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GEBZE TECHNICAL UNIVERSITY

GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES

EFFECTS OF PROCESS DESIGN IN THE PRODUCTION OF IMMEDIATE RELEASE TABLETS CONTAINING CIPROFLOXACIN HYDROCHLORIDE ON TABLET PROPERTIES

TUBA TORUN

A THESIS SUBMITTED FOR THE DEGREE OF

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PROF. DR. MURAT ÖZDEMİR

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T.C.
GEBZE TEKNİK ÜNİVERSİTESİ
FEN BİLİMLERİ ENSTİTÜSÜ

SİPROFLOKSASİN HİDROKLORÜR İÇEREN HIZLI SALIM TABLETLERİN ÜRETİMİNDE PROSES TASARIMININ TABLET ÖZELLİKLERİ ÜZERİNE ETKİLERİ

TUBA TORUN
YÜKSEK LİSANS TEZİ
KİMYA MÜHENDİSLİĞİ ANABİLİM DALI

DANIŞMANI
PROF. DR. MURAT ÖZDEMİR

GEBZE
2019

GEBZE TEKNİK ÜNİVERSİTESİ	**YÜKSEK LİSANS JÜRİ ONAY FORMU**

GTÜ Fen Bilimleri Enstitüsü Yönetim Kurulu'nun 03/07/2019 tarih ve 2019/30 sayılı kararıyla oluşturulan jüri tarafından 18/10/2019 tarihinde tez savunma sınavı yapılan Tuba TORUN'un tez çalışması Kimya Mühendisliği Anabilim Dalında YÜKSEK LİSANS tezi olarak kabul edilmiştir.

JÜRİ

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Gebze Teknik Üniversitesi Fen Bilimleri Enstitüsü Yönetim Kurulu'nun ...../...../..... tarih ve ...../..... sayılı kararı.

SUMMARY

The aim of this study was to investigate the effects of processing parameters (chopper speed, impeller speed and granulation time) in high shear mixer on the release characteristics of ciprofloxacin hydrochloride, weight variation, thickness, friability and disintegration time of the tablets using 2^3 factorial design, and determine the release profile of ciprofloxacin hydrochloride from the immediate release tablets in simulated gastric medium. The amount of ciprofloxacin hydrochloride was quantified with the assay analysis as 99.8% by mass. Bulk density of the powders changed between 0.368 and 0.403 g/ml while tapped density varied from 0.490 to 0.532 g/ml. Powders produced at 80 rpm impeller speed and 5 min granulation time gave the best percent compressibility index (CI) and Hausner ratio (HR) values, 23.88% and 1.31, respectively. Weight of the tablets ranged from 399.9 to 402.2 mg. Hardness of the tablets were found to be between 16.21 and 17.35 kp. Percent friability values of the tablets ranged from 0.074 to 0.175%. All the prepared tablet trials met the United States Pharmacopeia (USP) requirements for the weight variation, hardness and percent friability. The disintegration time of the tablets containing ciprofloxacin hydrochloride in deionized water changed between 70 and 97 s. Chopper speed, impeller speed and granulation time affected the ciprofloxacin hydrochloride release from the tablets. Tablets produced at the impeller speed of 80 rpm, granulation time of 2.5 min and when the chopper was off had the fastest dissolution rate (91.54%) at 60 min.

Key Words: Ciprofloxacin hydrochloride, factorial design, immediate release tablet, high shear mixer granulation, in vitro release.

ÖZET

Bu çalışmanın amacı, yüksek kesmeli karıştırıcı granülatörde proses parametrelerinin (parçalayıcı hızı, karıştırıcı hızı ve granülasyon süresi) 2^3 faktoriyel tasarım kullanılarak siprofloksasin hidroklorür içeren tabletlerin ağırlık değişimi, kalınlık, aşınma, dağılma zamanı ve ilaç salım özellikleri üzerine etkilerini araştırmak ve simüle edilmiş gastrik ortamda hızlı salım tabletlerden siprofloksasin hidroklorürün salım profilini belirlemektir. Siprofloksasin hidroklorür etkin maddesinin miktar tayini analizi ağırlıkça %99,8 olarak bulunmuştur. Tozların küme yoğunluğu 0,368 ile 0,403 g/ml arasında değişirken, sıkıştırılmış yoğunluk 0,490 ile 0,532 g/ml arasında değişmiştir. 80 rpm karıştırıcı hızında ve 5 dakika granülasyon süresinde üretilen toz, en iyi basılabilirlik indeksi (CI) olarak %23,88 ve Hausner oranı (HR) olarak 1,31 değerlerini vermiştir. Tabletlerin ağırlığı 399,9 ile 402,2 mg arasında değişmiştir. Tabletlerin sertliği 16,21 ile 17,35 kp arasında bulunmuştur. Tabletlerin yüzde aşınma değerleri %0,074 ile %0,175 arasında değişmiştir. Bütün hazırlanan tabletler ağırlık, sertlik ve yüzde aşınma bakımından Amerika Birleşik Devletleri Farmakopesi (USP) gereksinimleri karşılamaktadır. Deiyonize su içinde siprofloksasin hidroklorür içeren tabletlerin dağılma süresi 70 ile 97 saniye arasında değişmiştir. Parçalayıcı hızı, karıştırıcı hızı ve granülasyon süresi siprofloksasin hidroklorürün tabletlerden salınmasını etkilemiştir. Karıştırıcı hızı 80 rpm, granülasyon süresi 2,5 dakika ve parçalayıcı kapalıyken üretilen tabletler 60 dakikada en hızlı çözünme oranını (%91,54) vermiştir.

Anahtar Kelimeler: Siprofloksasin hidroklorür, faktöriyel tasarım, hızlı salım tablet, yüksek kesmeli karıştırıcı granülasyonu, laboratuvar ortamında salım.

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LIST of ABBREVIATIONS and ACRONYMS

Abbreviations and Acronyms		**Explanations**
V_0	:	Bulk Volume
V_{1250}	:	Tapped Volume
α	:	Alpha
kp	:	Kilopond
min	:	Minute
nm	:	Nanometer
rpm	:	Revolutions per minute
s	:	Second
CI	:	Compressibility Index
DSC	:	Differential Scanning Calorimetry
FT-IR	:	Fourier Transform Infrared Spectroscopy
HCl	:	Hydrochloric acid
HPLC	:	High Performance Liquid Chromatography
HR	:	Hausner Ratio
HSM	:	High Shear Mixer
IR	:	Infrared
KBr	:	Potassium Bromide
PVP	:	Polyvinylpyrrolidone
USP	:	United States Pharmacopeia
UV	:	Ultraviolet
UV-VIS	:	Ultraviolet-Visible

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1. INTRODUCTION

Ciprofloxacin is a widely prescribed oral fluoroquinolone-based antibiotic with broad spectrum in all over the world. It has been approved for use in treatment of 14 types of infections, particularly for the treatment of urinary tract infections, chronic bacterial prostatitis and acute uncomplicated cystitis [Li et al., 2007]. Ciprofloxacin hydrochloride is highly absorbed from the proximal portion of small intestines and stomach [Varshosaz et al., 2006]. Oral bioavailability of Ciprofloxacin is approximately 70%. It attains peak plasma concentration of 2.5 μg/ml within 1-2 hours after administration of 500 mg [Arza et al., 2009].

Granulation is the name given to the processes performed to bring the materials to the desired particle size. Granulation is generally used for production of solid dosage forms in the pharmaceutical industry. Either dry or wet granulation is used as the granulation method in the pharmaceutical industry. Wet granulation is used to granulate materials that are not sensitive to moisture. Wet granulation method is performed by spraying the granulation solution onto dry powders meanwhile the mixture was mixed in a high shear mixer (HSM), a fluidized bed, a tumbling drum or similar devices [Martinello et al., 2006]. HSM wet granulation process is commonly used in solid dosage forms. The main aim of wet granulation process is to improve final product homogeneity, compressibility characteristics and flow properties [Faure et al., 2001], [Stahl, 2004]. The most important process variables in HSM granulation were reported to be chopper speed, impeller speed and granulation time [Holm et al., 1984], [Schaefer et al., 1987].

The effect of the chopper presence and the impeller speed in a HSM during wet granulation process has been investigated [Chitu et al., 2011]. HSM without a chopper led to the formation of inhomogeneous granules with large percentage of lumps, and the presence of a chopper in HSM wet granulation process allowed better distribution of granules at low and moderate impeller speeds. Increasing the impeller speed regardless of the presence of chopper resulted in granules with similar size. The amount of water in wet granulation, wet massing time and impeller speed were found to affect the compressibility of the resultant granules and tablet formation [Badawy et al., 2000]. The increase in the amount of water or high moisture content increased the compressibility. Compressibility decreased with increasing the impeller speed during

wet granulation and prolonging the wet massing time. The amount of water added, impeller speed and kneading time were found to influence the granule properties including particle diameter, specific volume and morphology of the granules containing lactose, hydroxypropyl cellulose and micro-crystalline cellulose [Ohno et al., 2007]. The amount of water was the most significant factor affecting the granule properties. Although the particle diameter was highly affected by the amount of water added, a little change in particle diameter occurred by changing the impeller speed and kneading time. Impeller speed and kneading time had a significant effect on the morphology of the granules.

The dissolution rate of the granules is also important to obtain tablets with appropriate release properties [Al hassn et al., 2018]. They implemented multi-stage wet granulation process where the impeller speed was fixed throughout the granulation process. Granule properties had changed compared to the conventional HSM wet granulation. The change in the dissolution time resulted from the difference in the surface area of the granules where increasing the surface area decreased the dissolution time. Otsuka et al. [2018] used HSM wet granulation process to produce tablets containing a model active pharmaceutical ingredient, and observed that granulation time, amount of water added and blade speed affected the tablet dissolution rate. Tablets produced from wet masses containing 300 g water and granulated at 1 min with a blade speed of 600 rpm exhibited the lowest dissolution rate (25%) at the end of 60 min of dissolution time. Highest dissolution rate (> 40%) at 60 min of dissolution time was obtained for the tablets produced from wet masses containing 400 g water and granulated at 3 min with a blade speed of 400 rpm. Ohno et al. [2007] investigated the effect of different impeller speeds on the dissolution rate of granules produced from a mixture of lactose, hydroxypropyl cellulose and micro-crystalline cellulose, and reported that dissolution rate decreased with increasing the impeller speed.

