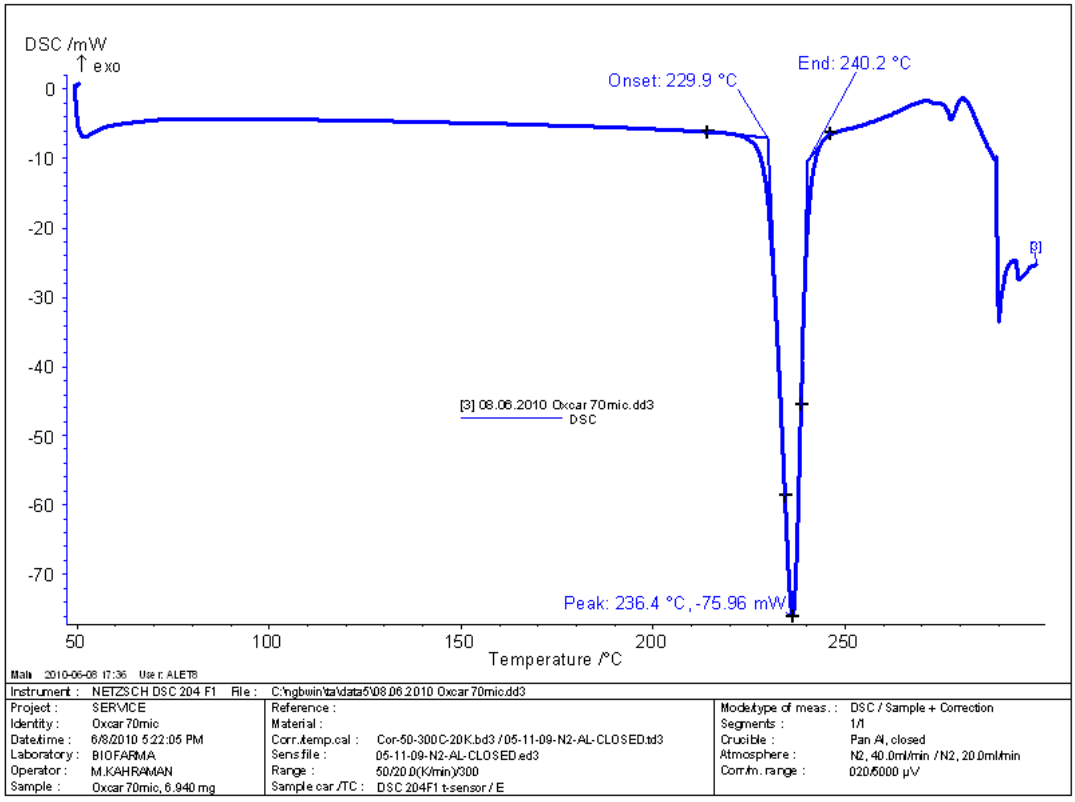


Figure 4.5 Oxcarbazepine API 70µm DSC Thermogram

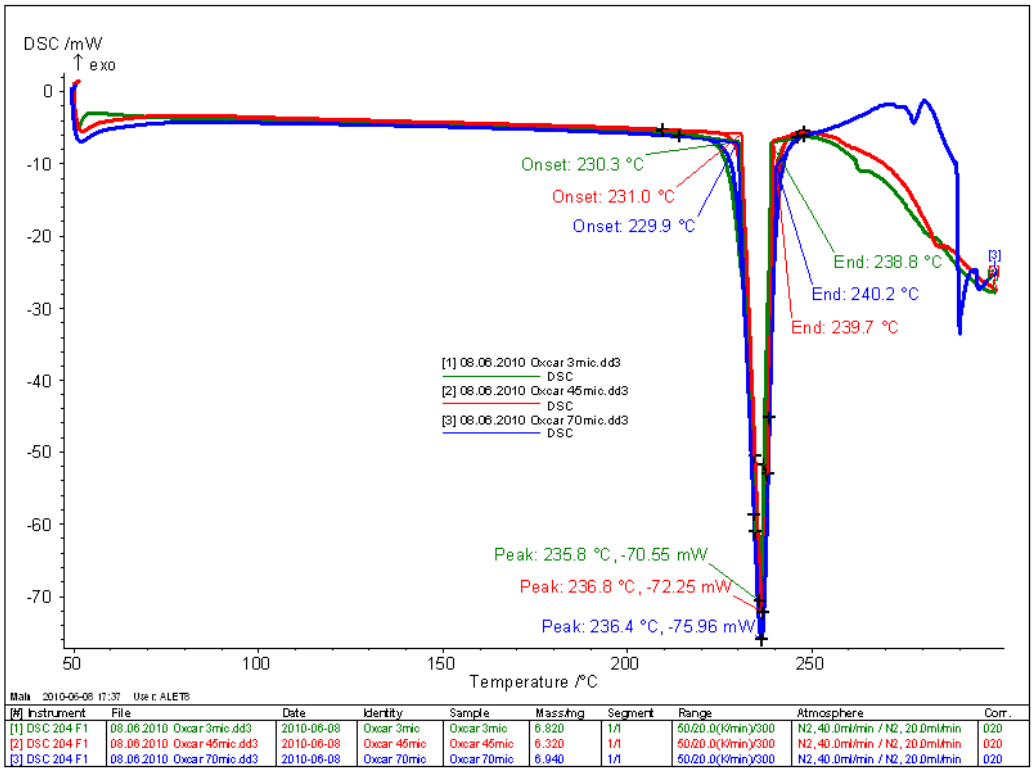


Figure 4.6 Oxcarbazepine API 3µm, 45µm and 70µm Comparative DSC Thermogram

4.2 Preparation and Analysis of Oxcarbazepine Tablet Formulation

Results obtained from the studies explained in detailed in section 3.2.2 are presented below.

4.2.1 Oxcarbazepine Unit Formula and FB Process Parameters

In order to define and optimize maximum and minimum parameters, the unit formula in Table 3.5 has been used and the trials that have been explained in detail have been performed.

Particle size testing has been performed on the dry granulate that has been obtained after the trials, and the processes whose process parameters have the highest effect on dry granule size. Process parameters and the particle size results are summarized in Table 4.4.

Maximum and minimum parameters are shaded in the table.

Table 4.4 FB Process parameters and particle size results

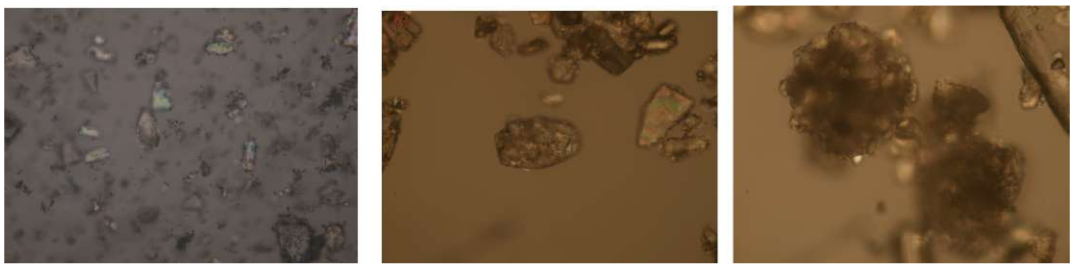
Code	Particle size results
D 1	100,911
D 2	Not determined
D 3	Not determined
D 4	65,076
D 5	Not determined
D 6	80,647
D 7	72,539
D 8	70,821
D 9	76,389
D 10	76,126

The study has been repeated at defined maximum and minimum parameters for all different particle size APIs.

4.2.2. Granule Analysis and calculations after FB Process

Granule analysis and calculations performed for all different particle size APIs are summarized below.

Lights microscope pictures of dry granulates obtained by applying maximum and minimum process parameters on 3 different particle size APIs presented in Table 3.8.



(F1_3BG) (F4_45KG) (F6_70BG)

Figure 4.7. Particle Photo of Dry Granules Obtained by Using 3µm (F1_3BG), 45µm (F4_45KG) and 70µm (F6_70BG) API By Light Microscope, (10x20) size

Particle Size Determination

Particle size analysis results of dry granulates obtained after FB wet granulation process are summarized in table 4.5.

Table 4.5 Particle Size Measurement Results Related to Dry Granules

Code	d(0,1)	d(0,5)	d(0,9)
F1_3BG	7,267	80,608	240,329
F2_3KG	3,037	43,986	130,480
F3_45BG	29,837	100,911	218,631
F4_45KG	16,573	65,076	142,733
F5_70BG	16,644	85,824	224,631
F6_70KG	15,261	61,933	146,950

- **Flowability**

Flowability results of dry granulated obtained after FB wet granulation process are presented in table 4.6.

Table 4.6. Flowability Results of Dry Granules

Code	25 mm	15 mm	10 mm
F1_3BG	No flow	No flow	No flow
F2_3KG	No flow	No flow	No flow
F3_45BG	1,8 sec	5,5 sec	14,5 sec
F4_45KG	2,5 sec	8,0 sec	25,0 sec
F5_70BG	2,2 sec	7,3 sec	23,6 sec
F6_70KG	2,7 sec	8,4 sec	29,2 sec

- **Bulk Density and Tapped Density**

Bulk density and tapped density results of dry granulated obtained after FB wet granulation process are presented in table 4.7.

Table 4.7. Bulk Density and Tapped Density Measurement Results of Dry Granules

Code	YD	SD
F1_3BG	0,518 g/ml	0,709 g/ml
F2_3KG	0,422 g/ml	0,631 g/ml
F3_45BG	0,609 g/ml	0,689 g/ml
F4_45KG	0,657 g/ml	0,763 g/ml
F5_70BG	0,657 g/ml	0,769 g/ml
F6_70KG	0,643 g/ml	0,786 g/ml

- **Carr's Index**

Carr's index calculations of dry granulated obtained after FB wet granulation process are presented in table 4.8.

Table 4.8. Carr's Index Calculations Related to Dry Granules

Code	Carr's Index
F1_3BG	26,94
F2_3KG	33,12
F3_45BG	11,16
F4_45KG	13,89
F5_70BG	14,56
F6_70KG	18,19

- **Hausner Ratio**

Hausner Ratio calculations of dry granulated obtained after FB wet granulation process are presented in table 4.9.

Table 4.9. Hausner Ratio Calculations Related to Dry Granules

Code	Hausner Ratio
F1_3BG	1,37
F2_3KG	1,50
F3_45BG	1,13
F4_45KG	1,16
F5_70BG	1,17
F6_70KG	1,22

- **Moisture**

Moisture results of dry granulated obtained after FB wet granulation process are presented in table 4.10.

Table 4.10. Moisture Results Related to Dry Granules

Code	Moisture
F1_3BG	% 0,68
F2_3KG	% 0,60
F3_45BG	% 0,96
F4_45KG	% 0,78
F5_70BG	% 0,88
F6_70KG	% 0,53

4.2.3. Tablet Compression Process

Granules, F3_45BG, F4_45KG, F5_70BG and F6_70KG that have good analysis results have been compressed to tablets by using the parameters explained in section 3.2.2.3 in detail.

Data obtained during the tablet compression process are presented in Figure 4.8, Figure 4.9, Figure 4.10, Figure 4.11, Figure 4.12, Figure 4.13, Figure 4.14, and Figure 4.15, comparative results are summarized in Table 4.11.

