NOUR ALKARAMI

Adınızı soyadınızı giriniz

İSTANBUL ÜNİVERSİTESİ SAĞ. BİL. ENST.

Tez kabul edildikten sonra eğer basılacak ise yapılan **sabit ciltte sırt yazısı** bu şablona göre yazılacak. Yazılar tek satır olacak
Cilt sırtı yazıların yönü yukarıdan aşağıya (sol yandaki gibi) olacak .

YÜKSEK LİSANS TEZİ

Tez, Yüksek Lisans'sa, YÜKSEK LİSANS TEZİ;
Doktora ise DOKTORA TEZİ ifadesi kalacak

İSTANBUL-2023

Tez Sınavının yapılacağı yılı yazınız

T.C.
İSTANBUL ÜNİVERSİTESİ
SAĞLIK BİLİMLERİ ENSTİTÜSÜ

(YÜKSEK LİSANS TEZİ)

OPTIMIZATION AND IN VITRO CHARACTERIZATION STUDIES OF ORALLY DISINTEGRATING TABLET (ODT) FORMULATIONS PREPARED BY DIFFERENT METHODS

NOUR ALAKRAMI

DANIŞMAN
DR. ÖGR. ÜYESİ EMİNE KAHRAMAN

FARMASÖTİK TEKNOLOJİ ANABİLİM DALI/
FARMASÖTİK TEKNOLOJİ PROGRAMI

İSTANBUL-2023

DEDICATION

To my precious family, my husband and my adorable daughter

ACKNOWLEDGMENT

I am deeply grateful to my advisor, Assist. Prof. Dr. Emine Kahraman, for her unwavering support and guidance throughout my master's program. Her expertise and patience have been invaluable to me and have played a crucial role in the success of this thesis.

To all the teachers who taught me during the study stage and provided their great and useful knowledge, I would like to express my sincere gratitude and appreciation. Prof. Dr. Yıldız Erginer, Prof. Erdal Cevher, and other teachers in the department.

I would like to extend my sincere thanks to Assist. Prof. Dr. Genada Sinani, Res. Assist. Mohammed Zeyad Mohammed Kalayi and Res. Assist. Emine Saldamlı for their wonderful help and support.

I would also like to thank Altınbaş University, Faculty of Pharmacy, Department of Pharmaceutical Technology, and Prof. Dr. Neşe Buket Aksu for giving us the opportunity to work in its laboratory.

I want to extend my thanks to Vem Pharmaceuticals and Ali Raif Pharmaceuticals for providing us with the active ingredients and the necessary excipients.

A special thanks to everyone at the Pharmaceutical Technology Department, Faculty of Pharmacy, Istanbul University, and to my friends Noor Alhaidar, Marwa Kake, Sewar Talal, Hanaa Ali, and all of my other friends who helped me in various ways.

I am deeply thankful to my husband and my family for their love and support during this process. Without their encouragement and motivation, I would not have been able to complete this journey.

Finally, I would like to thank all of the participants in my study for their time and willingness to share their experiences. This work would not have been possible without their contribution.

CONTENTS

LIST OF TABLE

LIST OF FIGURES

ABBREVIATIONS

ODT: Oral Disintegrating Tablet

FLB: Flurbiprofen

CDER: Center for Drug Evaluation and Research

NSAID: Non-Steroidal Anti-Inflammatory Drug

FDA: Food and Drug Administration

ICH: International Conference on Harmonization Guidelines

CD: Cyclodextrin

β-CD: Beta-cyclodextrin

UV: Ultraviolet

HPLC: High-Performance Liquid Chromatography

HP-β-CD/ HPβCD: Hydroxypropyl-β-cyclodextrin

mM: Millimole

COX: Cyclooxygenase

DC: Direct Compression

FD: Freeze Drying

WOW: WithOut Water

GRAS: Generally Regarded as Safe

Me-CDs: Methylated Cyclodextrin Derivatives

PVP: Polyvinyl Pyrrolidone

MCC: Microcrystalline cellulose

SSG: Sodium Starch Glycolate

MC: Methyl cellulose

EC: Ethyl cellulose

HPMC: Hydroxypropyl methylcellulose

CMC: Carboxymethyl cellulose

SLS: Sodium lauryl sulfate

PEG: Polyethylene glycol

ÖZET

Alakrami, N. (2023). Farklı Yöntemler ile Hazırlanan Ağızda Dağılan Tablet Formülasyonlarının Optimizasyonu ve in vitro Karakterizasyonları, İstanbul Üniversitesi Sağlık Bilimleri Enstitüsü, Farmasötik Teknoloji ABD. Yüksek Lisans Tezi. İstanbul.