Although there are some studies regarding the effect of process parameters in HSM wet granulation, there is no study conducted on the effect of process parameters including impeller speed, granulation time and chopper speed in HSM wet granulation process on bulk and tapped densities, Compressibility index and Hausner ratio of powders containing ciprofloxacin hydrochloride, hardness, friability and disintegration time of tablets and release characteristics of ciprofloxacin hydrochloride from the immediate release tablets in simulated gastric medium.

1.1. Hypothesis

Ciprofloxacin hydrochloride containing immediate release tablet formulations can be prepared by wet granulation method with variable process parameters in a HSM granulator and ciprofloxacin hydrochloride having different release profiles from the tablets can be obtained.

1.2. Objectives

The objectives of this study are to:

i) Investigate the effects of impeller speed, granulation time and chopper speed in HSM granulator on bulk and tapped densities, Compressibility index and Hausner ratio of powders containing ciprofloxacin hydrochloride, and hardness, friability and disintegration time of tablets using 2^3 factorial design,

ii) Determine the release profile of ciprofloxacin hydrochloride from the immediate release tablets in simulated gastric medium.

2. GENERAL INFORMATION

2.1. Ciprofloxacin Hydrochloride

Ciprofloxacin hydrochloride is an antibiotic from the fluoroquinolone group used in treatment of bacterial infections, particularly urinary tract. Ciprofloxacin and other fluoroquinolones are valued for their excellent tissue penetration, broad spectrum of activity and availability in both intravenous and oral formulations.

Chemical name of ciprofloxacin hydrochloride is l-Cyclopropyl-6-fluoro-4-oxo-7-(piperazin-l-yl)-l, 4dihydroquinoline-3-carboxylicacid hydrochloride, monohydrate. Molecular formula of ciprofloxacin hydrochloride is $C_{17}H_{21}ClFN_3O_4$, and molecular weight is 385.8 g/mol. Structural formula of ciprofloxacin hydrochloride is given below [Pandey et al., 2012]:

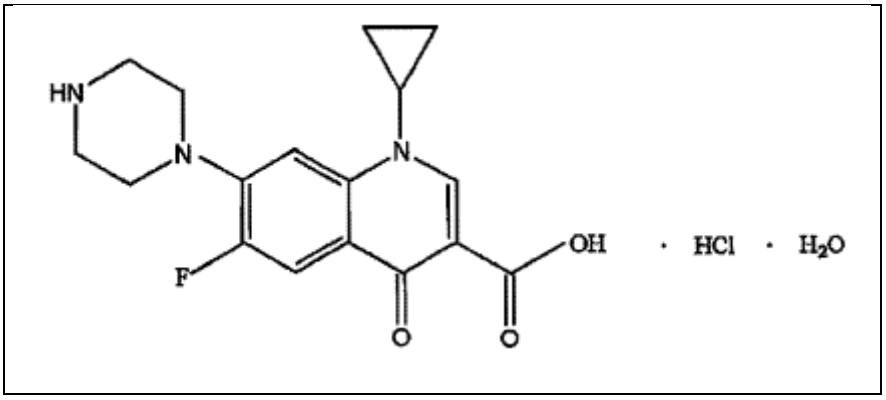

Figure 2.1: Structural formula of ciprofloxacin hydrochloride.

Ciprofloxacin hydrochloride is practically insoluble in ethyl acetate, methylene chloride and acetone, very slightly soluble in ethanol, slightly soluble in methanol and soluble in water. Ciprofloxacin hydrochloride is a yellowish to light yellow crystalline substance and slightly hygroscopic. No report on polymorphism has been cited in literature for ciprofloxacin hydrochloride. Ciprofloxacin hydrochloride has a high solubility and low permeability. DSC thermogram of ciprofloxacin hydrochloride is given in Figure 2.2 [Padhy et al., 2013].

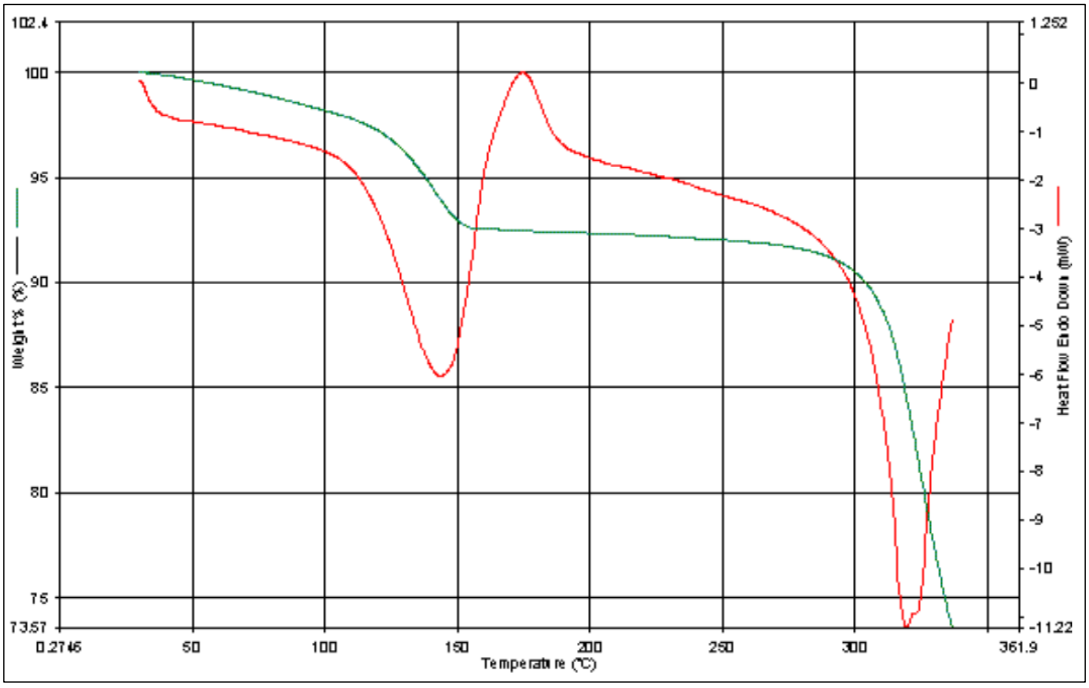

Figure 2.2: DSC thermogram of ciprofloxacin hydrochloride.

The UV spectrum of ciprofloxacin hydrochloride in methanol is presented in Figure 2.3 [Brittain, 2005]. Three peak maxima were observed at wavelengths of 278, 317 and 330 nm.

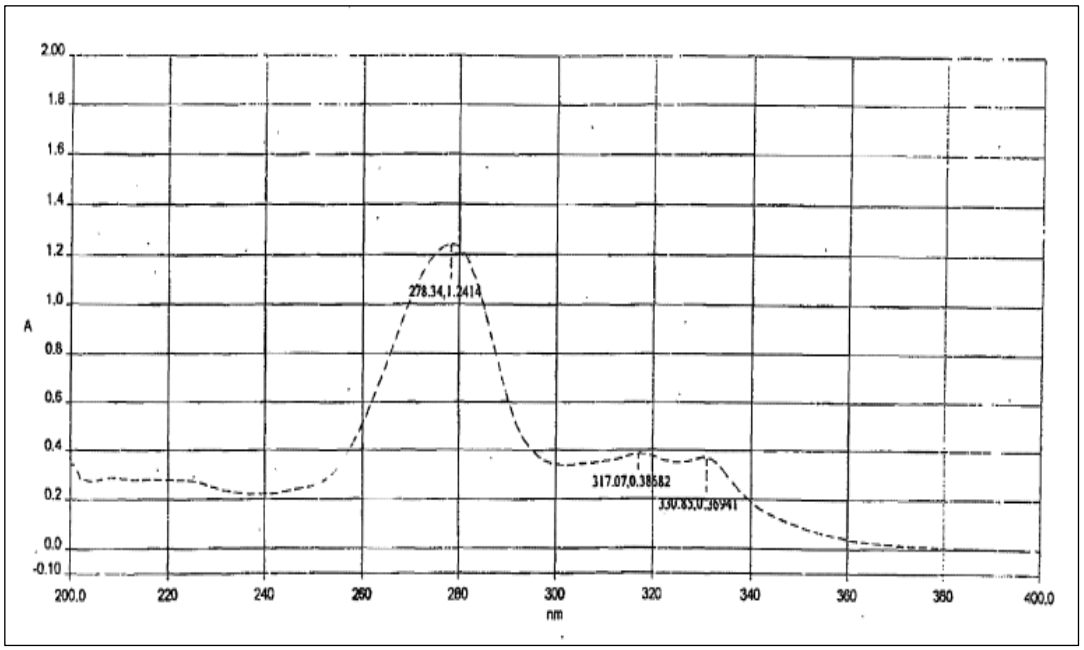

Figure 2.3: UV spectrum of ciprofloxacin hydrochloride in methanol.

The FT-IR spectrum (Figure 2.4) of ciprofloxacin hydrochloride was recorded with FT-IR as KBr pellet, and the assigned groups with respect to corresponding wavelengths are presented in Table 2.1 [Sahoo et al., 2011].