OYSTAR Manesty
R&D
Kitling Road
L24 9JS
Knowsley
Tel.: +44 151 547 8000
Fax: +44 151 547 8001

User: Demo

Date: 01.06.2010 Time11:10:38

Recipe:	**oxcarbazapin**						**Defaults**
Description:	**300 mg**						
Comment:	**1.06.2010**						
Batch:	**45um_T1**						
Tablet shape:	**round**						
Tablet size:	**8 mm**						
Tool reference no:	**piog45**						
Weight:	**300,00 mg**	**Fill cam:**	**10 mm**	**Feeder RPM:**	**12 RPM**	**Single value +:**	**18,0 %**
Tablet thickness:	**4,78 mm**	**Dead band:**	**0,30 %**	**RPM turret:**	**22 RPM**	**Mean value +:**	**17,0 %**
Hardness:	**12,00 N**	**Regulation sensitivity:**	**100**	**RSD (warn):**	**30 %**	**Set value:**	**5,00 kN**
Punch Sep:	**3,50 mm**	**Rev disguarded:**	**1**	**RSD (stop):**	**45 %**	**Mean value -:**	**17,0 %**
Fill depth:	**9,60 mm**	**Punch type:**	**Euro B**			**Single value -:**	**18,0 %**

Current settings

Punch Sep:	**3,57 mm**	**Feeder RPM:**	**12 RPM**
Fill depth:	**9,60 mm**	**RPM turret:**	**22 RPM**

	Pre compres.	Main compres.	Eject.force
Punch 2:	0,71 kN	4,56 kN	25 N
Punch 4:	0,70 kN	4,56 kN	30 N
Punch 6:	0,81 kN	4,66 kN	505 N
Punch 8:	0,81 kN	4,56 kN	705 N
MV:	0,75 kN	4,58 kN	316 N

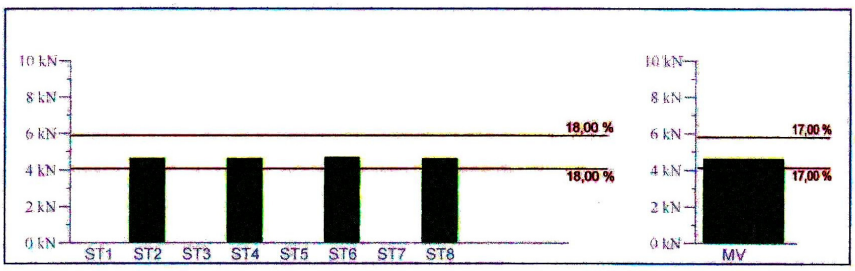


Figure 4.8 Data Related to F3_45BG Tablet Compression Process

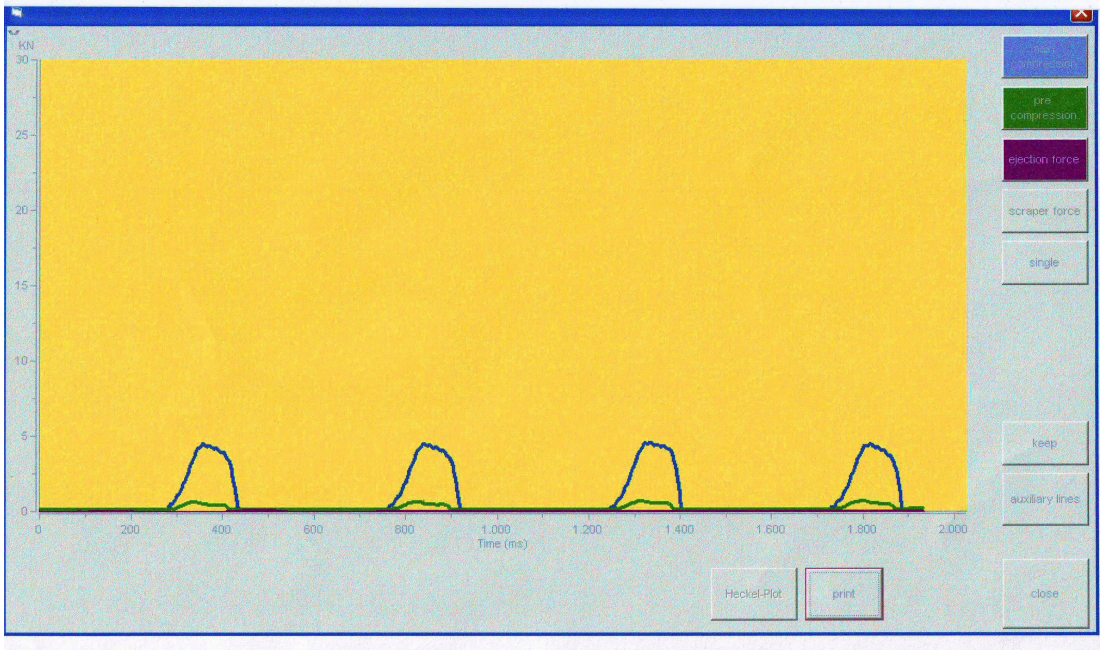


Figure 4.9 Each Punch Strength Related to F3_45BG Tablet Compression Process

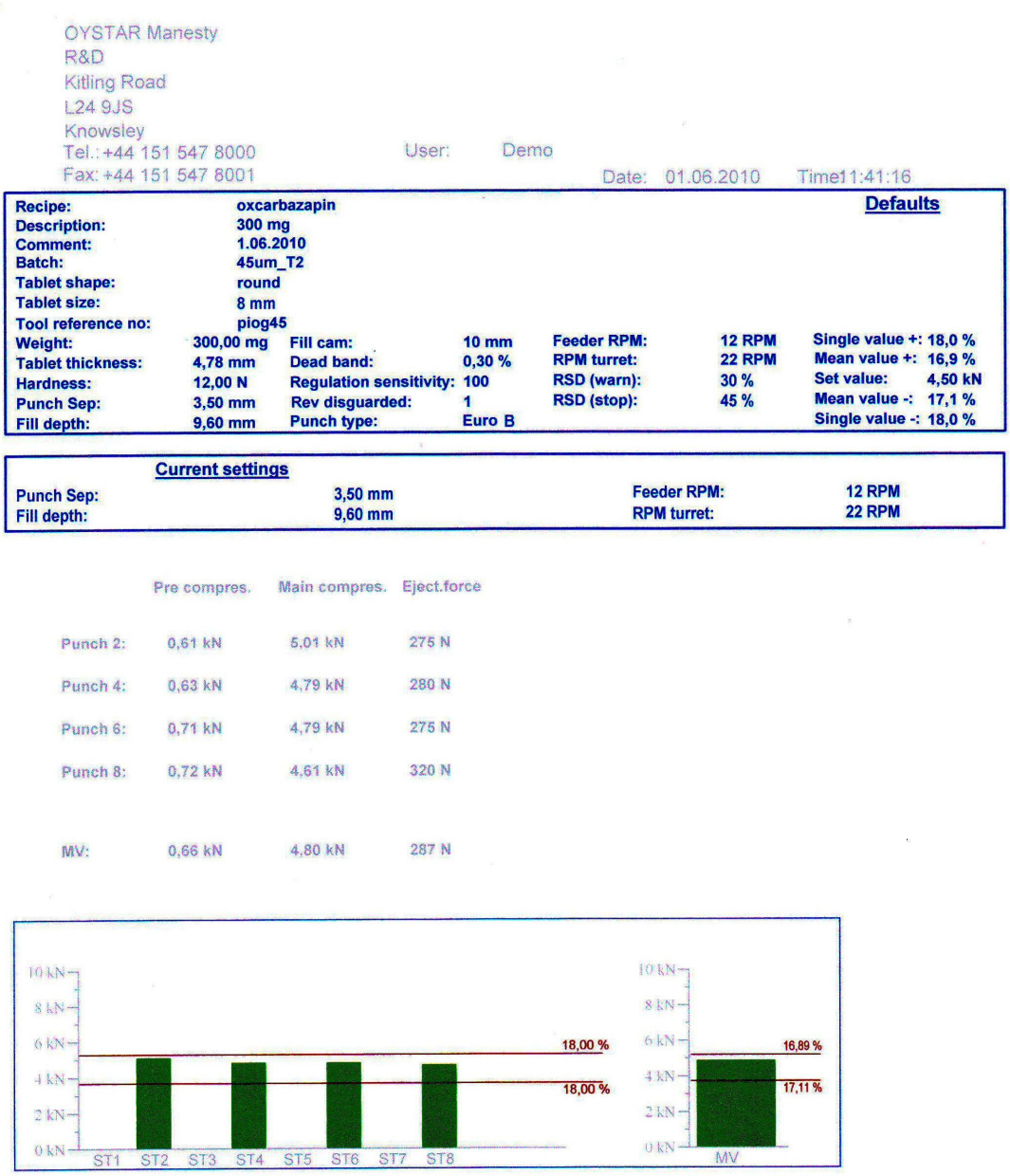


Figure 4.10 Data Related to F4_45KG Tablet Compression Process

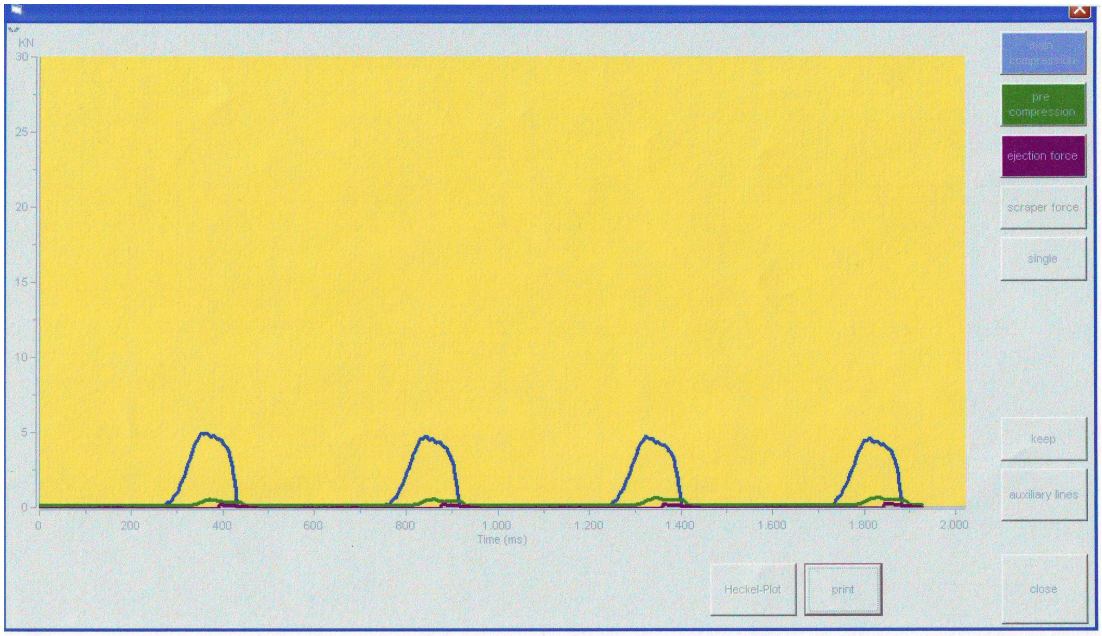


Figure 4.11 Each Punch Strength Related to F4_45KG Tablet Compression Process

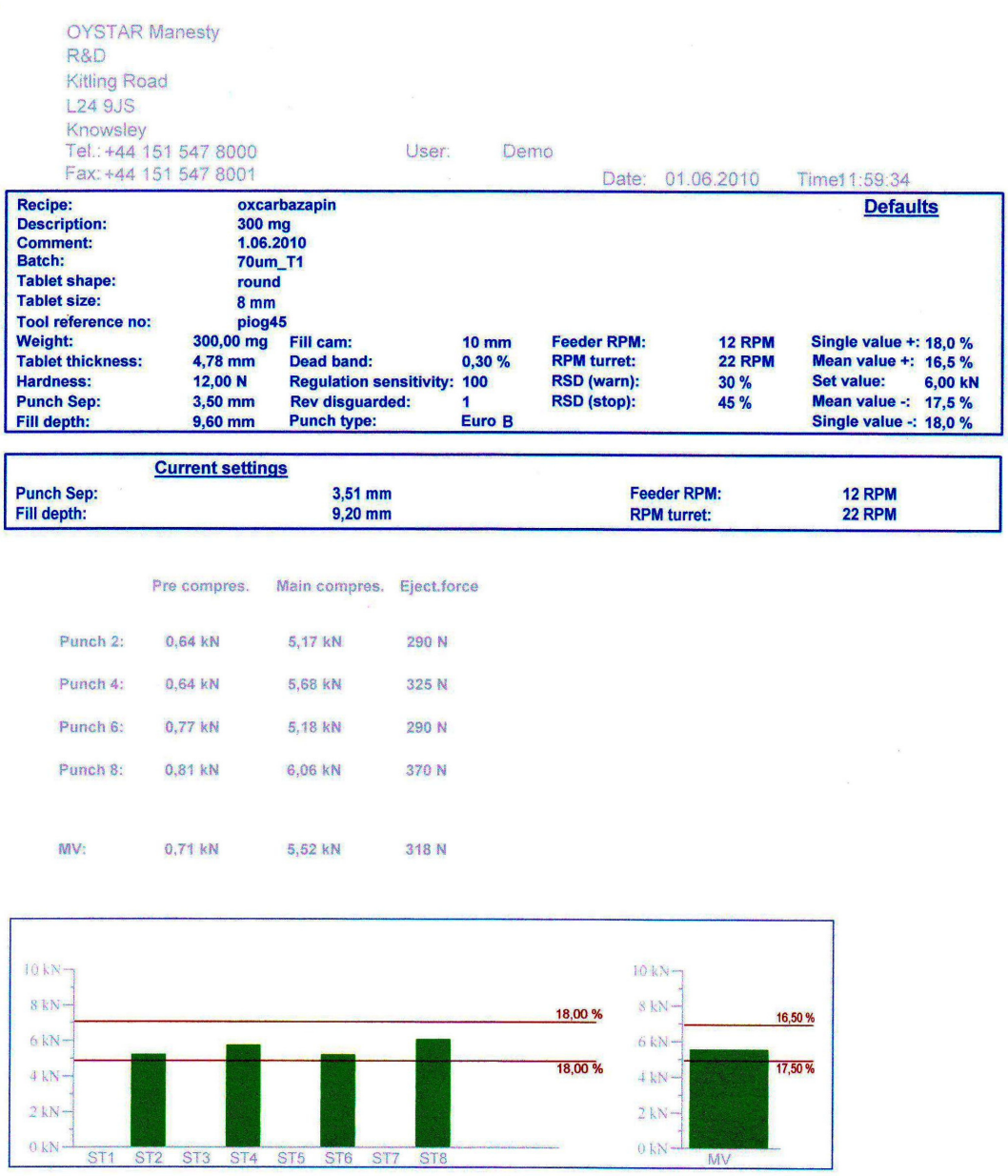


Figure 4.12 Data Related to F5_70BG Tablet Compression Process

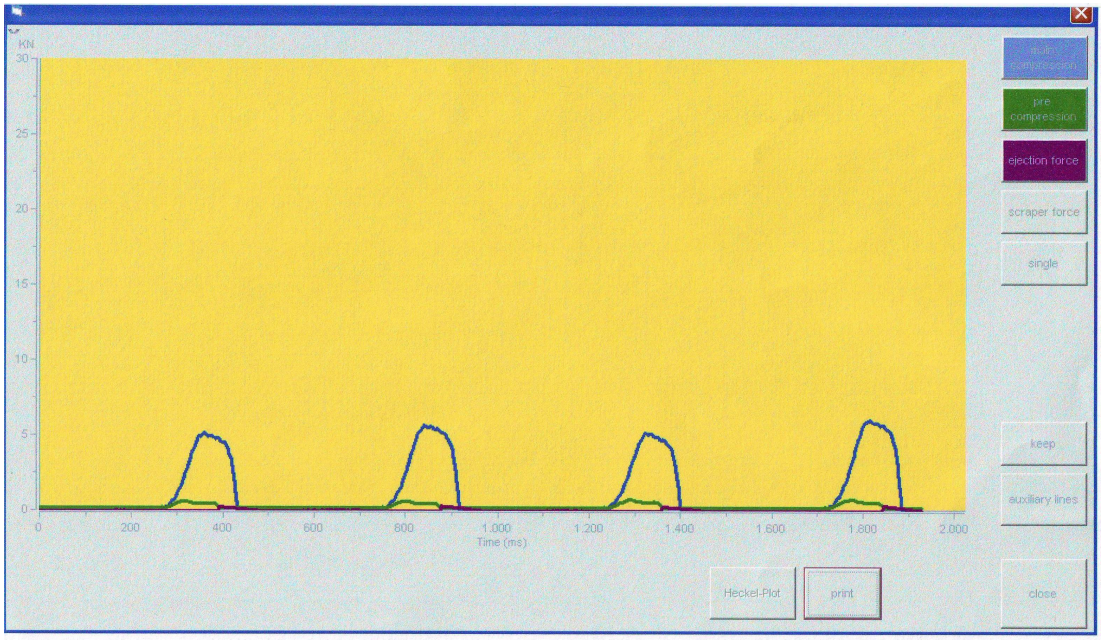


Figure 4.13 Each Punch Strength Related to F5_70BG Tablet Compression Process

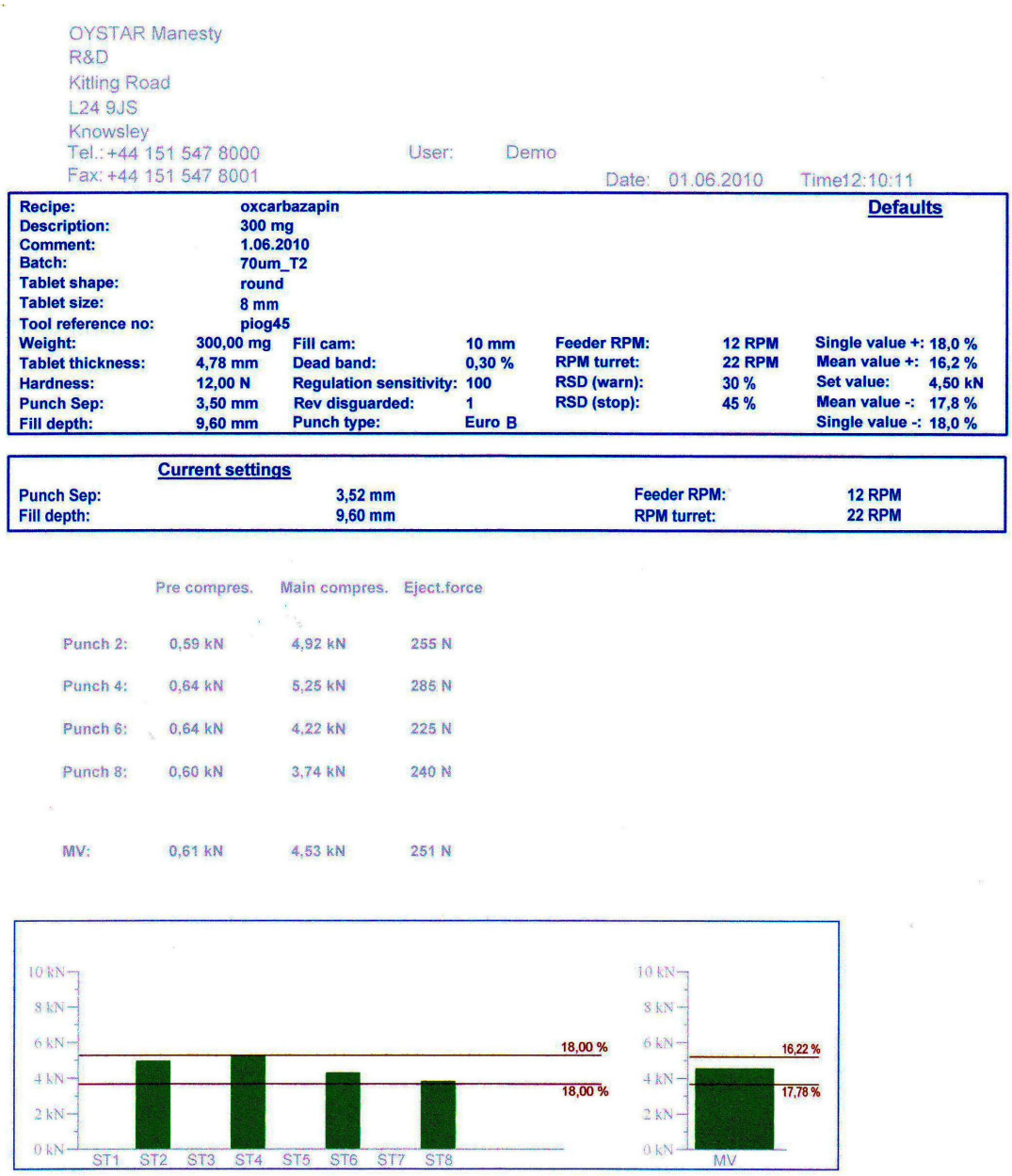


Figure 4.14 Data Related to F6_70KG Tablet Compression Process

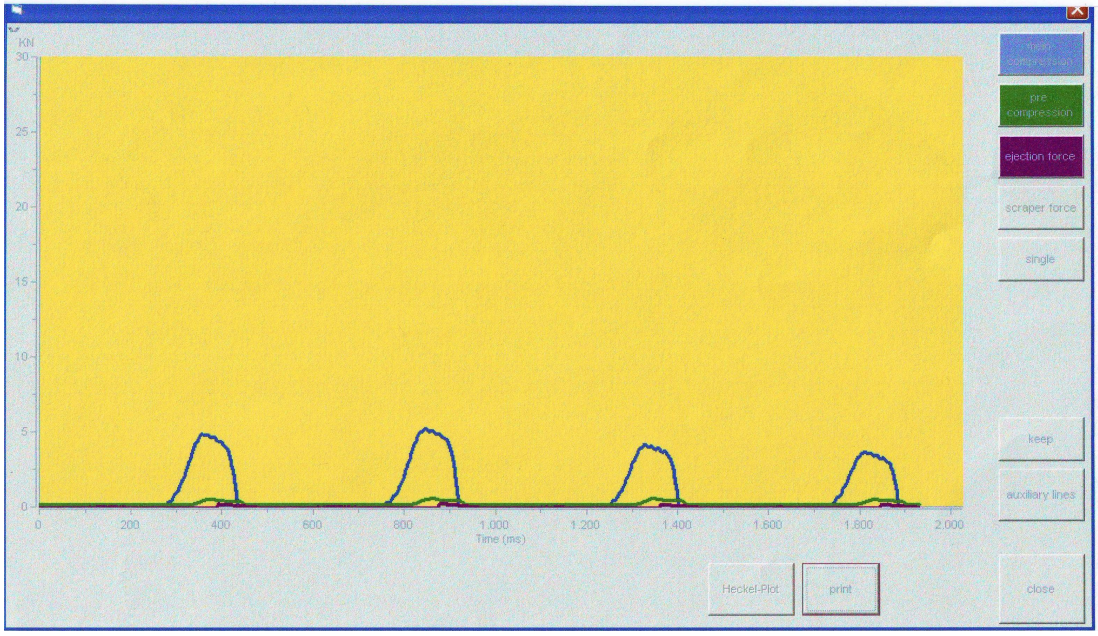


Figure 4.15 Each Punch Strength Related to F6_70KG Tablet Compression Process

Table 4.11. Tabulated Results of Compression Values of Tablets

Code	Pre-compression	Main Compression	Power on Mould
F3_45BG	0,61 kN	4,53 kN	251 N
F4_45KG	0,71 kN	5,52 kN	318 N
F5_70BG	0,66 kN	4,80 kN	287 N
F6_70KG	0,75 kN	4,58 kN	316 N

4.2.4. Physical and Chemical Analysis After Tablet Compression Process

Physical and chemical analysis results obtained from the tablets produced by compressing the 4 different granules are presented below.

- **Average Tablet Weight**

Average tablet weight results of tablets obtained by the compression process are summarized in Table 4.12.

Table 4.12 Average Tablet Weight Results of Tablets

Code	Average tablet weight
F3_45BG	300,11 mg
F4_45KG	300,84 mg
F5_70BG	299,97 mg
F6_70KG	300,07 mg

- **Hardness**

Hardness results of tablets obtained by the compression process are summarized in Table 4.13.

Table 4.13 Hardness Results of Tablets

Code	Average hardness
F3_45BG	10,96 kP
F4_45KG	9,99 kP
F5_70BG	9,38 kP
F6_70KG	7,29 kP

- **Friability**

Friability results of tablets obtained by the compression process are summarized in Table 4.14.

Table 4.14 Friability Results of Tablets

Code	Friability
F3_45BG	% 0,01
F4_45KG	% 0,01
F5_70BG	% 0,02
F6_70KG	% 0,04

- **Disintegration**

Disintegration results of tablets obtained by the compression process are summarized in Table 4.15.

Table 4.15 Disintegration Results of Tablets

Code	Disintegration
F3_45BG	1.06 min.
F4_45KG	1.14 min.
F5_70BG	2.06 min.
F6_70KG	1.36 min.

- **HPLC Assay Analysis of Oxcarbazepine Tablet Formulation**

HPLC assay results of tablets obtained by the compression process are summarized in Table 4.16.

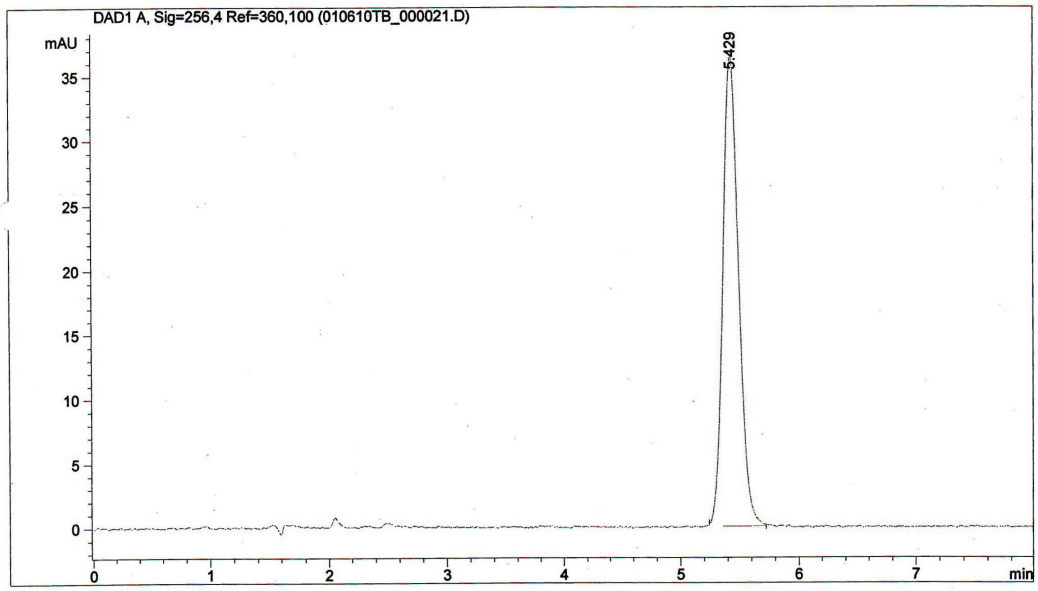
Corresponding HPLC chromatogram related to assay analysis is presented in Figure 4.16.