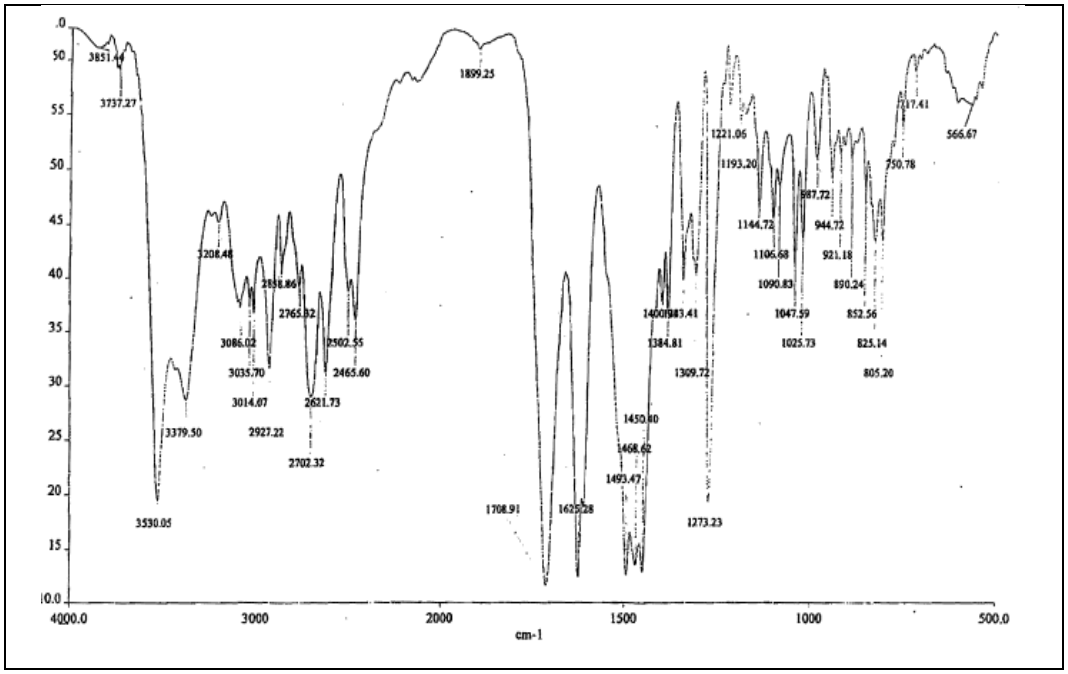

Figure 2.4: Fourier transform infrared spectrum of ciprofloxacin hydrochloride.

Table 2.1: Assigned groups with respect to corresponding wavelengths for ciprofloxacin hydrochloride.

Assignment	Wave number (cm^{-1})	Mode of vibration
O-H / N-H	3530-3380	Stretching
Aromatic C-H	3086-3014	Stretching
Aliphatic C-H	2927	Stretching
N^{+}-H	2702-2622-2466	Stretching
Acid C=O	1709	Stretching
Ketone C=O	1625	Stretching
Aromatic C=C	1494	Stretching
Acid C-O/O-H	1450	Stretching
C-N	1273	Stretching
C-F(Aryl)	1145	Stretching
Aromatic C-H	805	Bending

The atmospheric pressure chemical ionization mass spectrum of ciprofloxacin hydrochloride (Figure 2.5) was recorded with a liquid chromatography-mass spectrometer.

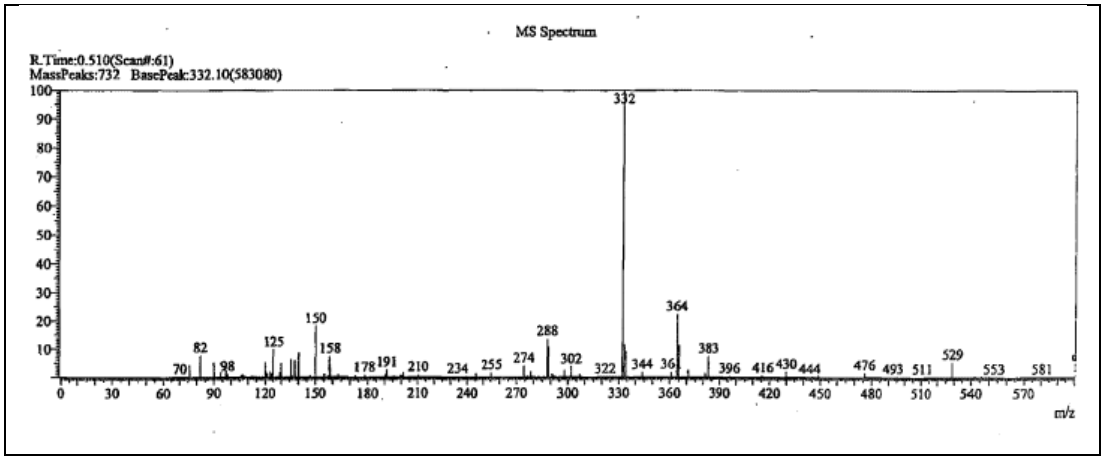

Figure 2.5: Atmospheric pressure chemical ionization mass spectrum of ciprofloxacin hydrochloride.

Ciprofloxacin is rapidly and intensely absorbed from small intestine. It reaches peak plasma concentrations after 1-2 hours. Oral bioavailability of ciprofloxacin is about 70-80% [Vance-Bryan et al., 1990]. Ciprofloxacin is available in the plasma in a substantially non-ionized form. Protein binding is low between 20 and 30%. Ciprofloxacin attains high concentrations in various tissues like sinuses, the urogenital tract (endometrium, prostate and urine), lung (biopsy tissue, alveolar macrophages and epithelial fluid) and inflamed lesions (cantharides blister fluid). Ciprofloxacin is highly excreted from the kidneys and lesser extent by faeces. Serum elimination half-life is about 4-7 hours in volunteers with normal renal function.

2.2. Granulation Process and Granulators

Granulation is the combination of powder particles with the aid of a binder or mechanical force to form solid dry aggregates. It is important for the active ingredient or excipients to be homogeneous in the pharmaceutical powder mixtures without being decomposed. Granulation retains particles in the powder to behave as a single element without being separated from the agglomerated powder. Granulation is regarded as a preparation step prior to tablet formation.

Granulation process improves compressibility and flowability of the mixture in order to prevent agglomeration, densify the powder mixture and reduce dust, provide narrow particle size distribution of the powder mixture, ensure uniform distribution of the drug in the powder mixture and improve the dissolution characteristics of the finished tablets [Lieberman et al., 1989]. The choice of the granulation method is important in the pharmaceutical industry for the tablet formation. Wet and dry granulations are commonly used granulation methods in the pharmaceutical industry.

One of the most widely used granulators in the manufacture of granules is HSM granulators [van den Dries et al., 2003]. HSM granulators include a chopper, mixing bowl and impeller. The impeller is used for mixing the dry powder and homogeneous spreading of granulation solution. HSM granulator could be designed either horizontal or vertical by considering the position and orientation of the impeller.

2.2.1. Wet Granulation

Wet granulation process is achieved by spraying the granulation solution onto the dry materials. Drying and milling are required for the desired final particle size [Cantor et al., 2009]. HSM granulator or fluidized bed dryer can be used for wet granulation. The prepared granules can be dried in a tray, in a fluidized bed dryer or under vacuum. Wet granulation is the best-known general tablet production method. In general, composition of a powder mixture consists of a variety of excipients such as binder, filler and disintegrant. HSM wet granulation has the following processing steps: loading all of excipients to mixing bowl, mixing of dry components, adding granulation solution to powder mixture while both chopper and impeller operate, removing of wet granules from high shear mixer granulator, drying of wet granules and sifting the dried granules [Gokhale et al., 2007].

The HSM wet granulation process has some advantages according to the other granulation processes. HSM wet granulation allows the manufacturing of reproducible granules having homogeneous particle size distribution, produces less friable and more dense granules, uses less binder solution, has short processing time and minimizes the exposure of workers to less dust [Gokhale et al., 2007].

2.2.2. Dry Granulation

In the dry granulation method, powder particles are transformed into aggregates with high pressure. This method is particularly appropriate for the active ingredients sensitive to moisture or materials which are sensitive to elevated temperatures [Ansel and Popovich, 1990]. Two approaches used in dry granulation in the pharmaceutical industry are roller compaction and slugging. In both methods, binder can be used to improve the bonding strength. In roller compaction, the powder is compressed by feeding the powder between two cylindric rollers. After the sheets are produced, the compressed layers are milled and sieved. The roller compaction requires less lubricant than the slugging. In slugging, the production of large compacts is achieved by direct compression. The slugs manufactured are larger than the tablets. Lubricants can be added to prevent the sticking of the compacts to the dies and punches. The compressed powder is crushed and sieved. The sieved granules are mixed with the disintegrant and lubricant, and compressed in a tablet compression machine [Gibson, 2007]. Compared to the wet granulation, dry granulation requires less equipment and does not need binder solutions and drying step. Dry granulation can usually be used for moisture and heat sensitive materials.

2.3. General Information about Tablets

Solid oral dosage forms tablets are the largest groups of tablets in the pharmaceutical industry and have the utmost importance in pharmaceutical formulations. Solid dosage forms tablets are prepared with active and inactive ingredients. Depending on production method and their intended use, they may vary in size, shape, weight, hardness, thickness, dissolution and disintegration properties. Most of the tablets are used in oral implementation of drugs [Allen et al., 2011].

Tablets are prepared by compression with appropriate punches in tablet compression machine. Their dimensions and shapes are determined using dies and punches in various sizes and shapes. Introducing a successful tablet dosage form for patient use requires an appropriate formulation and process optimization. This can be achieved by knowing all the properties of the excipients, selecting the most suitable production method and packaging form. The tablets should have mechanically stable

structure suitable for coating, packaging and transportation, and be easily recognized and swallowed by the patients. The advantages of the tablet dosage form include [Web 1, 2007]:

- Dosage accuracy
- Minimum cost
- Packaging and stripping are easy and inexpensive
- Easy to swallow
- Bitter taste and odor can be masked with coating technique
- Chemical and physical stability of the active substance can be kept for a long time
- Suitable for large scale manufacture.

2.4. Excipients Used in Tablets

Drugs are usually administered in the form of dosage forms containing excipients. Excipients are added to the formulations for the purpose of ease of preparation, functioning of the dosage form as a drug delivery system and patient acceptability [Aulton and Taylor, 2013]. The excipients should have the following properties [Jivraj et al., 2000]:

- chemically inert
- when in contact with heat, air and moisture, chemically and physically stable
- compatible with packaging materials
- receivable preferably from multiple suppliers

The common excipients used in the pharmaceutical industry are diluents, disintegrants, binders, glidants and lubricants, and sweetening, flavoring and coloring agents.