Table 4.16 Assay Analysis Results of Tablets

Code	Assay
F3_45BG	100,55%
F4_45KG	102,26%
F5_70BG	98,23%
F6_70KG	102,59%

ata File C:\CHEM32\...OXCARBAZEPINE TB\010610-OXCTB 2010-06-01 18-26-08\010610TB_000021.D
ample Name: 10. dak - 4

Acq. Operator : SG Seq. Line : 14
Acq. Instrument : ALET_2 Location : Vial 12
Injection Date : 6/1/2010 9:32:39 PM Inj : 1
Inj Volume : 10 µl
Sequence File : C:\Chem32\1\DATA\OXCARBAZEPINE TB\010610-OXCTB 2010-06-01 18-26-08\010610-OXCTB.S
Method : C:\Chem32\1\DATA\OXCARBAZEPINE TB\010610-OXCTB 2010-06-01 18-26-08\OXCDISS.M
Last changed : 5/19/2010 12:36:24 PM by EY
Method Info : OXCARBAZEPINE OS DISS



Area Percent Report with Performance

Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=256,4 Ref=360,100

RetTime [min]	k'	Area [mAU*s]	Height [mAU]	Symm.	Width [min]	Plates	Resolution	Selectivity
5.429	-	341.32758	36.46714	0.89	0.1433	7947	-	-

Figure 4.16 HPLC Chromatogram Related to Assay Analysis

- **HPLC Dissolution Analysis of Oxcarbazepine Tablet Formulation**

Dissolution analysis results of the tablets obtained after the tablet compression process, at purified water are presented in Table 4.17 and the dissolution analysis results at surfactant added water are presented in table 4.18.

The comparative dissolution graphs with different variations are presented in Figures 4.17, 4.18, 4.19, 4.20 and 4.21.

The corresponding HPLC chromatograms are presented in Figure 4.22.

Table 4.17 Dissolution Analysis Results of Tablets in Purified Water

Purified Water, 900 ml, 60 rpm, Apparatus II (paddle), auto sampling				
Time	**Oxcarbazepine 60 mg TB F3_45BG**	**Oxcarbazepine 60 mg TB F4_45KG**	**Oxcarbazepine 60 mg TB F5_70BG**	**Oxcarbazepine 60 mg TB F6_70KG**
0	0,0	0,0	0,0	0,0
5	17,7	22,9	10,9	17,8
10	27,6	32,6	22,2	29,0
15	33,3	37,7	29,1	35,4
20	36,2	41,4	33,8	39,8
30	39,6	46,4	40,0	43,3
45	42,5	49,9	44,7	46,7
60	44,4	53,0	47,7	49,8
75	46,5	54,6	49,8	51,3
90	47,7	56,0	51,4	52,9
120	50,6	57,6	53,0	55,2

Table 4.18 Dissolution Assay Analysis Results of Tablets in Surfactant Added Purified Water

Purified Water + 0,1%SDS, 900 ml, 60 rpm, Apparatus II (paddle), auto sampling				
Time	**Oxcarbazepine 60 mg TB F3_45BG**	**Oxcarbazepine 60 mg TB F4_45KG**	**Oxcarbazepine 60 mg TB F5_70BG**	**Oxcarbazepine 60 mg TB F6_70KG**
0	0,0	0,0	0,0	0,0
5	21,2	20,9	19,9	23,5
10	31,8	32,3	29,8	31,8
15	37,2	39,3	34,7	35,2
20	39,5	43,8	37,8	37,1
30	43,7	49,4	41,7	38,9
45	46,7	54,9	45,1	40,4
60	48,5	58,2	47,6	41,2
75	49,9	60,9	49,4	42,5
90	50,9	63,0	51,1	42,6
120	53,1	65,7	53,9	44,9

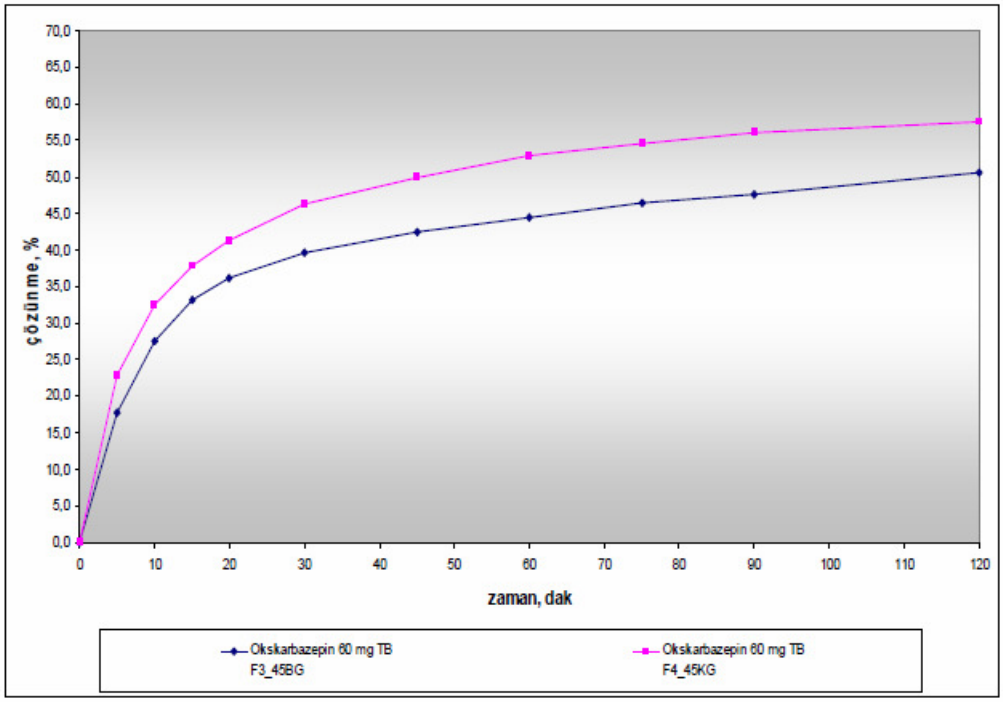


Figure 4.17 Dissolution Profiles of F3_45BG and F4_45KG Tablets in Purified Water

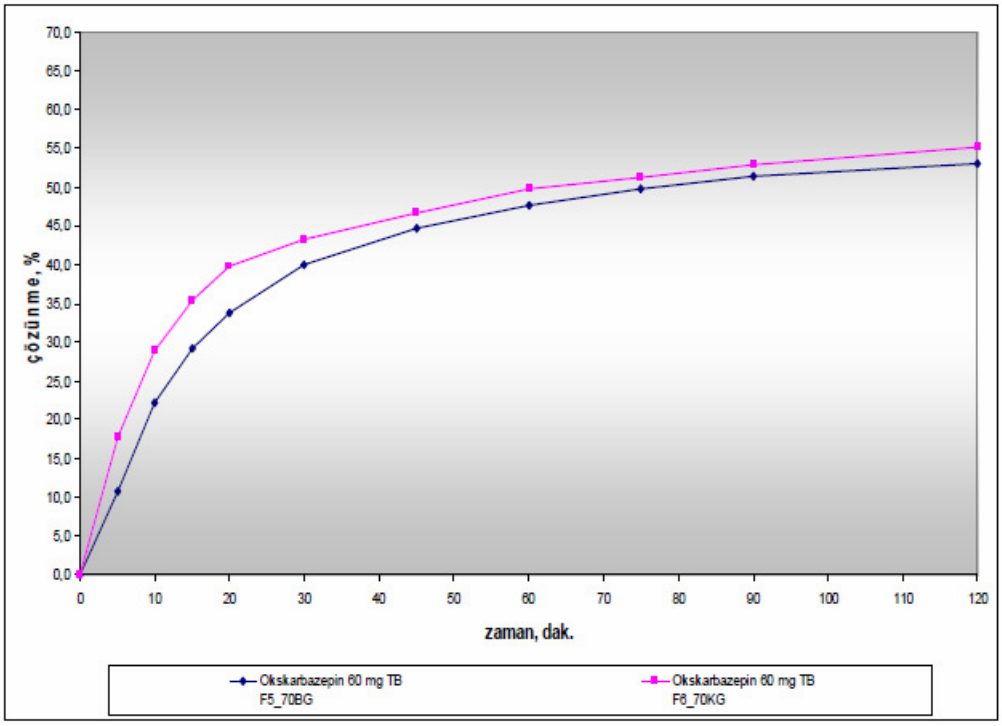


Figure 4.18 Dissolution Profiles of F5_70BG and F6_70KG Tablets in Purified Water

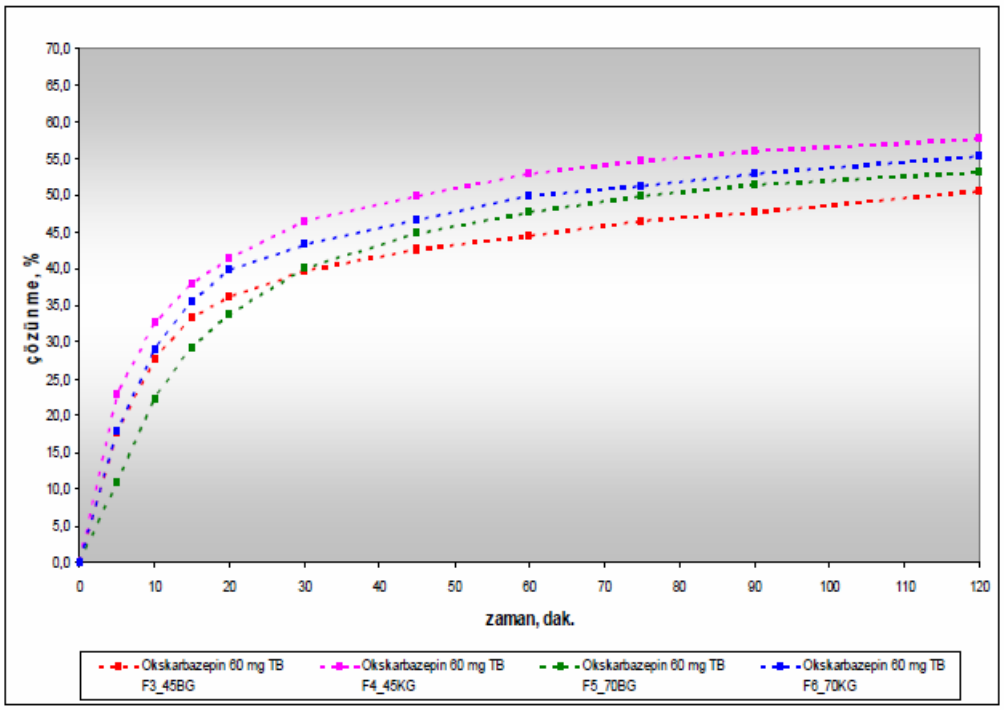


Figure 4.19 Dissolution Profiles of F3_45BG, F4_45KG, F5_70BG and F6_70KG Tablets in Purified Water

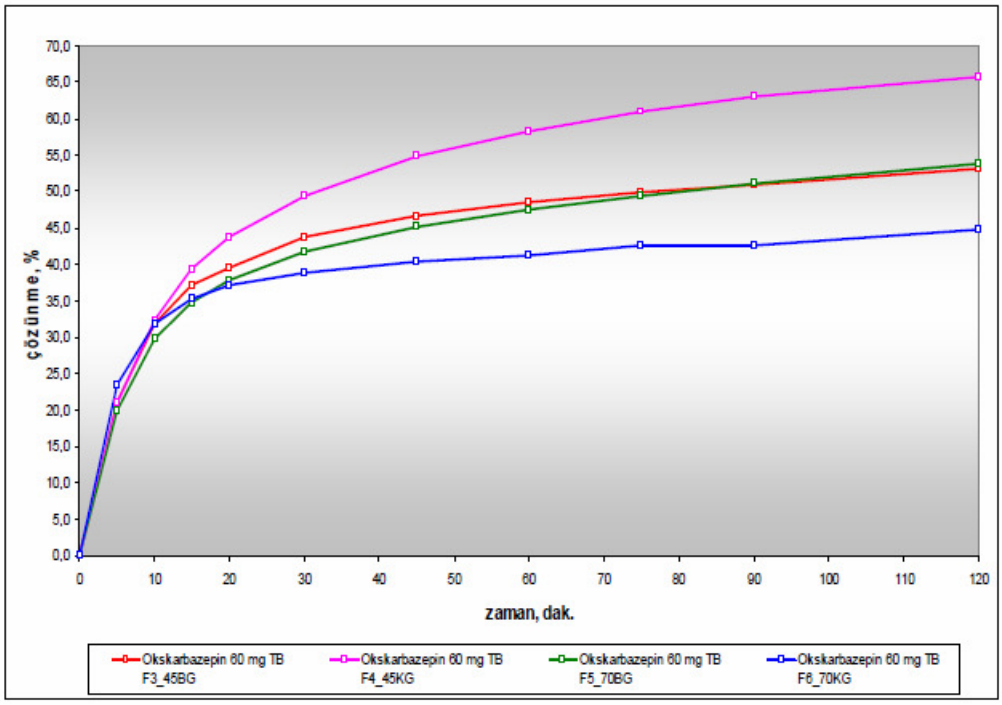


Figure 4.20 Dissolution Profiles of F3_45BG, F4_45KG, F5_70BG and F6_70KG Tablets in Surfactant Added Purified Water.