2.4.1. Diluents

The dosage of use is important in preparation of tablets containing very low or very high doses of active ingredient. In that case, diluents are used to obtain tablets

with better properties such as improved cohesion and suitability to direct compression. A diluent should have following properties [Web 1, 2007]:

- It must be physiologically inert
- It must be not toxic
- It should be easily available
- It should be color compatible
- It should not change the bioavailability of drug
- It should be chemically and physically stable on its own and in combination with drugs
- It should be inexpensive.

Commonly used tablet diluents in the pharmaceutical industry are microcrystalline cellulose, lactose, calcium sulphate, starch, dibasic calcium phosphate, mannitol, sucrose, dextrose and sorbitol.

2.4.2. Binders

Binders are used to keep active pharmaceutical ingredient and inactive materials together in the formulation of solid dosage forms. The binders are the substances necessary for the formation of granules from the powders and the tablets from the granules. The binders may be added by dissolving them in a solvent such as water or alcohol or may be added directly to the dry mixture. The binder products generally differ depending on the production process used. Binders used for wet granulation are hydrophilic and soluble in water while binders used for dry granulation must exhibit cohesive and adhesive forces so that when compacted the particles agglomerate. The robustness and integrity of a tablet can be achieved by means of binders. The most preferred binders in the pharmaceutical industry are cellulose derivatives and povidone (polyvinylpyrrolidone, PVP) which are used in formulations between 1 and 5% [Wade and Weller, 1994].

2.4.3. Disintegrants

Disintegrants are substances which facilitates the disintegration of tablets to granules and powders which form granules in the gastrointestinal tract in order to contribute to the nature of local effects or dissolving of a drug and join to bloodstream. Disintegrants are rapidly swell in contact with water and cause tablets to break into pieces. Disintegrants can be added to the tablets by the method of internal or external addition which is the most common method used in the pharmaceutical industry. The external addition method is addition to the sieved dry granules by blending just prior to tablet compression. In the internal addition, disintegrant is blended with other powders prior to wetting the powder mixture with the granulating solution. The most commonly used disintegrants in the pharmaceutical industry are starch and its derivatives, cellulose and its derivatives, alginate and polyvinylpyrrolidone, croscarmellose, crospovidone and sodium starch glycolate [Wade and Weller, 1994]. The amount of the disintegrant in the tablet formulation usually changes in the range of 1-10%.

2.4.4. Lubricants and Glidants

Lubricants are used to improve the rate of flow of tablet granulation, reduce inter particle friction and prevent adhesion of the powder to surface of punches and dies. Lubricants usually used in the pharmaceutical industry are stearic acid, stearic acid salts such as magnesium stearate, talc, polyethylene glycols and surfactants [Web 1, 2007]. Lubricants should be added in the final blending step after granulation. The addition of both lubricant and disintegrant together in one blending step causes the disintegrant to become coated with lubricant and it generally results in both a decrease in porosity of disintegrant and a decrease in the efficiency of disintegrant. Instead of adding the lubricant and disintegrant simultaneously, a better approach is to add lubricant and disintegrant separately, with a disintegrant being the first [Banker and Rhodes, 2002]. Glidants are used to promote flow of granules or powder materials by reducing the friction between the particles. Starches particularly potato starch, talc and silaceous materials such as pyrogenic silica and hydrated sodium aluminosilicate have been used successfully to induce flow [Banker and Rhodes, 2002].

2.4.5. Coloring Agents

Coloring materials are added to improve the appearance of a tablet formulation and allow easy identification of a medication or drug. Titanium dioxide is the widely used coloring agent in tablet formulations. All coloring agents used in tablet formulations must be certified and approved by legal authorities. Two forms of coloring agents are used in tablet preparations which are Drug and Cosmetic, and Food Drug and Cosmetic dyes [Web 1, 2007].

2.4.6. Flavoring Agents

Flavors can be used to improve the acceptance of a medication by the patients and mask unpleasant tastes caused by active ingredients. Flavorings may be natural, such as fruit extracts, or artificial. The increase in the availability of a drug depends on making a formulation tasty enough to be chewed. Such a tablet may be the only reasonable alternative for patients who are unable to swallow a tablet whole such as children. The potential incompatibilities that may exist between the flavoring agent and the active ingredient must be carefully assessed before selecting a flavoring agent in tablet formulations [Banker and Rhodes, 2002]. Flavoring agents are usually added just before compression to prevent loss through volatilization.

2.4.7. Sweetening Agents

Sweetening agents are added to make the ingredients more palatable, especially in chewable tablets such as antacid or liquids like cough syrup. Natural and artificially derived sweetening agents can be used in formulations. Commonly used sweetening agents in the pharmaceutical industry are sucrose, sorbitol, xylitol, mannitol, maltitol, dextrose, glucose, glycerin, saccharin, aspartame, acesulfame potassium and sodium cyclamate.

2.5. Excipients Used in Ciprofloxacin Hydrochloride Tablets

2.5.1. Microcrystalline Cellulose

Microcrystalline cellulose is partially depolymerized cellulose and it is in white color, tasteless, odorless and crystalline powder composed of porous particles [Rowe et al., 2009]. It is produced by controlled hydrolysis of α-cellulose obtained from fibrous plants with dilute mineral acid solutions. It is insoluble in dilute acids, organic solvents and water. Microcrystalline cellulose is widely used in pharmaceutical formulations, primarily as a binder or diluent in oral tablet and capsule formulations where it is used in both wet granulation and direct compression processes. Microcrystalline cellulose has high dilution potential, good dispersing properties and can be compressed even at low compression forces [Suzuki and Nakagami, 1999]. It improves flow and compressibility of powder mixtures [Jivraj et al., 2000].

2.5.2. Povidone

Povidone is a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, and it is produced by polymerization of vinyl pyrrolidone by the reaction of pyrrolidone with acetylene under pressure. It is a white or yellowish white colored, odorless or very light odor, fine particulate hygroscopic powder [Rowe et al., 2009]. Povidone is soluble in water, ethanol, methanol, ketones and chloroform. It is insoluble in ether, hydrocarbons and liquid paraffin. Although povidone is used in many pharmaceutical dosage forms, it is mainly used in solid dosage forms. It is used as the tablet binder, tablet diluent or coating agent in wet granulation and direct compression processes [Albertini et al., 2003], [Desai et al., 2008].

2.5.3. Croscarmellose Sodium

Croscarmellose sodium is a cross-linked carboxymethylcellulose sodium polymer. It is an odorless, white or grayish white powder. It is an inactive ingredient used as disintegrant in oral pharmaceutical formulations such as capsules, tablets and granules [Rowe et al., 2009]. Croscarmellose sodium may be used in both wet

granulation and direct compression processes for tablet formulations. It should be added in both intragranular and extragranular stages of wet granulation process so that the swelling and wicking ability of disintegrant material is best utilized [Gordon et al., 1993], [Khattab et al., 1993]. It is partially soluble in water; practically insoluble in alcohol, acetone, ether, toluene and many other organic solvents.

2.5.4. Colloidal Silicon Dioxide

Colloidal silicon dioxide is a submicroscopic fumed silica with a particle size of about 15 nm. Colloidal silicon dioxide is prepared by flame hydrolysis of chlorosilanes, such as silicon tetrachloride, at 1800 °C using a hydrogen–oxygen flame. Rapid cooling from the molten state during manufacture causes the product to remain amorphous. It is a bluish white colored, loose, light, fine, tasteless, odorless, hygroscopic and amorphous powder [Rowe et al., 2009]. It is practically insoluble in alcohol, water, mineral acids (excluding hydrofluoric acid) and other organic solvents, and soluble in hot solutions of alkali hydroxide. Colloidal silicon dioxide is used in pharmaceuticals products, cosmetics and food products. Its large specific surface area and small particle size give it desirable flow characteristics that are used to improve the flow properties of dry powders specifically for capsule filling and tableting. Silicon dioxide is an important excipient used as adsorbent, glidant, suspending agent, disintegrant and viscosity enhancer in various types of pharmaceutical formulations.

2.5.5. Magnesium Stearate

Magnesium stearate is prepared either by the interaction of aqueous solutions of magnesium chloride with sodium stearate or by the interaction of magnesium oxide, hydroxide or carbonate with stearic acid at elevated temperatures. The raw materials used in the manufacturing of magnesium stearate are refined fatty acids, a mixture of palmitic and stearic acid. It is a white colored, fine particles, milled or precipitated powder with a characteristic taste and odor [Rowe et al., 2009]. It is insoluble in water, ether and ethanol, and partially soluble in hot benzene and hot ethanol. Magnesium stearate is used in pharmaceutical formulations such as capsule and tablet formulations, cosmetics and food products as a lubricant and to a lesser extent as an

anti-adherent and glidant to prevent adhesion of pharmaceutical products to industrial equipment [Wang et al., 2010].

3. MATERIALS and METHODS

3.1. Materials

Ciprofloxacin hydrochloride was provided by Dr. Reddy's Laboratories, Hyderabad, India (Lot# ABDH005980). Microcrystalline cellulose (Avicel PH-101) was provided by JRS Pharma, Weissenborn, Germany (Lot# 6610133211). PVP K-30 (Povidone) was purchased from BASF, Ludwigshafen, Germany (Lot# 52705556P0). Ac-Di-Sol (Croscarmellose sodium) was provided from FMC BioPolymer, Wallingstown, Ireland (Lot# T0922C). Colloidal silicon dioxide (Aerosil) was provided by Evonik Degussa, Rheinfelden, Germany (Lot# 3152033014). Magnesium stearate was provided by FACI, Carasco GE, Italia (Lot# MGSV130313). Hydrochloric acid (HCl) was purchased from Merck, Darmstadt, Germany. Deionized water was supplied by Biofarma Pharmaceutical Industry Co. Inc., İstanbul, Turkey. All reagents were of analytical grade and used as received.

3.2. Methods

3.2.1. Analysis of Ciprofloxacin Hydrochloride as Active Ingredient

3.2.1.1. Ultraviolet-Visible (UV-Vis) Measurements

Ciprofloxacin hydrochloride reference standard equivalent to 0.1 g ciprofloxacin was weighed using a pre-calibrated analytical balance (Mettler Toledo XP205DR, Greifensee, Switzerland) and dissolved in 100 ml of deionized water. This solution was used as stock solution. Ten ml of resulting solution was diluted to 100 ml with deionized water. Then 5 ml of final solution was diluted to 100 ml with the same solvent. The UV-Vis absorption spectrum of the active ingredient was recorded at room temperature over the wavelength range of 200–400 nm with an UV-Vis spectrophotometer (Shimadzu UV-2450, Kyoto, Japan) using 1 cm path quartz cells, and the maximum absorbance value was obtained at 278 nm [Fereja et al., 2015].

3.2.1.2. Differential Scanning Calorimetry (DSC)

Thermal analysis of ciprofloxacin hydrochloride was performed by using a differential scanning calorimeter (Netzsch DSC 204 F1 Phoenix, Selb, Germany). Sample was sealed to aluminum pans. Approximately 2-3 mg sample was used. Samples were scanned at a heating rate of 10 °C/min under nitrogen with a flow rate of 30 ml/min for prevent oxidation. The thermogram was recorded between 40 °C and 350 °C.

3.2.1.3. Particle Size Distribution

Particle size distribution of the ciprofloxacin hydrochloride was determined by a laser diffraction particle size analyzer equipped with a Scirocco 2000 dry disperser (Mastersizer 2000, Malvern Instruments Co., Worcestershire, UK) run at an inlet air pressure of 2 bars and a vibration feed rate of 40% for efficient dispersion of small particles during measurement. Obscuration was maintained at 0.42%. Approximately 1 g of ciprofloxacin hydrochloride powder was scooped into the dry powder unit using a metal spatula. Particle size distribution was characterized by the volume percentile of the diameters d10, d50 and d90 which correspond to 10th, 50th and 90th percentiles of the distribution, respectively.

3.2.1.4. Assay Analysis of Ciprofloxacin Hydrochloride

Ciprofloxacin hydrochloride (25 mg) was accurately weighed to a 50 ml volumetric flask and completed to volume by dissolving with mobile phase. The mobile phase consisted of a volumetric mixture (13:87 v/v) of acetonitrile and a buffer solution (containing 0.025 M phosphoric acid adjusted to pH of 3.0 ± 0.1 with triethylamine). The solution was filtered through a 0.45 µm membrane filter and transferred into a high-powered liquid chromatography (HPLC) vial. HPLC analysis was carried out using a Waters 2695 Separation Module with a Waters 2489 UV/Visible detector (Waters, Milford, MA, USA). The analytical column used was Spherisorb C_8 column with an I.D. (inner diameter) of 4.6 mm, length of 250 mm, particle size of 5 µm and pore size of 80 °Angstrom (Waters, Milford, MA, USA). The

column temperature was set to 30 ± 1 °C while the sample temperature was kept at 10 ± 1 °C. Injection volume was 10 µl and the flow rate was 1.5 ml/min. For the chromatography according to the absorption spectrum of ciprofloxacin, a detection wavelength of 278 nm was chosen.

3.2.2. Experimental Design

A two-level three factor (2^3) full factorial design was used as the experimental design (Table 3.1). Eight different trials were conducted in a random order to investigate the effects of granulation time, impeller speed and chopper speed on the release characteristics of ciprofloxacin hydrochloride, weight variation, disintegration time, thickness and friability of the tablets. The levels of the independent variables or factors (chopper speed, impeller speed and granulation time) were determined based on the manufacturing practice and preliminary experiments by single factor design.

Table 3.1: Experimental design including process variables and their levels[1].

Trial Code	Coded variables			Uncoded variables		
	x_1	x_2	x_3	Chopper speed (rpm)	Impeller speed (rpm)	Granulation time (min)
T1	–1	–1	+1	0	80	5
T2	+1	–1	+1	1000	80	5
T3	–1	+1	+1	0	160	5
T4	+1	+1	+1	1000	160	5
T5	–1	–1	–1	0	80	2.5
T6	+1	–1	–1	1000	80	2.5
T7	–1	+1	–1	0	160	2.5
T8	+1	+1	–1	1000	160	2.5

[1]Experimental runs were performed in random order.

3.2.3. Powder Formulation and Tablet Preparation

Tablets containing 291 mg ciprofloxacin hydrochloride (equivalent to 250 mg ciprofloxacin) were prepared by wet granulation method (Table 3.2) according to the experimental design given in Table 3.1. All contents of formulation were weighed precisely with a calibrated precision balance (Mettler Toledo XS32001LX, Greifensee, Switzerland) so that for each trial 400 tablets can be produced. Ciprofloxacin hydrochloride (116.4 g), Avicel PH-101 (33.8 g) and croscarmellose sodium (1.8 g) were passed through a US 20 mesh-size sieve (841 μm). Sieved powders were mixed in a high shear mixer (Hüttlin Mycromix, Schopfheim, Germany) for 5 min. Granulation solution was prepared with dissolving 2.4 g Povidone K-30 in 33 ml of deionized water. Mixed powders were wet granulated with the granulation solution in a 1-liter HSM granulator with process parameters given in Table 3.1. Wet granules were dried in an oven (Binder-FD 240, Tuttlingen, Germany) at 50 ± 3 °C up to final moisture contents of the granules attained to 0.009 ± 0.001 g water/g dry solid. The dried granules were passed through the US 20 mesh-size sieve. Croscarmellose sodium (1 g) and colloidal silicon dioxide (1.4 g) were added to sieved dry granules and mixed for 10 min. After then magnesium stearate (3.2 g) was added to mixed powders and mixed for 3 min. Finally, resultant powders from each trial were compressed with tablet compression machine (model EP-1, Erweka GmbH, Heusenstamm, Germany) at a final weight of 400 mg per tablet at a hardness value 16.5 ± 1.5 kilopond (kp) using a hardness tester (model TBH 30, Erweka GmbH, Heusenstamm, Germany).

Table 3.2: Ciprofloxacin hydrochloride tablet formulation.

Name of the ingredient	Unit formula (mg/tablet)	Percent (%)
Ciprofloxacin Hydrochloride	291	72.7
Avicel PH-101	84.5	21.1
Croscarmellose Sodium	7	1.8
Povidone K-30	6	1.5
Colloidal Silicon Dioxide	3.5	0.9
Mg Stearate	8	2
Total	400	100

3.2.4. Analysis Performed in Resultant Powders

3.2.4.1. Bulk Density

The density of a powder sample is generally defined as bulk density. The bulk density is obtained by dividing the weight of the powder (m) to its volume (V_0) as given by Equation (3.1). The bulk density was measured with cautiously pouring 100 grams of powder weighed with a precision balance (Mettler Toledo XS32001LX, Greifensee, Switzerland) into a 250 ml graduated cylinder. The bulk density was calculated by dividing the mass of powder (g) to its volume (ml) occupied in graduated cylinder [USP, 2018]. Triplicate measurements were done, and average value was reported as the bulk density.

$$\text{Bulk density} = m / V_0 \tag{3.1}$$

where m = mass (g) and V_0 = apparent bulk volume (ml).

3.2.4.2. Tapped Density

By mechanically tapping on graduated cylinder containing the powder sample, fine particles are placed in the spaces between the large particles and volume of powder is measured. The tapped density of a powder sample is defined as ratio of weight of a tapped powder sample (m in grams) to its volume as given by Equation (3.2). The tapped density was measured by carefully pouring 100 grams of powder weighed with a precision balance (Mettler Toledo XS32001LX, Greifensee, Switzerland) into a pre-weighed 250 ml graduated cylinder tapped 1250 times in a tapped density tester (model SVM 102, Erweka GmbH, Heusenstamm, Germany). The tapped volume (V_{1250} in ml) was determined until difference between two consecutive measurements was less than 2% [USP, 2018]. Triplicate measurements were done, and average value was reported as the tapped density.

$$\text{Tapped density} = m / V_{1250} \tag{3.2}$$

where m = mass (g) and V_{1250} = apparent tapped volume (ml).

3.2.4.3. Hausner Ratio and Compressibility Index

The flow characteristics of the powder was evaluated with Hausner ratio (HR) and Compressibility index (CI) as given by Equations 3.3 and 3.4, respectively [USP, 2018].

$$\text{HR} = \frac{\text{Tapped density}}{\text{Bulk density}} \tag{3.3}$$

$$\text{CI (\%)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \text{ x } 100 \tag{3.4}$$

3.2.5. Analysis Performed in Tablets

3.2.5.1. Weight Variation

Twenty tablets were randomly selected from each trial. The selected tablets were individually weighed using a precision balance (LE623S, Sartorius Instruments, Gottingen, Germany). The results were presented as the mean weight of twenty separate measurements.

3.2.5.2. Tablet Diameter and Thickness

A vernier caliper (model 234990, TCM GmbH, Hamburg, Germany) was used to determine thickness and diameter of 10 randomly selected tablets from each trial. The results were presented as the mean of ten individual measurements.

3.2.5.3. Friability

According to the USP specifications [USP, 2018], 10 tablets were randomly selected. The selected tablets were carefully dedusted prior to testing. The tablets were accurately weighed. The weighed tablets were placed in drum of a tablet friability test apparatus (Aymes FR1, Istanbul, Turkey). The drum was adjusted to rotate for 4 min at 25 rpm. The tablets were removed from drum, dedusted and then accurately weighed. Three individual measurements were performed, and the percent friability was calculated using the below equation:

$$\% \text{ Friability} = (1 - W/W_0) \times 100 \quad (3.5)$$

where W_0 = total initial weight of tablets (g) and W = total final weight of tablets (g).