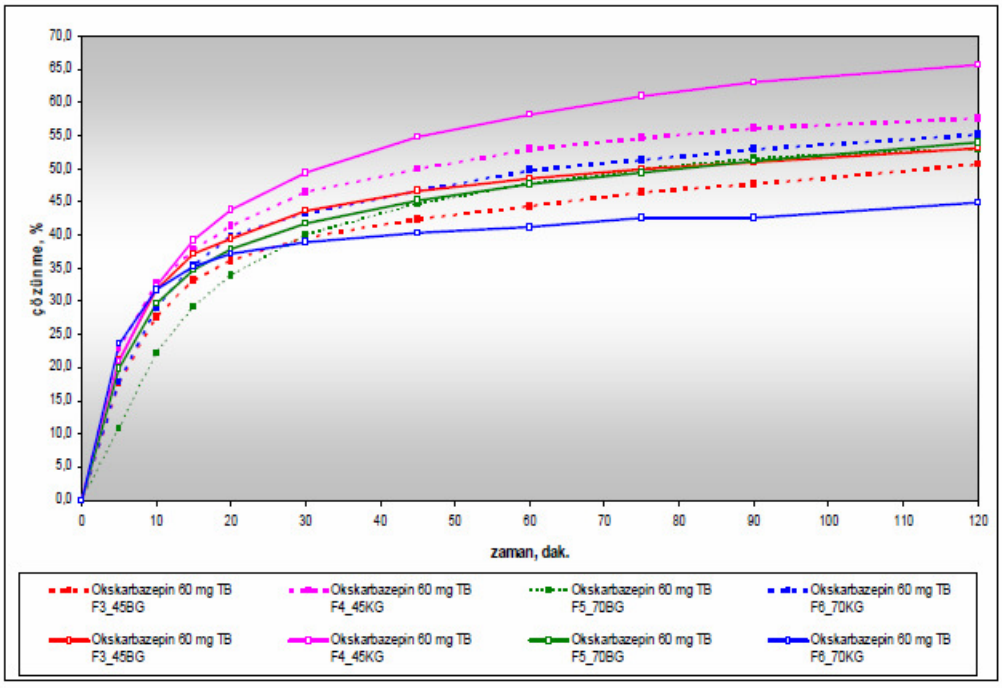
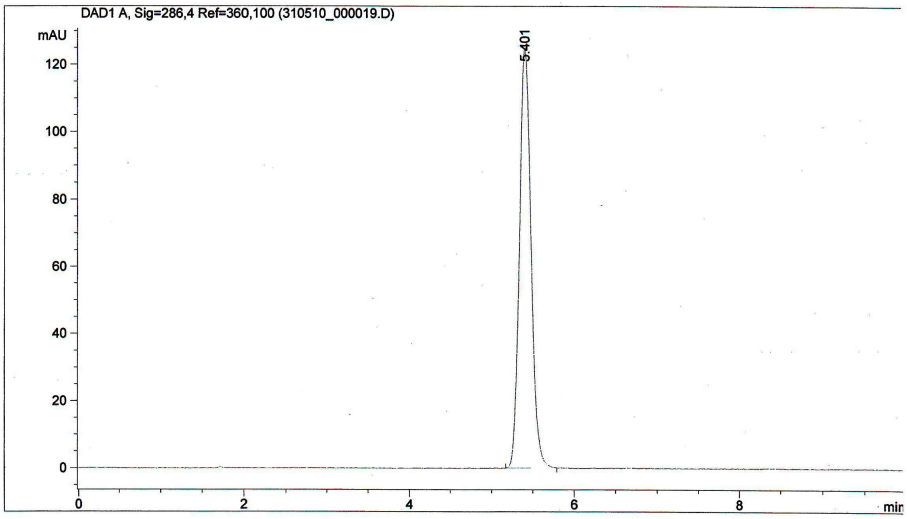


Figure 4.21 Dissolution Profiles of F3_45BG, F4_45KG, F5_70BG and F6_70KG Tablets in Purified Water and in Surfactant Added Purified Water.

Data File C:\CHEM32\1\DATA\OXCARBAZEPINE TB\310510TBMT 2010-05-31 17-27-09\310510_000019.D
Sample Name: 70um_T1_1

Acq. Operator : SG
Seq. Line : 7
Acq. Instrument : ALET_2
Location : Vial 7
Injection Date : 5/31/2010 8:51:54 PM
Inj : 2
Inj Volume : 10 µl
Sequence File : C:\Chem32\1\DATA\OXCARBAZEPINE TB\310510TBMT 2010-05-31 17-27-09\310510TBMT.S
Method : C:\Chem32\1\DATA\OXCARBAZEPINE TB\310510TBMT 2010-05-31 17-27-09\OXCMT.M
Last changed : 5/31/2010 5:25:21 PM by SG
Method Info : OXCARBAZEPINE OS MIKTAR TAYINI



Area Percent Report with Performance

Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=286,4 Ref=360,100

RetTime [min]	k'	Area [mAU*s]	Height [mAU]	Symm.	Width [min]	Plates	Resolution	Select ivity
5.401	-	1221.10779	124.55003	0.84	0.1483	7345	-	-

Figure 4.22 HPLC Chromatogram Related to Dissolution Assay Analysis

4.2.5. Analytical Method Validation

4.2.5.1 Specificity

Solutions of excipients (placebo), known impurities of the active ingredient (carbamazepine, methoxycarbamazepine) and the chemicals used in the analysis (mobile phase, media) have been prepared at original concentrations and analyzed with HPLC in order to determine if they elute at the same conditions. It was determined that the samples do not elute at the same conditions with Oxcarbazepine.

4.2.5.2 Linearity

In order to determine the linearity parameter in assay method validation study, a stock solution of 2,4 mg/ml concentration level in mobile phase and the following dilutions have been made; 0.15, 0.30, 0.45, 0.60, 0.75 and 0.90 mg/ml Oxcarbazepine. The prepared solutions have been filtered through 0.45µm membrane filter and then injected to the HPLC column. From the chromatograms, Oxcarbazepine peak area has been calculated and the calibration line has been drawn by using the average of areas of six studies of each of the concentration levels. Calibration line and the equation are presented in Figure 4.23.

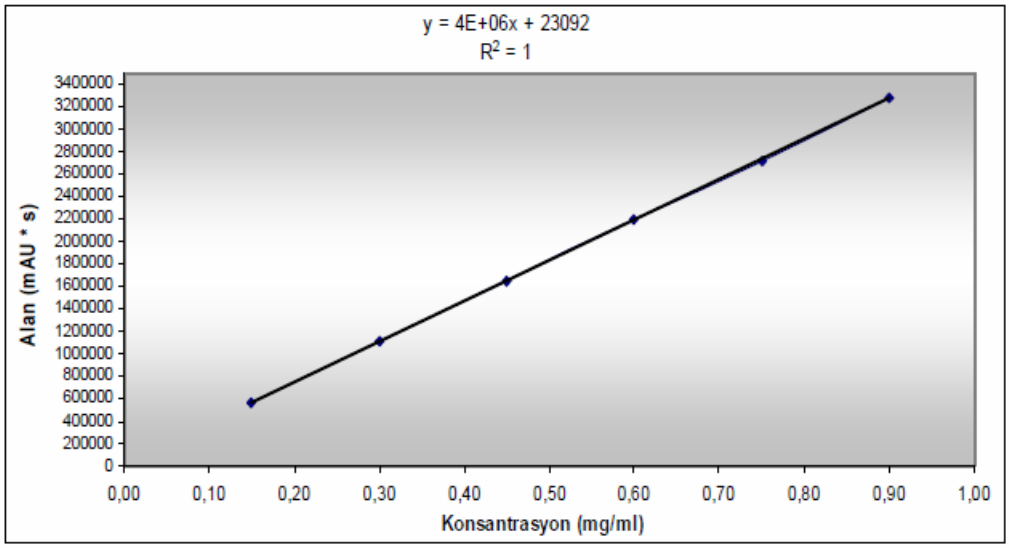


Figure 4.23 Oxcarbazepine Assay Calibration Line and Equation

In order to determine the linearity parameter in dissolution method validation study, a stock solution of 0.264 mg/ml concentration level in mobile phase and the following dilutions have been made; 0.0066, 0.0165, 0.0330, 0.0495, 0.0660 and 0. 0825 mg/ml Oxcarbazepine. The prepared solutions have been filtered through 0.45µm membrane filter and then injected to the HPLC column. From the chromatograms, Oxcarbazepine peak area has been calculated and the calibration line has been drawn by using the average of areas of six studies of each of the concentration levels. Calibration line and the equation are presented in Figure 4.24.

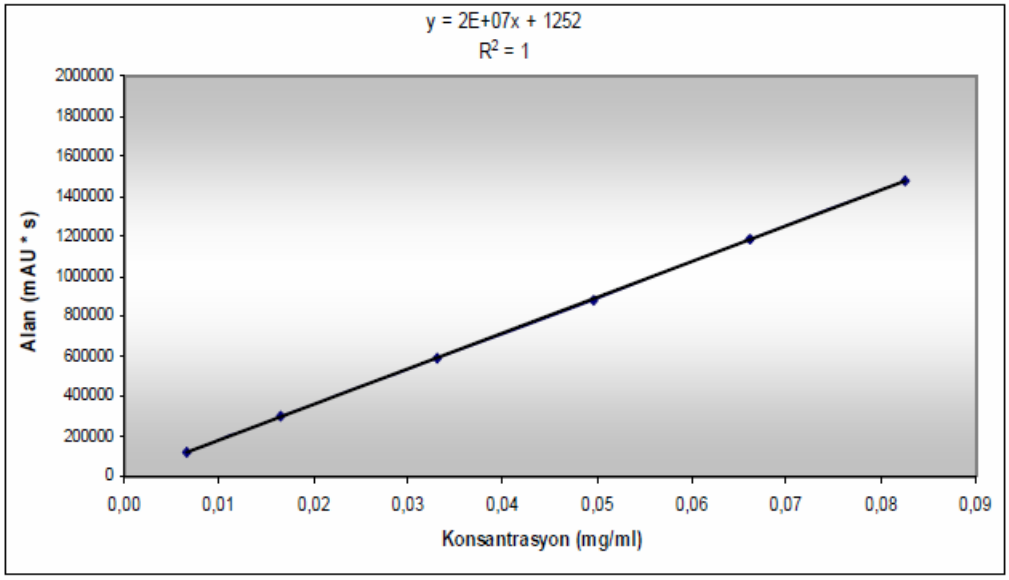


Figure 4.24 Oxcarbazepine Dissolution Calibration Line and Equation

2.4.5.3. Recovery

In order to determine the recovery parameter of assay method validation, three sample solutions at; 75%, 100% and 125% concentration levels (placebo+oxcarbazepine) have been prepared. These solutions have been taken into 100 ml glass flask , 60 ml of mobile phase is added and dissolved in ultrasonic bath. Samples have been made up to volume with mobile phase, filtered through 0.45µm filter and then injected to HPLC column. From the chromatograms, Oxcarbazepine peak are ahs been taken and recovery has been calculated. Obtained results are summarized in Table 4.19.

Table 4.19 Recovery Results of Oxcarbazepine Assay

%	Concentration	Average Peak Area	% Recovery	%Average Recovery
75	**0,45**	1639184,50	100,3	100,1
	0,45	1631338,00	99,9	
	0,45	1637123,00	100,2	
100	**0,60**	2183213,00	100,2	100,2
	0,60	2182264,00	100,2	
	0,60	2178888,00	100,1	
125	**0,75**	2724878,50	100,1	100,0
	0,75	2721296,50	100,0	
	0,75	2719314,00	99,9	
% Average Recovery				100.1
SD				0.13
%RSD				0.13

In order to determine the recovery parameter of dissolution method validation, three sample solutions at; 80%, 100% and 120% concentration levels (placebo+oxcarbazepine) have been prepared. These solutions have been subjected to dissolution analysis with 900 ml purified water, at 37°C and 60 rpm for 120 minutes. At the end of the process, 2 ml of solution from each vessel are withdrawn and filtered through 0.45µm filter and then injected to HPLC column. From the chromatograms, Oxcarbazepine peak are ahs been taken and recovery has been calculated. Obtained results are summarized in Table 4.20.

Table 4.20 Recovery Results of Oxcarbazepine Dissolution

%	Concentration	Average Peak Area	% Recovery	%Average Recovery
80	**0,0528**	920714	101,16	99,4
	0,0528	962827	98,91	
	0,0528	906301	97,98	
100	**0,0660**	1155933	98,88	97,7
	0,0660	1138851	96,97	
	0,0660	1160841	97,35	
120	**0,0792**	1395534	97,76	98,4
	0,0792	1393003	99,08	
	0,0792	1420891	98,27	
			% Average Recovery	98,5
			SD	1,24
			% RSD	1,26

4.2.5.4. Precision

In order to determine the precision parameter of assay analytical method validation, six samples of 100% concentration (oxcarbazepine+placebo) level have been prepared. Samples have been taken into 100 ml glass flasks and dissolved with 60 ml of mobile phase and sonicated for 15 minutes. Then samples have been made up to volume with mobile phase and filtered through 0.45µm membrane filter and injected to the HPLC column. In the chromatograms, oxcarbazepine peak areas were taken, recovery was calculated and the precision values of the six samples were calculated as summarized in table 4.21.