3.2.5.4. Disintegration Time

Tablet disintegration time is time required for the breakdown of a tablet into smaller particles and/or granules which will completely pass through a US 10 mesh.

The disintegration time was determined according to the USP specifications [USP, 2018] using a tablet disintegration tester (model ZT 221, Erweka GmbH, Heusenstamm, Germany). Six separate tablets were randomly selected, and they were individually placed in each of six tubes of the basket containing deionized water at 37 ± 0.5 °C. The average disintegration time was given as the mean of six separate measurements.

3.2.5.5. Assay

Ten randomly selected tablets were crushed in pestle mortar. Approximately 40 mg of tablet powder equivalent to 25 mg ciprofloxacin was accurately weighed into a 50 ml volumetric flask. Approximately 30 ml of mobile phase consisted of a volumetric mixture (13:87 v/v) of acetonitrile and a buffer solution (containing 0.025 M phosphoric acid adjusted to pH 3.0 with triethylamine) was added and sonicated in an ultrasonic bath for 30 minutes to dissolve ciprofloxacin. The solution was diluted to volume with the mobile phase and mixed ultrasonically. Then, the solution was filtered through a 0.45 μm membrane filter and transferred into a high-powered liquid chromatography (HPLC) vial. HPLC analysis was carried out using a Waters 2695 Separation Module with a Waters 2489 UV/Visible detector (Waters, Milford, MA, USA). The analytical column used was Spherisorb C_8 column with an I.D. (inner diameter) of 4.6 mm, length of 250 mm, particle size of 5 μm and pore size of 80 °Angstrom (Waters, Milford, MA, USA). The column temperature was set to 30 ± 1 °C. Injection volume was 10 μl and the flow rate was 1.5 ml/min. For the chromatography according to the absorption spectrum of ciprofloxacin, a detection wavelength of 278 nm was chosen.

3.2.5.6. Dissolution Studies

Dissolution studies were performed with a dissolution tester (Distek Evolution 6300 Dissolution System, North Brunswick, NJ) in which six randomly selected tablets were placed into 900 ml of 0.01 N HCl solution at 37 ± 0.5 °C. The paddle stirring speed was set to 25 rpm according to the USP Apparatus II paddle method [USP, 2018]. Seven ml of aliquots were withdrawn at predetermined time intervals

(2.5, 5, 7.5, 10, 15, 20, 30, 45 and 60 min). After each sampling, the amount equivalent to the sampling volume was replaced with the fresh 0.01 N HCl at 37 ± 0.5 °C. Samples were filtered through a 0.45 μm membrane filter and 2 ml of filtrate was diluted to 100 ml with the fresh buffer (containing 0.025 M phosphoric acid adjusted to pH 3.0 with triethylamine). Diluted solution was analyzed at the wavelength of maximum absorbance at 278 nm with an UV-Vis spectrophotometer (Shimadzu UV-2450, Kyoto, Japan) using 1 cm path quartz cells.

3.2.5.7. Statistical Analysis

At least three separate measurements were taken from each trial and the esults were reported as average of three measurements ± standard deviation. All statistical analyses were performed using IBM SPSS Statistics version 22 (SPSS, 2013). One-way analysis of variance (ANOVA) followed by post hoc multiple comparisons using Duncan's multiple range test with a significance level (α = alpha) of 0.05 was performed to determine statistical differences between the means of the results for the bulk density, tapped density, Compressibility index, Hausner ratio, tablet weight, thickness, diameter, hardness, friability, disintegration time, assay and drug released for the ciprofloxacin hydrochloride tablet trials. The differences between the means are regarded as statistically significant if the p-value ≤ 0.05.

4. RESULTS and DISCUSSION

4.1. UV Spectrum, DSC Thermogram, Particle Size Distribution and Assay Analysis for Ciprofloxacin Hydrochloride

As shown in Figure 4.1, the wavelength of maximum absorbance for ciprofloxacin hydrochloride was obtained at 278 nm. The λ_{max} obtained for the ciprofloxacin hydrochloride in this study was consistent with the λ_{max} value found by Brittain [Brittain, 2005].

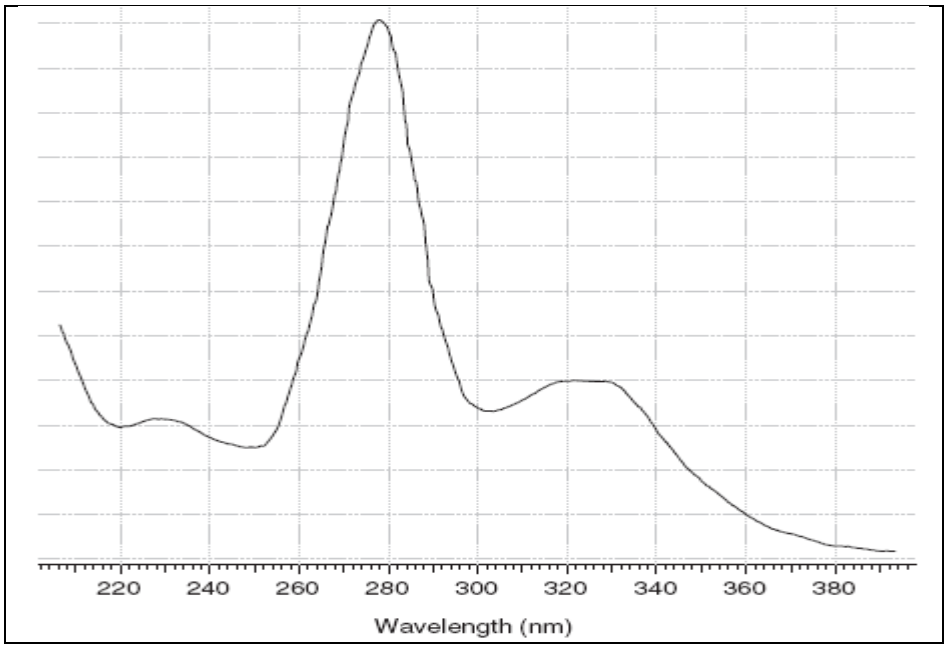

Figure 4.1: UV spectrum of ciprofloxacin hydrochloride.

Differential scanning calorimeter (DSC) thermogram of ciprofloxacin hydrochloride showed a broad endothermic peak at 145 °C with an onset temperature at 112 °C followed by a broad exothermic peak at 178 °C with an onset temperature at 165 °C. The endothermic peak at 318 °C with an onset temperature at 310 °C was identified as the melting peak for the ciprofloxacin hydrochloride (Figure 4.2). Melting point of 318 °C for the ciprofloxacin hydrochloride was also reported by Elkheshen et al. and Padhy et al. [Elkheshen et al., 2013], [Padhy et al., 2013].

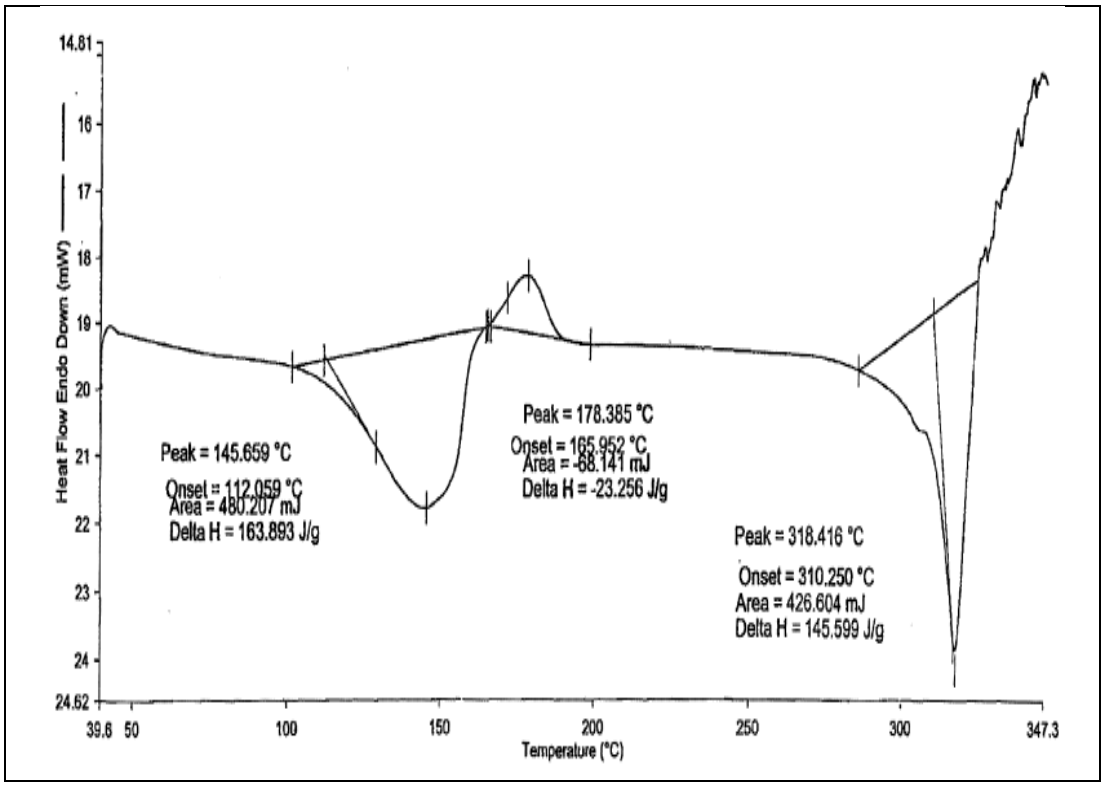

Figure 4.2: DSC thermogram of ciprofloxacin hydrochloride.

Particle size distribution of the ciprofloxacin hydrochloride is given in Table 4.1. The d10 was found to be 3.718 μm which meant that 10% of the population lied below this value. The d50 refers to the median diameter where half of the population lied below 10.949 μm. The d90 was found to be 29.916 μm which meant that 90% of the population lied below this value.

Table 4.1: Particle size analysis of ciprofloxacin hydrochloride[1].

d10 (μm)	d50 (μm)	d90 (μm)
3.718 ± 0.034	10.949 ± 0.054	29.916 ± 0.067

[1]Values are expressed as mean ± standard deviation (n=3).