Table 4.21 Precision Results of Oxcarbazepine Assay

Sample	Average peak area	% recovery
1	2183213	100,2
2	2182264	100,3
3	2188888	100,6
4	2180820	100,1
5	2182108	100,3
6	2187401	100,5
% Recovery		100,3
SD		0,17
%SD		0,17

In order to determine the intermediate precision of the assay method , one analyst repeated the precision parameter. Obtained results are summarized in Table 4.22.

Table 4.22 Intermediate Precision Results of Oxcarbazepine Assay

Sample	Analyst I , % Recovery	Analyst II , % Recovery
1	100,2	99,6
2	100,3	99,1
3	100,6	100,5
4	100,1	100,1
5	100,3	100,1
6	100,5	99,4
% Average Recovery	100,3	99,8
SD	0,17	0,53
%RSD	0,17	0,53
% Difference	0,36	

In order to determine the system precision in assay method validation, Standard solution has been injected 5 times and the % RSD has been calculated. Obtained results are summarized in Table 4.23.

Table 4.23 System Precision Results of Oxcarbazepine Assay

Injection	Peak Area
1	2199864
2	2197379
3	2197435
4	2198762
5	2197896
Average	2198267
SD	1050,46
% RSD	0,05

In order to determine the precision parameter of dissolution method validation, six sample solutions at; 100% concentration level (placebo+oxcarbazepine) have been prepared. These solutions have been subjected to dissolution analysis with 900 ml purified water, at 37°C and 60 rpm for 120 minutes. At the end of the process, 2 ml of solution from each vessel are withdrawn and filtered through 0.45µm filter and then injected to HPLC column. From the chromatograms, Oxcarbazepine peak has been taken and recovery has been calculated. Obtained results are summarized in Table 4.24.

Table 4.24 Precision Results of Oxcarbazepine Dissolution

Sample	Average peak area	% Recovery
1	1155933	98,48
2	1138851	96,58
3	1160841	96,96
4	1180880	98,77
5	1146724	97,18
6	1157668	97,79
% Recovery		97,63
SD		0,87
%RSD		0,89

In order to determine the intermediate precision parameter in dissolution method validation, an analyst repeated the precision parameter analysis. Obtained results are summarized in Table 4.25.

Table 4.25 Intermediate Precision Results of Oxcarbazepine Dissolution

Sample	Analyst I , % Recovery	Analyst II , % Recovery
1	98,48	99,05
2	96,58	97,62
3	96,96	98,12
4	98,77	96,82
5	97,18	97,24
6	97,79	98,54
% Average Recovery	97,63	97,90
SD	0,87	0,83
% RSD	0,89	0,85
% Difference	0,04	

In order to determine the system precision parameter in dissolution method validation, the Standard solution has been injected five times and % RSD has been calculated. Obtained results are summarized in Table 4.26.

Table 4.26 System Precision Results of Oxcarbazepine Dissolution

Injection	Peak area
1	1167913
2	1167684
3	1167433
4	1170316
5	1169371
Average	1168543
SD	1244,59
% RSD	0,11

4.2.5.5 Robustness

In order to determine the robustness parameter in assay and dissolution analytical method validation, the 100% sample and standard solutions prepared in precision parameter are used. Standard and sample injections were made by changing only one of the chromatographic conditions each time.

The difference between the recovery value of the 100% sample prepared during precision parameter of the assay and dissolution analysis and the recovery value calculated in robustness parameter, has been calculated. Obtained results are presented in Table 4.27, Table 4.28, Table 4.29 and 4.30.

Table 4.27. Robustness Results of Oxcarbazepine Assay

Sample	**0,8 ml/min.**		**1,0 ml/min (validation conditions)**		**1,2 ml/min.**	
OX	**Retention time (min)**	**%**	**Retention time (min)**	**%**	**Retention time (min)**	**%**
	5,633	99,95	5,422	100,00	5,283	99,92

Table 4.28. Robustness Results of Oxcarbazepine Assay

Sample	**35°C**		**40°C (validation conditions)**		**45°C**	
OX	**Retention time (min)**	**%**	**Retention time (min)**	**%**	**Retention time (min)**	**%**
	5.435	99,72	5.422	100,00	5.401	99,63

Table 4.29. Robustness Results of Oxcarbazepine Dissolution

Sample	**0,8 ml/min.**		**1,0 ml/min (validation conditions)**		**1,2 ml/min.**	
OX	**Retention time (min)**	**%**	**Retention time (min)**	**%**	**Retention time (min)**	**%**
	5,616	98,54	5,401	100,00	5,264	99,21

Table 4.30. Robustness Results of Oxcarbazepine Dissolution

Sample	**35°C**		**40°C (validation conditions)**		**45°C**	
OX	**Retention time (min)**	**%**	**Retention time (min)**	**%**	**Retention time (min)**	**%**
	5.419	99,36	5.401	100,00	5.435	99,57

4.2.5.6. Stability

In order to show that oxcarbazepine is stable throughout the analysis period, the Standard and 100% precision sample solutions prepared for assay and dissolution methods, have been injected 48 hours later and the obtained results are presented in Table 4.31. and Table 4.32.

Table 4.31. Stability Results of Oxcarbazepine Assay

OX	**% Conformity of Standard Solution (50 hours)**	**% Conformity of Sample Solution (48 hours)**
	98,3	100,3

Table 4.32. Stability Results of Oxcarbazepine Dissolution

OX	% Conformity of Standard Solution (38 hours)	% Conformity of Sample Solution (31 hours)
	100,2	100,4

4.2.6. Surfactant Added Oxcarbazepine Formulation Study

As a final study, different levels of surfactant added to the unit Formula by using the API with particle size distribution chosen based on the analysis results obtained from the studies explained in section 4.2.4. and dissolution study has been performed. Results are presented in Table 4.33. Dissolution graph is presented in section 4.25.

Table 4.33 Dissolution Analysis Results of Surfactant Added Tablets in Purified Water Medium

Purified Water, 900 ml, 60 rpm, Apparatus II (paddle), automatic sampling				
Time	**Oxcarbazepine 60 mg TB F7 45KG %0,25 SDS**	**Oxcarbazepine 60 mg TB F8 45KG %0,50 SDS**	**Oxcarbazepine 60 mg TB F9 45KG %1,00 SDS**	**Oxcarbazepine 60 mg TB F10 45KG %2,00 SDS**
0	0,0	0,0	0,0	0,0
5	26,5	35,3	47,5	58,4
10	41,7	49,7	56,6	67,1
15	48,2	55,2	62,4	74,9
20	53,6	60,1	69,9	86,6
30	59,2	64,4	75,2	97,2
45	63,4	68,0	79,1	101,0
60	67,1	73,5	84,5	99,9
75	69,0	76,9	91,3	102,1
90	70,8	78,2	95,4	102,2
120	71,6	80,6	99,7	102,6

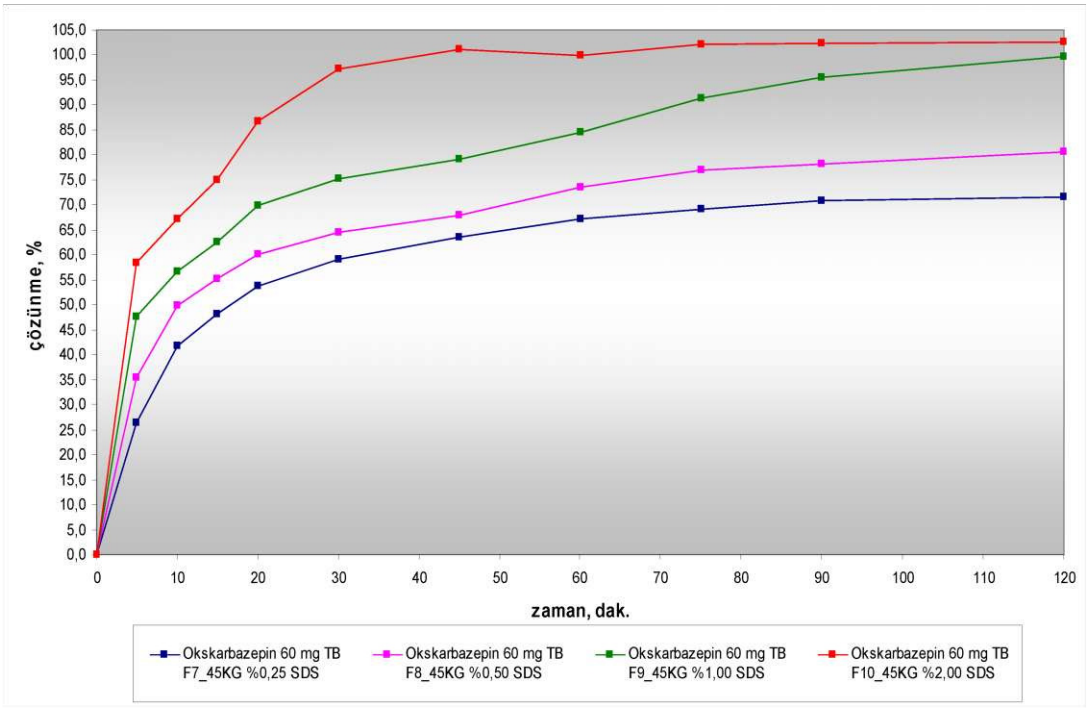


Figure 4.25. Dissolution Profiles of F7_45KG %0,25 SDS, F8_45KG %0,50 SDS, F9_45KG %1,00 SDS and F10_45KG %2,00 SDS Tablets in Purified Water

5. DISCUSSION

5.1. Studies Performed on Oxcarbazepine API

Dissolution assay and DSC analysis that have been explained in section 3.2.1. have been performed on oxcarbazepine API.

- **HPLC Assay Analysis of Oxcarbazepine API**

API with three different particle size distributions has been tested at purified water medium. According to Çapan (2400), particle shape and size has an effect on solubility and dissolution. Decrease of particle size increases the solubility. Same has been observed with the performed studies.

- **HPLC Dissolution Assay Analysis of Oxcarbazepine API**

API with three different particle size distributions has been tested at purified water medium. According t o Çapan (2400), particle shape and size has an effect on solubility and dissolution. Decrease of particle size increases the solubility. Same has been observed with the performed studies.
Although there is difference between the solubilities, at the end of 120 minutes it was observed that none of them reached 100% and ended up at approximately the same levels.

- **DSC Analysis**

API with three different particle size distributions has been tested. According to Hıncal and Bilensoy (2004), DSC analysis helps to determine the polymorphism, melting point and determination of phase changed during melting, during pre-formulation phase. Observing the DSC thermograms individually and comparatively, it was determined that; “peak”, “onset” and “end” points do not show significant

differences, that the materials show peaks at the same melting point. No other peaks have been observed except the main peak in the DSC thermograms of the materials. And this shows that the three different particle sizes of the material have the same polymorphic structure.

5.2. Preparation and Analysis of Oxcarbazepine Tablet Formulation

Discussions of the results obtained from the studies explained in detail in section 3.2.2. are presented below in detail.

5.2.1. Oxcarbazepine Unit Formula and FB Process Parameters

In order to determine and optimize the maximum and minimum parameters, 10 trial studies have been performed using different parameters with the unit formula given in section 3.2.2.1., by using the 45µm API.

According to Knöll (2010), during the FB studies, high inlet air temperature, air inlet flow, low spray pressure and spray ratio results with small particle size granules, and low inlet air temperature, air inlet flow, high spray pressure and spray ratio results with big particle size granules. In other words, when the powder to be granulated is close to the spray unit and wet, the granules form bigger.

Obtained results supported the theory.

At the end of the trials, too much agglomeration has been observed at trials D_2 and D_5, and granulation was not successful for trial D_3. In the other trials which were accepted as successful, the particle size distribution has been tested and the trials in which the highest effect of process parameters on the particle size has been determined.

Trial study D_1 in which the biggest particles has been observed was accepted as the maximum parameter and the trial study D_4 in which the smallest particle has been observed was accepted as the minimum parameter.

These maximum and minimum parameters have been repeated with 3µm, 45µm and 70µm APIs and the dry granule analysis have been performed.

5.2.2. Granule Analysis and Calculations After FB Process

Discussions of the results obtained from the studies performed on different particle size APIs are presented below. All results are summarized in Table 5.1.

- **Particle Size Analysis**

Based on the studies performed by using the 3µm API with codes F1_3BG and F2_3KG according to the particle size analysis of granules obtained after the FB wet granulation process, granules obtained did not have acceptable flowability results. Due to the agglomerates occurred because of the micronized structure of the powder, particle size distribution has not been tested.

Based on the studies of 2_45BG, F3_45KG, F4_70BG and F5_70KG, it was determined that when minimum parameters are used, the obtained granules have small particle size distribution and when maximum parameters are used, the obtained granules have big particle size distribution.

- **Flowability**

According to Baykara (2004), in order to determine the flow properties, flow rate and bulk angle methods are used. In order to determine the flow rate, the time that a certain amount of powder flows through a funnel is measured. The powder flowing continuously is accepted as good flowing powder. However, the powder that is

accepted as the stable flowing powder is not the quickest one but the powder whose average of ten replicate flowability showing minimum variability.

Based on this theory, obtained results are evaluated.

Based on the studies performed by using the dry granules obtained after FB wet granulation process with 3µm API with codes F1_3BG and F2_3KG, granules obtained did not have acceptable flowability results.

Based on the studies of 2_45BG, F3_45KG, F4_70BG and F5_70KG, it was determined that small particle size granules obtained by using the minimum parameters have better flowability properties than the big particle size granules obtained by using the maximum parameters.

- **Bulk Density and Tapped Density**

According to Baykara (2004), the first steps of solid dosage forms, powder, powder mixture and granules' volume/weight relation must stay stable.

With this purpose, each used intermediate product must have a certain bulk density before possible dosing, so that it will be possible to obtain tablets with same or within the acceptable tolerance limits tablet weight.

And tapped density, bulk volume must decrease when tapped on powder or granule as the smaller size particles go into the spaces between the bigger size particles.

According to the bulk density and tapped density results related to the dry granules obtained from FB wet granulation process, it has been observed that the desired ratio between the particle sizes and tapped density of obtained granules was provided.

- **Carr's Index**

According to the Carr's Index results of dry granules obtained after the FB wet granulation process calculated in Table 3.8, the results of F1_3BG and F2_3KG studies are not good, and the results of studies F2_45BG, F3_45KG, F4_70BG are good and the result of study F5_70KG is in between.

- **Ratio**

According to the Hausner Ratio results of dry granules obtained after the FB wet granulation process calculated in Table 4.9, the results of F1_3BG and F2_3KG studies are not good, and the results of studies F2_45BG, F3_45KG, F4_70BG and F5_70KG are good.

- **Moisture**

According to the moisture results of the dry granules obtained after the FB wet granulation process, there is no significant difference between the granules.

Table 5.1. FB Granulation Results Summary Table

Code	PSD	Flow	Density	Carr's Index	Hausner Ratio	Moisture
F1_3BG	d(0,1):7,267 d(0,5):80,608 d(0,9):240,329	No flow	YD: 0.518 g/ml SD: 0.709 g/ml	26,94	1,37	0,68%
F2_3KG	d(0,1):3,037 d(0,5):43,986 d(0,9):130,480	No flow	YD: 0.422 g/ml SD: 0.631 g/ml	33,12	1,50	0,60%
F3_45BG	d(0,1):29,837 d(0,5):100,911 d(0,9):218,631	25mm:1.8 sec 15mm:5.5 sec 10mm:14,5 sec	YD: 0.609 g/ml SD: 0.689 g/ml	11,16	1,13	0,96%
F4_45KG	d(0,1):16,573 d(0,5):65,076 d(0,9):142,733	25mm:2.5 sec 15mm:8.0 sec 10mm:25 sec	YD: 0.657 g/ml SD: 0.763 g/ml	13,89	1,16	0,78%
F5_70BG	d(0,1):16,644 d(0,5):85,824 d(0,9):224,631	25mm:2.2sec 15mm:7.3sec 10mm:23,6sec	YD: 0.657 g/ml SD: 0.769 g/ml	14,56	1,17	0,88%
F6_70KG	d(0,1):15,261 d(0,5):61,933 d(0,9):146,950	25mm:2.7sec 15mm:8.4sec 10mm: 29,2sec	YD: 0.643 g/ml SD: 0.786 g/ml	18,19	1,22	0,53%

5.2.3. Tablet Compression Process

According to the granule analysis results, since the granule properties of the studies F1_3BG and F2_3KG are insufficient for tablet compression process, it was decided to continue with the F3_45KG, F4_70BG ve F5_70KG studies. Tablet compression studies of F2_45BG, F3_45KG, F4_70BG ve F5_70KG studies have been performed successfully.

5.2.4. Physical and Chemical Analysis After Tablet Compression Process

Physical and chemical analyses have been performed and dissolution results have been evaluated of the tablets obtained from the F2_45BG, F3_45KG, F4_70BG ve F5_70KG studies. All physical and chemical results obtained from the studies are summarized in Table 5.2.

Table 5.2. Tablet Compression Results Summary Table

Code	Average tablet weight	Hardness	Friability	Disintegration	Assay
F3_45BG	300,11mg	10,96 kP	0,01%	66 sec.	%100,55
F4_45KG	300,84mg	9,99 kP	0,01%	74 sec.	% 102,26
F5_70BG	299,97mg	9,38 kP	0,02%	126 sec.	% 98,23
F6_70KG	300,07mg	7,29 kP	0,04%	96 sec.	% 102,59

Evaluating the physical and chemical analysis results of the tablets, it was observed that all studies gave good results.

After the evaluation of dissolution results, based on the results of dissolution profiles summarized in Table 4.15, it was determined that the dissolution of small particle size granules obtained using the minimum parameters is faster than the dissolution of big particle size granules obtained using the maximum parameters.

By these results, it was proven that the process parameters have effect on the physicomechanical properties of the granules to be obtained and the dissolution rate of the tablets Baykara (2004).

Study F4_45KG was chosen as the most successful study taking into account all granule and tablet analysis results. Despite this, the maximum dissolution that can be obtained by changing the API particle size and FB process parameters after 120 minutes was determined as 57,6%.

5.2.5. Analytical Method Validation

5.2.5.1. Specificity

It was observed that there is no peak interfering with Oxcarbazepine.

5.2.5.2. Linearity

In order to plot the assay method calibration line, in 0.15-0.90 mg/ml mobile phase, between 2.4 mg/ml concentrations constitutes the working range. Calibration line was plotted by using peak areas against concentration. Calibration line equation is y=4E+06x + 23092 and the R2=1,0000.

In order to plot the dissolution analysis method calibration line, concentrations between 0.00660-0825 mg/ml constitute the working range. Calibration line was plotted by using peak areas against concentration. Calibration line equation is y=2E+07x + 1252 and the R2=1,0000.

In validation studies, R2 value is expected to be between 0.9900 and 1.0000, and the obtained values are acceptable.

5.2.5.3. Recovery

In order to evaluate the recovery parameter in the assay analytical method validation, triple samples of solutions containing 75%, 100% and 125% API (placebo+oxcarbazepine) and injected into the HPLC. Oxcarbazepine peak area is taken from the chromatograms and the recovery was calculated. The recovery values of all samples must be between 98-102%. Obtained results are within the acceptable limits.

In order to evaluate the recovery parameter in the dissolution analytical method validation, triple samples of solutions containing 80%, 100% and 120% API (placebo+oxcarbazepine) and injected into the HPLC. Oxcarbazepine peak area is taken from the chromatograms and the recovery was calculated. The recovery values of all samples must be between 95-105%. Obtained results are within the acceptable limits.

5.3.5.4. Precision

In order to analyze the precision parameter of assay method validation, solution having 100% API concentration (placebo+oxcarbazepine) was prepared six times and injected into the HPLC. Oxcarbazepine peak area is taken from the chromatograms and the recovery was calculated. The recovery values of all samples must be between 98-102%. Obtained results are within the acceptable limits.

In order to analyze the intermediate precision parameter of assay method validation, at the end of the validation another analyst repeated the precision parameter. The maximum difference between the % recovery of both analysts and the %RSD must be less than 3%. Obtained results are in between the limits.

In order to analyze the system precision parameter of assay method validation, Standard solution was injected 5 times and RSD% was calculated. The maximum RSD between areas of 5 consecutive injections must be the 2.0%. Obtained results are in between the limits.

In order to analyze the precision parameter of dissolution method validation, solution having 100% API concentration (placebo+oxcarbazepine) was prepared six times and injected into the HPLC. Oxcarbazepine peak area is taken from the chromatograms and the recovery was calculated. The recovery values of all samples must be between 95-105%. Obtained results are within the acceptable limits.

In order to analyze the intermediate precision parameter of dissolution method validation, at the end of the validation another analyst repeated the precision parameter. The maximum difference between the % recoveries of both analysts must be 5% and the %RSD must be less than 2%. Obtained results are in between the limits.

In order to analyze the system precision parameter of assay method validation, Standard solution was injected 5 times and RSD% was calculated. The

maximum RSD between areas of 5 consecutive injections must be the 2.0%. Obtained results are in between the limits.

5.2.5.5. Robustness

In order to determine the robustness parameter in assay and dissolution analytical method validation, the 100% sample and standard solutions prepared in precision parameter are used. Standard and sample injections were made by changing only one of the chromatographic conditions each time.

The difference between the recovery value of the 100% sample prepared during precision parameter of the assay and dissolution analysis and the recovery value calculated in robustness parameter, has been calculated.

Oxcarbazepine retention times are changed by the changes of the flow rate. On the other hand there was no change observed with the recovery values. A change of ± 0,2 ml/min. In flow rate does not affect the analysis results negatively.

Upon changes on the column temperatures, no change in the oxcarbazepine retention times and % recovery values are observed. A change of ± 5 °C in column temperature does not have a significant effect on the results.

5.2.5.6.Stability

In order to show that oxcarbazepine is stable throughout the analysis, Standard and 100% precision solutions were injected again after 48 hours.

Standard solution for assay analysis is stable for 50 hours, and the sample solution is stable for 48 hours at 10°C.

Standard solution for dissolution analysis is stable for 38 hours, and the sample solution is stable for 31 hours at 10°C.

5.2.6. Surfactant Added Oxcarbazepine Formulation Study

Different levels of surfactant were added to the unit Formula presented in Table 3.5., and the formulation in which the dissolution reaches 99.7% was determined.

According to that, F9_45KG study in which 1% SDS was used has found to be successful.

6. RESULTS AND PROPOSALS

Below listed results were obtained from the studies performed in order to increase the solubility of oxcarbazepine molecule which has a low solubility.

- Particle size of the used API has an effect on the dissolution of the product in the final pharmaceutical form.

- Used technology and the parameters of the used technology have effect on the product in the final pharmaceutical form.

- Using these two different variables together has a positive synergic effect on the solubility of the product in the final pharmaceutical form.

- Maximum solubility that can be obtained by changing API particle size distribution and AY process parameters has been determined as 56.7%.

- It was concluded that dissolution cannot be increased any further without a change in the formulation. Thus, surfactant was added to the formulation in order to determine the formulation in which dissolution reaches up to 100%. It was determined that 1%SDS addition, increases the dissolution to 99.7%.

As a summary, with this study it was proven that it is possible to develop a therapeutically effective finished product from a crystalline active material having a low solubility by changing the formulation and process parameters. In case smaller particles are obtained without changing the crystalline structure, then it is possible to increase the solubility without negatively affecting the stability. Also it was once again proven that with the addition of surfactants to the formulation will increase the dissolution as already been shown in the literature. The necessity of optimization studies in the fluidized bed granulation technology was shown by proving the effect of changes in these parameters on active ingredient solubility and drug release characteristics.

These studies to show the effect of changes on fluidized bed technology process parameters on solubility of active ingredient, can be widened by performing studies on other low solubility active ingredients. Also, the effect of other granulation method process parameters (i.e. high-shear) different than this technology on the drug release can be investigated.

REFERENCES

Badawy S. I. F. et al., (2000), Effect of process parameters on compressibility of granulation manufactured in a high shear mixer. Int. J. Pharm. 198:51-61

Badawy S. I. F. and Hussain M. A., (2004), Effects of starting material particle size on its agglomeration behavior in high shear wet granulation, AAPS Pharm. Sci. Tech. 5, Art:38

Banakar U. V., (1992), Factors that Influence Dissolution Testing, Pharmaceutical Dissolution Testing, (5.bs), (s:133-137), NY, Informa Healthcare USA, Inc.

Banker G. D. et al., (1980), Tablet Formulation and Design. Liebermann H. A., Lachman L. (Eds.), Pharmaceutical Dosage Forms-Tablets, vol.1, NY, Marcel Dekker, Inc.

Baykara T., (2004), Tozlar, Granüller ve Mikropelletler. Gürsoy, A. Z., (Ed.) Farmasötik Teknoloji-Temel Konular ve Dozaj Şekilleri, (s.313-329), İstanbul-Kontrollü Salım Sistemleri Derneği Yayını No:2

Birudaray R. et al., (2007), Granulation Characterization. Parikh D.M. (Ed.), Handbook of Pharmaceutical Granulation Technology, (2.bs) (s.513- 531), NY, Informa Healthcare USA, Inc.