The amount of ciprofloxacin hydrochloride was quantified with the assay analysis, and assay analysis yielded that ciprofloxacin hydrochloride was found to be 99.8% (w/w).

4.2. Flow Properties of Resultant Powders

Bulk density, tapped density, CI and HR values for the resultant powders used in the preparation of tablets containing ciprofloxacin hydrochloride are given in Table 4.2. Bulk density changed between 0.368 to 0.403 g/ml while tapped density varied from 0.490 to 0.532 g/ml. There was no statistically significant difference ($p > 0.05$) between the CI and HR values for T1 and T4. T1 and T4 gave CI values of 23.88% and 24.19%, respectively, while HR values were 1.31 and 1.32, respectively. These values indicated that T1 and T4 had passable flow character among the other trials since CI is below 25% and HR is less than 1.34 [USP, 2018].

Table 4.2: Bulk density, tapped density, CI and HR values for resultant powders used in the preparation of tablets containing ciprofloxacin hydrochloride[1].

Trial Code	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner Ratio
T1	0.373 ± 0.003^{a}	0.490 ± 0.005^{a}	23.88 ± 0.18^{a}	1.31 ± 0.01^{a}
T2	0.368 ± 0.003^{b}	0.495 ± 0.005^{a}	25.74 ± 0.19^{b}	1.35 ± 0.01^{b}
T3	0.376 ± 0.003^{ac}	0.515 ± 0.006^{bd}	27.07 ± 0.20^{c}	1.37 ± 0.01^{c}
T4	0.403 ± 0.004^{d}	0.532 ± 0.006^{c}	24.19 ± 0.20^{a}	1.32 ± 0.01^{a}
T5	0.382 ± 0.003^{ef}	0.521 ± 0.006^{d}	26.72 ± 0.20^{d}	1.36 ± 0.01^{d}
T6	0.385 ± 0.003^{f}	0.521 ± 0.006^{d}	26.15 ± 0.21^{e}	1.35 ± 0.01^{be}
T7	0.376 ± 0.003^{ac}	0.510 ± 0.005^{b}	26.32 ± 0.20^{e}	1.36 ± 0.01^{de}
T8	0.379 ± 0.003^{ce}	0.521 ± 0.006^{d}	27.27 ± 0.21^{c}	1.38 ± 0.01^{c}

[1]Values are expressed as mean ± standard deviation, and values with the same letter within the same column are not statistically significant at $p > 0.05$.

4.3. In Vitro Evaluation of Prepared Tablets

4.3.1. Physicochemical Properties and Assay Analysis

The physicochemical properties and results of assay analysis of prepared tablets are summarized in Table 4.3. Weight of tablets ranged from 399.9 ± 3.0 to 402.2 ± 3.7 mg, and no significant difference ($p > 0.05$) existed among the tablet weights

belonging to the different trials. All the prepared tablet trials met the USP [USP, 2018] requirements for the weight variation in which the percent variation was not exceeded by ± 5% when the weight of a tablet is more than 324 mg. Although thickness of tablets is not included in the pharmacopoeia standards, it is important to determine the thickness of the tablets because thickness may change due to the difference in bulk density, pressure applied and speed during the tablet formation. Uniformity in thickness of tablets is not only important to form reproducible tablets identical in its appearance but also to ensure that the produced tablets comply with the packaging requirements, withstand mechanical compression, provide better oral intake and are accepted by the consumers. The thickness of tablets lied within the range of 4.70 ± 0.01 to 4.72 ± 0.01 mm. The results revealed that no statistical difference ($p > 0.05$) was observed among the tablets belonging to the different trials, and the percent deviation in thickness was less than 0.3%, which is a well-accepted value showing the uniformity of tablets in routine tablet manufacturing in the pharmaceutical industry [Morkhade, 2017]. Its proximity to each other of average values in thickness and being too low of the deviation from the average thickness value provide being uniform of the tablet weight. The tablets in different size may procure the patient to think that the tablets or drugs have different amount of active ingredient. The uniformity in diameter of tablets is important to avoid them from being confused with the tablets in different size and increase the patient compliance. There was no statistically significant difference ($p < 0.05$) among the tablet diameters for the different trials. The diameter of the tablets changed between 11.02 ± 0.01 and 11.03 ± 0.01 mm which conformed to USP [USP, 2018] requirements for the tablets which state that the deviation from the average diameter should not exceed ± 3% for diameter of 12.5 mm or more and ± 5% for tablets with diameter of less than 12.5 mm. Determination of hardness is important to determine the need for pressure settings on the tablet compression. If the tablet is compressed too soft, tablets with low friability are obtained and will not be able to withstand the conditions of packaging, use and transport. If the tablet is compressed too hard, it may not meet the dissolution specifications, dissolution will be delayed. The hardness of the tablets ranged from 16.21 ± 0.68 to 17.35 ± 0.58 kp. Statistical analysis showed that there was no statistically significant difference ($p > 0.05$) among the hardness values belonging to the different trials. The tablets will not break in the film coating process and the packaging process, however, it should be friable enough to disintegrate in the gastrointestinal tract. In other words, from

production stage to packaging of tablets and in the process up to the shipping and during use of tablets by the patients must be mechanically sound and durable to retain their physical integrity. Therefore, the measure of friability is important. The percent friability values of the tablets ranged from 0.074% to 0.175%, where the percent friability for all trials was less than 1%, indicating that tablets have good mechanical resistance. Statistical analysis also revealed that there existed no significant difference ($p > 0.05$) among the friability values of the tablets belonging to the different trials.

The disintegration time of the tablets containing ciprofloxacin hydrochloride in deionized water changed between 70 ± 5 and 97 ± 7 s. T2 gave the shortest disintegration time (70 ± 5 s) while T6 had the longest disintegration time (97 ± 7 s). There was a significant difference ($p \leq 0.05$) among the disintegration times of the tablets produced from the trials T1 through T4 and the tablets produced from the trials T5 through T8. When the granulation time was set to 5 min, regardless of the chopper and impeller speeds used in the HSM wet granulation process, the disintegration time of the tablets was minimum. In other words, the tablets produced from the trials T1 through T4 dissolved in less time than the tablets produced from the trials T5 and T8. These results met the limit of disintegration time (< 30 min) for the uncoated core tablets specified by the USP [USP, 2018]. In assay tests, the percentage of ciprofloxacin hydrochloride ranged from $97.11 \pm 0.48\%$ to $99.80 \pm 0.01\%$ among the different trials. The assay tests performed for the tablets containing ciprofloxacin hydrochloride were found to comply with the USP specifications where the deviation should be between 90% and 110% from the average value.

Table 4.3: Physicochemical properties of tablets and assay analysis results[1].

Trial Code	Weight (mg)	Thickness (mm)	Diameter (mm)	Hardness (kp)	Friability (%)	Disintegration Time (s)	Assay (%)
T1	401.1 ± 2.7^{a}	4.71 ± 0.01^{a}	11.02 ± 0.01^{a}	16.42 ± 0.54^{a}	0.124 ± 0.050^{a}	72 ± 3^{a}	97.11 ± 0.48^{a}
T2	402.1 ± 4.3^{a}	4.71 ± 0.01^{a}	11.02 ± 0.01^{a}	16.36 ± 1.52^{a}	0.098 ± 0.024^{a}	70 ± 5^{a}	97.15 ± 0.25^{a}
T3	400.9 ± 2.4^{a}	4.71 ± 0.01^{a}	11.02 ± 0.01^{a}	16.21 ± 0.68^{a}	0.121 ± 0.073^{a}	72 ± 8^{a}	99.45 ± 0.07^{b}
T4	402.2 ± 3.7^{a}	4.70 ± 0.01^{a}	11.02 ± 0.01^{a}	17.02 ± 0.97^{a}	0.098 ± 0.049^{a}	72 ± 6^{a}	99.35 ± 0.07^{b}
T5	399.9 ± 3.0^{a}	4.71 ± 0.02^{a}	11.03 ± 0.01^{a}	16.70 ± 0.94^{a}	0.150 ± 0.050^{a}	80 ± 2^{b}	99.80 ± 0.01^{c}
T6	400.6 ± 2.2^{a}	4.71 ± 0.01^{a}	11.02 ± 0.01^{a}	16.95 ± 1.57^{a}	0.175 ± 0.050^{a}	97 ± 7^{c}	98.35 ± 0.07^{d}
T7	401.8 ± 1.9^{a}	4.72 ± 0.01^{a}	11.03 ± 0.01^{a}	17.35 ± 0.58^{a}	0.172 ± 0.025^{a}	83 ± 5^{b}	99.05 ± 0.07^{e}
T8	400.1 ± 2.7^{a}	4.71 ± 0.01^{a}	11.02 ± 0.01^{a}	16.84 ± 0.86^{a}	0.074 ± 0.024^{a}	81 ± 5^{b}	98.70 ± 0.14^{f}

[1]Values are expressed as mean ± standard deviation, and values with the same letter within the same column are not statistically significant at $p > 0.05$.

4.3.2. Dissolution Analysis

Granulation time, impeller speed and chopper speed were found to affect the ciprofloxacin hydrochloride release from the tablets. The dissolution analysis of the tablets performed in 0.01 N HCl are presented in Table 4.4. Tablets formed at the highest chopper speed, highest impeller speed and longest granulation time resulted in tablets with the slowest dissolution rate of the drug from the tablets (Figure 4.4).

Tablets produced at the granulation time of 2.5 min, impeller speed of 80 rpm and when the chopper was off (T5) had the fastest dissolution rate while the tablets formed at the impeller speed of 160 rpm, granulation time of 5 min and chopper speed of 1000 rpm (T4) exhibited the slowest dissolution behavior. At the end of 60 min, $91.54 \pm 1.97\%$ of the drug was released from T5 while $74.07 \pm 4.12\%$ of the drug was released from T4. There was a significant difference ($p \leq 0.05$) among the dissolution rates of the tablets produced from the trials T4 and T5. The change in the dissolution time can be attributed to the difference in the surface area of the granules where increasing the surface area decreases the dissolution time [Al hassn et al., 2018]. Regardless of the chopper speed, tablets produced at the lowest impeller speed of 80 rpm and the shortest granulation time of 2.5 min (T5 and T6) gave the highest dissolution rates compared to the rest of the trials. There was no statistically significant difference ($p > 0.05$) among the dissolution rates of the tablets produced from the trials T5 and T6. Regardless of the chopper speed and granulation time, the tablets produced at the lowest impeller speed of 80 rpm (T1, T2, T5 and T6) gave the highest dissolution rates compared to the tablets produced at the highest impeller speed of 160 rpm (T3, T4, T7 and T8) which gave the lowest dissolution rate. There was a significant difference ($p \leq 0.05$) among the dissolution rates of the tablets produced at the impeller speeds of 80 and 160 rpm.

Table 4.4: Percent ciprofloxacin hydrochloride released with time in 0.01 N HCl (n=6)[1].

Time (min)	T1	T2	T3	T4	T5	T6	T7	T8
2.5	51.10 ± 5.00^{Aa}	42.88 ± 9.30^{Ba}	15.82 ± 2.21^{Ca}	10.87 ± 1.58^{Ca}	62.96 ± 6.49^{Da}	66.94 ± 2.83^{Da}	12.82 ± 1.64^{Ca}	14.49 ± 2.68^{Ca}
5	64.51 ± 4.46^{Ab}	55.37 ± 7.74^{Bb}	28.45 ± 0.60^{CDb}	24.59 ± 2.93^{Db}	72.22 ± 2.57^{Eb}	76.28 ± 1.70^{Eb}	26.58 ± 2.40^{CDb}	31.38 ± 9.85^{Cb}
7.5	71.07 ± 4.63^{Ac}	63.51 ± 5.18^{Bc}	37.79 ± 0.44^{Cc}	34.47 ± 4.54^{Cc}	80.80 ± 1.25^{Dc}	82.47 ± 1.81^{Dc}	36.45 ± 2.95^{Cc}	40.37 ± 9.82^{Cc}
10	74.53 ± 4.12^{Ac}	67.88 ± 4.33^{Bc}	43.66 ± 3.54^{Cd}	45.30 ± 3.54^{Cd}	$86,98 \pm 4.89^{Dd}$	82.73 ± 1.58^{Dc}	48.79 ± 7.51^{Cd}	47.05 ± 9.53^{Cc}
15	80.51 ± 3.42^{ADd}	76.03 ± 2.72^{Ad}	57.54 ± 2.22^{Be}	53.54 ± 5.82^{Be}	89.79 ± 5.79^{Cd}	85.39 ± 1.86^{CDd}	59.18 ± 5.45^{Be}	56.74 ± 7.39^{Bd}
20	83.75 ± 2.59^{ADde}	80.87 ± 1.98^{Ade}	63.41 ± 1.97^{BEf}	59.67 ± 6.11^{Bf}	90.73 ± 5.28^{Cd}	85.78 ± 2.09^{CDde}	66.56 ± 5.26^{Ef}	63.41 ± 5.84^{BEd}
30	86.81 ± 0.54^{ACef}	85.02 ± 1.38^{Aef}	71.23 ± 1.49^{BDg}	66.97 ± 5.91^{Bg}	91.29 ± 4.40^{Cd}	86.88 ± 2.17^{ACde}	74.04 ± 6.58^{Dg}	71.97 ± 3.82^{De}
45	87.98 ± 0.98^{Af}	87.63 ± 1.12^{Af}	76.11 ± 3.28^{BCh}	72.25 ± 5.53^{Bgh}	91.95 ± 3.08^{Ad}	88.25 ± 1.87^{Ae}	79.55 ± 7.12^{Cg}	78.85 ± 1.72^{Cef}
60	88.45 ± 0.65^{ACf}	87.38 ± 0.79^{Af}	77.59 ± 3.17^{BDh}	74.07 ± 4.12^{Bh}	91.54 ± 1.97^{Cd}	89.57 ± 1.39^{ACde}	80.73 ± 6.90^{Dg}	80.94 ± 1.53^{Df}

[1]Values are expressed as mean ± standard deviation. Different uppercase letters (A-E) show that values in the same row within each group are significantly different ($p \leq 0.05$). Different lowercase letters (a-h) show that values in the same column within each group are significantly different ($p \leq 0.05$).

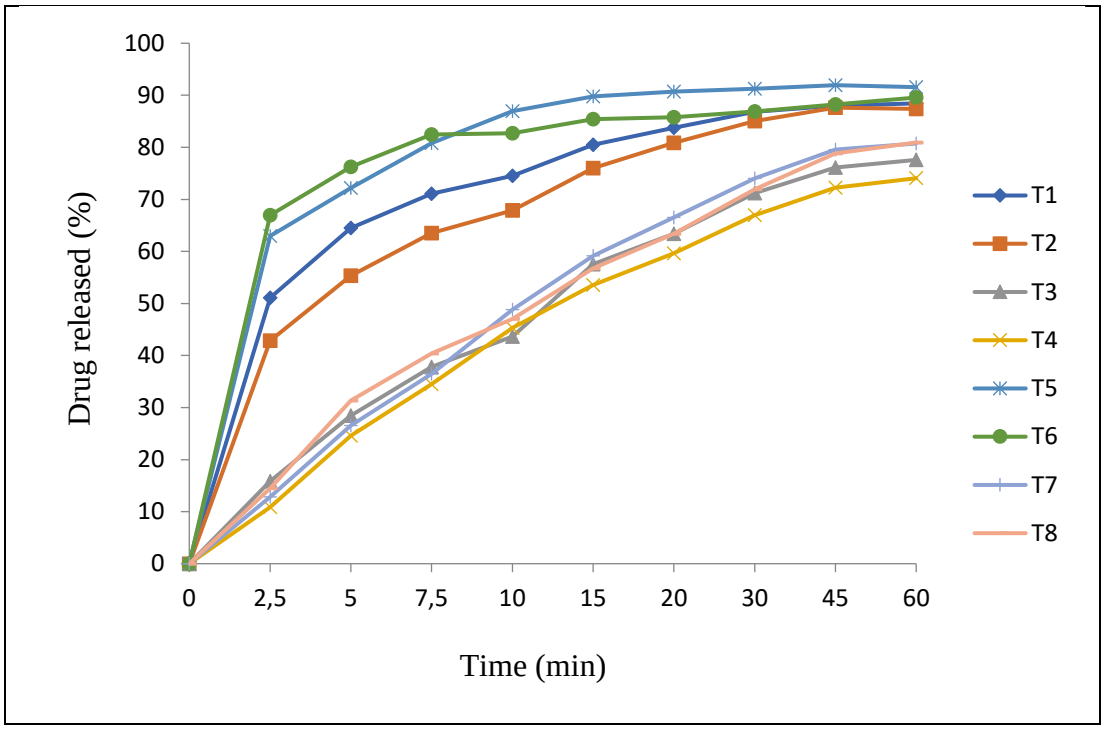

Figure 4.3: Drug released (%) values for trials T1 through T8 in 0.01 N HCl (n=6).

5. CONCLUSION

In this study, the effects of processing parameters (granulation time, impeller speed and chopper speed) in HSM granulator on the release characteristics of ciprofloxacin hydrochloride, weight variation, disintegration time, thickness and friability of the tablets using 2^3 factorial design were investigated and the release profiles of ciprofloxacin hydrochloride from the immediate release tablets in simulated gastric medium were determined. Particle size analysis revealed a uniform normal PSD for the ciprofloxacin hydrochloride. The amount of ciprofloxacin hydrochloride was quantified with the assay analysis as 99.8% (w/w). Bulk density of the powders changed between 0.368 to 0.403 g/ml while tapped density varied from 0.490 to 0.532 g/ml. Powders produced at 80 rpm impeller speed and 5 min granulation time gave the best percent CI and HR values, 23.88% and 1.31, respectively.

Weight of the tablets ranged from 399.9 to 402.2 mg. All the prepared tablet trials met the United States Pharmacopeia (USP) requirements for the weight variation in which the percent variation was not exceeded by ± 5% although the average weight of a tablet is more than 324 mg. Thickness of tablets lied within range of 4.70 to 4.72 mm. The percent deviation in thickness was less than 0.3%, which is a well-accepted value showing the uniformity of tablets in routine tablet manufacturing in the pharmaceutical industry. The diameter of the tablets changed between 11.02 and 11.03 mm which conformed to USP requirements, if tablets have a diameter of less than 12.5 mm, the deviation from the average diameter should not exceed ± 5%. Friability values of the tablets ranged from 0.074 to 0.175%, where the percent friability for all trials was less than 1%, indicating that the tablets have good mechanical resistance.

The disintegration time of the tablets containing ciprofloxacin hydrochloride in deionized water changed between 70 and 97 s. The tablets produced at the chopper speed of 1000 rpm, impeller speed of 80 rpm and granulation time of 5 min disintegrated at 70 s while the tablets produced at the chopper speed of 1000 rpm, impeller speed of 80 rpm and granulation time of 2.5 min disintegrated at 97 s.

Assay results were found to be consistent among different trials where the percentage of ciprofloxacin hydrochloride ranged from 97.11 to 99.80% in which the tablets containing ciprofloxacin hydrochloride were found to comply with the USP

specifications where the deviation should be between 90 and 110% from the average value.

Impeller speed, chopper speed and granulation time affected the ciprofloxacin hydrochloride release from the tablets. Regardless of the chopper speed and granulation time, the tablets produced at the lowest impeller speed of 80 rpm (T1, T2, T5 and T6) gave the highest dissolution times while the tablets produced at the highest impeller speed of 160 rpm (T3, T4, T7 and T8) had the lowest dissolution times. Tablets produced at the impeller speed of 80 rpm, granulation time of 2.5 min and when the chopper was off had the fastest dissolution rate (91.54%) at 60 min.

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