Brittain H. G. et al., (1991), Physical characterization of pharmaceutical solids, Pharm. Res., 8:963

Çapan Y., (2004), Çözünürlük ve çözünme hızına etki eden faktörler. Gürsoy A. Z., (Ed.), Farmasötik Teknoloji-Temel Konular ve Dozaj Şekilleri (s.89-99), İstanbul, Kontrollü Salım Sistemleri Derneği Yayını No:2

Çapan Y., (2005), An overwiev of dissolution and bioequivalence, FIP/TUFTAD Hands on dissolution workshop, Istanbul

Çelik M. and Driscoll C. E., (1993), An Overview Of The Effects Of Some Physico-Chemical And Mechanical Characteristics Of Particulates On The Compaction And Post-Compaction Properties Of Compacts, Drug Development And Industrial Pharmacy, 19 (17&18), 2119-2141

Çelik M., (1996), The Past, Present, and Future of Tableting Technology, Drug Development And Industrial Pharmacy, 22 (1), 1-10

Çelik M., (2008), General Formulation and Process Development Guidelines, Formulation & Process Development & Troubleshooting. 18-19 Haziran 2008-İstanbul. Bildiriler (s.1-96), İstanbul-Academia.

Çelik M., (2008), Theory And Practice Of Pharmaceutical Compaction, Mod. 6

Gao J. Z. H. et al., (2002), Fluid bed granulation of a poorly water soluble, low density, micronized drug: comparison with high shear granulation, Int. J. of Pharma 237:1-14

Tableting/Compaction, New Jersey, USA

Chirkot T. and Propst C., (2007), Low-shear Granulation. Parikh, D M. (Ed.), Handbook of Pharmaceutical Granulation Technology, (2.bs) (s.229-235), NY, Informa Healthcare USA, Inc.

Contini S. and Atasoy K., (1966), Pharm Ind 28, 144-146

Davies W. and Gloor W., (1971), Batch production of pharmaceutical granulations in a fluidized bed I: Effects of process variables on physical properties of final granulation, Jour. of Pharm. Sci., V60, 12:1869-1874

Diederich A. et al., (2009), Manufacture of Solid Dispersion in the Fluid Bed, Novartis Pharma AG, Poster.

Ennis B. J., (2007), Theory of Granulation: An Engineering Perspective. Parikch D.M (Ed.), Handbook of Pharmaceutical Granulation Technology, (2.bs) (s.7-77), NY, Informa Healthcare USA, Inc.

Erdil M. S. et al., (2009), The Effect of Fluidized Bed Systems on Granule Flowability and Compaction Properties, FIP Congress, İstanbul, TÜRKİYE

Farber L. et al., (2003), Use of X-ray tomography to study the porosity and morphology of granules, Powder Technology 132(1), 57-63

Faure et al., (2001), Process control and scale-up of pharmaceutical wet granulation processes, Eur. J. of Pharm. and Biopharm., 52:269-277.

Fonner D. E. et al., (1981), Granulation and Tablet Characteristics, Liebermann H.A., Lachman, L (Eds.), Pharmaceutical Dosage Forms-Tablets, vol. 2., NY, Marcel Dekker, Inc.

Gao J. Z. H. et al., (2002), Fluid bed granulation of a poorly water soluble, low density, micronized drug: comparison with high shear granulation, Int. J. of Pharma 237:1-14

Gerald F., (2004), Overview of the clinical pharmacokinetics of oxcarbazepine, Clinical Drug Investigation 24(4), 185-203.

Gil E. C. et al., (2010), Tablet Design, Pharm. Sci. Ency. Drug Discovery, Development and Manufacturing

Giry K. et al., (2009), Comparison of single pot and multiphase granulation Part I: Effect of the high shear granulator on granule properties according to the drug substance and its concentration, Pharm. Dev. and Tech., 14(2):138-148.

Gokhale R. and Sun Y., (2007), High-shear Granulation, Parikh, D.M. (Ed.), Handbook of Pharmaceutical Granulation Technology, (2.bs)(s.191-204), NY, Informa Healthcare USA, Inc.

Hamed E. et al., (2007), Batch Fluid Bed Granulation, Parikh D.M. (Ed.), Handbook of Pharmaceutical Granulation Technology, (2.bs), NY, Informa Healthcare USA, Inc.

Hausman D. S., (2004), Comparison of low shear, high shear and fluid bed granulation during low dose tablets process development, Drug Dev. And Ind. Pharm. Vol.30, No 3:259-266

Hıncal A. A. and Bilensoy M. E., (2004), Ön formülasyon ve ürün gelistirme, Gürsoy A.Z. (Ed.), Farmasötik Teknoloji-Temel Konular ve Dozaj Sekilleri (s.89-99), İstanbul, Kontrollü Salım Sistemleri Dernegi Yayını No:2

Holm P. et al., (1996), Pelletization by granulation in a rotoprocessor RP-2, Part I, Effects of process and product variables on granule growth, Pharm. Tech. Eur., 8:22-36

Holm P. et al., (2001), End point detection in a wet granulation process, Pharm. Dev. Tech. 6:181-192

ICH Harmonized Tripartite Guideline, Validation of Analytical Procedures, Text and Methodology, Q2 (R1)

Jäger K. F. and Bauer K. H., (1982), Effects of material motion on agglomeration in the rotary fluidized bed granulator, Drug Made Ger., 25:61-

65

Khatry S., (2010), PharmaTimes, Vol 42 - No 2

Knight P. C. et al., (2000), An investigation of the effects on agglomeration of changing the speed of a mechanical mixer, Powder Tech., 110:204-209

Knight P. C., (1993), An investigation of the kinetics of granulation using a high shear mixer, Powder Tech., 77:159-169

Knöll M., (2010), Process Parameters of High Shear and Fluid Bed Granulators, Granulation Form Powder to Tablet Seminar II, Schopfheim, Germany

Kristensen H. G. et al., (1985), Mechanical properties of moist agglomerates in relation on granulation mechanisms, Part I, 44:227-237

Kristensen H. G. and Shaefer T., (1987), Granulation, A Review on Pharmaceutical Wet Granulation, Drug Dev. Ind. Pharm., 13(4-5): 803-873

Kristensen H. G., (1988), Agglomeration of Powders, Acta Pharm Succ., 94:245-258

Kristensen H. G., (1998), Agglomeration of Powders, Acta Pharm. Succ., 25:187-204.

Kristensen H.G. et al., (1985), Mechanical properties of moist agglomerates in relation on granulation mechanisms, Part II, 44:239-247

Kristensen J. and Hansen V. W., (2006), Wet granulation in Rotary Processor & Fluid Bed: Comparison of Granule & Tablet Properties, AAPS Pharm. Sci. Tech. 7, Art. 22

Leuenberger H. et al., (1990), New development in the control of a moist agglomeration and pelletization process, STP Pharma Sci., 6:303-309

Leuenberger H., (1982), Granulation, new technique, Pharm. Acta Helv., 57:72-80

Lieberman H. et al., (1990), Granulation technology and tablet compression, In Pharmaceutical Dosage Forms Tablets, 2nd Ed., Marcel Dekker Inc., New York, Vol 2:245-316.

Liske and Mobus, (1968), The manufacture and comparative aspects of fluidized layer spray granulation, Drugs Made Germany, XI:172-189

Marshall K., (1989), 'Monitoring Punch Forces And Punch Movements As An Aid To Developing Robust Tablet Formulations', Drug Development And Industrial Pharmacy, 15 (13), 2153-2176

Menon A. et al., (1996), Identifying fluid-bed parameters affecting product variability, International Journal of Pharmaceutics, V140, I2, 207-218

Nielsen P. G., (2010), Enhancing the bioavailability of poorly soluble drugs, Pharm. Tech.

Nouh A. T. I., (1986), The effect of variations in concentration and type of binder on the physical characteristics of sulfadiazine tablets and granulations prepared by wet and fluidized-bed granulation method, Pharm. Ind., 48(6):670-673

Othmer Donald F., (1956), 'Fluidization', Rheinhold, New York

Oxcarbazepine Drug Master File, (2009), Jubilant Organosys Limited

Parikh D. M., (2007), Batch Fluid Bed Granulation, Parikch D. M. (Ed.), Handbook of Pharmaceutical Granulation Technology, (2.bs) (s.247-306), NY, Informa Healthcare USA, Inc.

Parikh D. M., (2007), Handbook of Pharmaceutical Granulation Technology, Drugs and the Pharmaceutical Sciences, Marcel Dekker Inc. New York, Vol.154

Parikh D. M., (2008), Granulation, Çelik M. (Haz.), Formulation & Process Development & Troubleshooting, 18-19 Haziran 2008-İstanbul Bildiriler (s.1-96), İstanbul-Academia

Parrott E. L., (1981), Compression, Lierbermann H.A., Lachman, L. (Eds.), Pharmaceutical Dosage Forms-Tablets, vol. 2., NY, Marcel Dekker, Inc.

Rankell et al., (1964), Continuous production of tablet granulations in a fluidized bed II. Operation and performance of equipment, J. Pharma. Sci.; 53(3):320

Robinson Manford J. et al., (1968), Apparatus and method for the coating of solid particles, J. Pharm. Sci. 57, 983-1988

Rupp R., (1977), Flow & other properties of granulates, Bol. Chim. Pharm.,116:251

Rupp et al., (1977), Flow and other properties of granules, Bol. Chim. Pharm., 116-251

Rx Media Pharm, (2010), İnteraktif İlaç Bilgi Kaynagı, Ed. Prof. Dr. Levent Üstünes

Schaefer T. et al., (1986), Granulation in different types of high speed mixers, Part I: Effects of process variables and up-scaling, Pharm. Ind., 48(9): 1083-1089

Schaefer T. et al., (1987), Granulation in different types of high speed mixers, Part II: Comparison between mixers, Pharm. Ind., 49(3), 297-304

Schaefer T. ve Woerst O., (1978b), Control of fluidized bed granulation, V. Factors effecting granule growth, Arch. Charm. Chemi. Sci. Ed.6, 69-82

Schaefer T. and Worts O., (1977), Control of fluidized bed granulation. I. Effects of spray angle, nozzle height and starting materials on granule size and size distribution, Arch. Pharm. Chemi Sci. Ed. 5, 51-60

Schafer T. and Worts O., (1978), Control of fluidized-bed granulation III: Effects of inlet air temperature and liquid flow rate on granule size and size distribution. Control of moisture content of granules in the drying phase, Arch. Pharm. Chemi Sci. Ed. 6, 1-13

Scott M. W. et al., (1963), Drying as a unit operation in the pharmaceutical industry I, Drying of tablet granulations in fluidized beds, J. Pharm. Sci. 52, 284-291

Scott M. W. et al., (1964), Continuous production of tablet granulations in a fluidized bed I. Theory and design considerations, J. Pharm. Sci. 53(3), 314-319

Sherif I. et al., (2000), Effect of process parameters on compressibility of granulation manufactured in a high-shear mixer. Int. J. of Pharm., 198:51-61

Sheskey P. J. and Williams D. W., (1996), Comparison of low-shear wet granulation techniques and the influence of percent water addition in the preparation of a controlled-release matrix tablet containing HPMC and a highdose, highly water-soluble drug, Pjarm. Tech. 20(3):80-92

Sheth B. B. et al., (1980), Compressed Tablets, Lierbermann H. A., Lachman L. (Eds.), Pharmaceutical Dosage Forms-Tablets, vol. 1., NY, Marcel Dekker, Inc.

Stout T. H. and Dorsey J. G., (2002), Handbook of Pharmaceutical Analysis, Ed. by Lena Ohannesian Anthony, 1st Recter, Marcel Dekker

Strahl H., 2004, Comparing different granulation techniques, Pharm. Tech. Eur., 11:23-33.

Türkoğlu M. et al., (1995), Evaluation of rotary fluidized-bed as a wet granulation equipment, Eur. J. Pharm. Biopharm., 41:388-394

Türkoğlu M., (2004), Tabletler, Gürsoy A. Z. (Ed.), Farmasötik Teknoloji-Temel Konular ve Dozaj Sekilleri (s.349-361), İstanbul, Kontrollü Salım Sistemleri Dernegi Yayını No:2

USP 32-NF 27, (2009), Description And Solubility / Reference Tables, 890

USP 32-NF 27, (2009), General Information / <1151> Pharmaceutical Dosage Forms, 673-674

Vanecek V. et al., (1966), 'Fluidized Bed Drying', Leonard Hill London

Vuppala M. K. et al., (1997), Application of powder layering technology and film coating for manufacture of sustained-release pellets using a rotary fluid bed processor, Drug Dev. Ind. Pharm, 23:687-694

Wadke D. A. and Jacobson H., (1980), Preformulation Testing, Lierbermann, H.A., Lachman, L. (Eds.), Pharmaceutical Dosage Forms-Tablets, vol. 1., NY, Marcel Dekker, Inc.

Wan et al., (1992), Incorporation and distribution of a low dose drug in granules, Ind. J. Pharm., 88:159-163

Wolf G., (1968), Drugs Made Germany; 11:172-180

Wong T. W. et al., (2007), Melt Granulation and Pelletization, Parikh D.M. (Ed.), Handbook of Pharmaceutical Granulation Technology, (2.bs) (s.385-401), NY, Informa Healthcare USA, Inc.

Wurster D. E., (1959), Air suspension technique of coating drug particles, J. Ame. Pharm. Assoc. Sci. Ed., 48(8):451-454

Wurster D. E., (1960), Preparation of compressed tablet granulations by the air suspension technique II, J. Amer. Pharm. Assoc. Sci. Ed. 49, 82-84

Zenz Frederick A. and Othmer Donald F., (1960), Fluidization and Fluid-Particle Systems