Tabletler; kolay hazırlanmaları ve yüksek hasta uyuncu nedeniyle en çok kullanılan oral dozaj şeklidir. Bununla birlikte, tabletlerin disfajik, pediatrik, geriatrik ve nörolojik hastalar için dezavantajları vardır. Ağızda dağılan tabletler (ODT), suya ihtiyaç duymadan ağız boşluğunda hızla parçalanan belirgin katı dozaj formlarıdır. ODT'lerin üretimi için geleneksel veya patentli yöntemler olmak üzere birçok teknoloji kullanılmaktadır. Bu dozaj şekillerinde siklodekstrinlerin formülasyona dahil edilmesiyle ilaç çözünürlüğünün, biyoyararlanımın artırılması, ilaç stabilitesinin ve tadının iyileştirilmesi hedeflenmektedir. Bu çalışmada ise çeşitli yöntemlerin (direkt basım ve yaş granülasyon), yardımcı maddelerin ve siklodekstrinlerin kullanılması ile flurbiprofen içeren ağızda dağılan tabletlerin kalite özellikleri ve tat maskeleme üzerindeki etkilerinin incelenmesi amaçlanmıştır. Çalışmada öncelikle liyofilizasyon yöntemi ile flurbiprofen-β-CD ve flurbiprofen-HPβCD ile kompleksleri hazırlandı. Ardından tablet formülasyonları için toz karışımları hazırlanıp gerçek yoğunluk, sıkıştırılmış yoğunluk, yığın açısı, sıkıştırılabilirlik (Carr indeksi), Hausner oranı saptandı. Bütün formülasyonlarda aynı tablet basım parametreleri sağlanarak tabletler (F1-F7) basıldı ve tabletlerde ağırlık sapması, çap-kalınlık, sertlik, friabilite, içerik tekdüzeliği, ıslanma süresidağılma süresi, çözünme hızı ve tat maskeleme testleri yapıldı. Ağırlık sapması, çap-kalınlık, içerik tekdüzeliği ve tat maskeleme sonuçları hazırlanan bütün formülasyonlar için kabul edilen değerlerde bulunmuştur. Formülasyonların sertlik sonuçları ise 18,5±1,26 N ile 106,9±14,60 N arasında tespit edilmiştir. Formülasyonda flurbiprofen siklodekstrin komplekslerinin bulunması ise farmakope kabul limitlerinin aşılmasına yol açmıştır. Formülasyonların ıslanma süreleri 7,11±0,72 saniye ile 549,33±71,06 saniye arasında değişirken dağılma süreleri ise 10,67±3,50 saniye ile 223,17±18,94 saniye arasında saptanmıştır. Formülasyonların çözüme hızları ise 45 dakika sonunda % 85,45 ile %101,79 arasında değişim göstermiştir. Sonuç olarak, üretim yönteminin, formülasyonda kullanılan yardımcı maddelerin ve siklodekstrinlerin aynı tablet basım parametreleri kullanılarak hazırlanan ağızda dağılan tabletlerin kalite parametrelerini ve tat maskelemesini önemli ölçüde etkilediği bulunmuştur.

Anahtar Kelimeler: Ağızda dağılan tablet, Siklodekstrin, Direkt basım, Yaş granülasyon, Tat maskeleme

ABSTRACT

Tablets are the most widely used form of oral dosage due to their easy preparation and high patient compliance. However, tablets have disadvantages for dysphagic, pediatric, geriatric, and neurological patients. Orally disintegrating tablets (ODT) are distinct solid dosage forms that rapidly disintegrate in the oral cavity without the need for water. Many technologies are used to produce ODTs, either traditional or patented methods. The inclusion of cyclodextrins in the formulation of these dosage forms is aimed at increasing drug solubility, bioavailability, and improving drug stability and taste. This study aimed to examine the effects of various methods (direct compression and wet granulation), excipients, and cyclodextrins on the quality characteristics and taste masking of orodispersible tablets containing flurbiprofen. In the study, firstly, flurbiprofen-β-CD and flurbiprofen-HPβCD complexes were prepared by the lyophilization method. Then, powder mixtures were prepared for tablet formulations, and bulk density, tapped density, angle of repose, compressibility (Carr index), and Hausner ratio were determined. Tablets (F1-F7) were prepared by providing the same tableting parameters in all formulations, and weight variation, diameter-thickness, hardness, friability, content uniformity, wetting time, disintegration time, dissolution rate, and taste masking tests were performed on the tablets. Weight deviation, diameter-thickness, content uniformity, and taste masking results were found to be within accepted values for all prepared formulations. The hardness results of the formulations were determined between 18.5±1.26 N and 106.9±14.60 N. The presence of flurbiprofen cyclodextrin complexes in the formulation led to exceeding the pharmacopeia acceptance limits. The wetting times of the formulations ranged from 7.11±0.72 seconds to 549.33±71.06 seconds, while the disintegration times were between 10.67±3.50 seconds and 223.17±18.94 seconds. The dissolution rates of the formulations varied between 85.45% and 101.79% after 45 minutes. As a result, it was found that the production method, excipients, and cyclodextrins used in the formulation significantly affected the quality parameters and taste masking of the orally disintegrating tablets prepared using the same tablet pressing parameters.

Keywords: Orally disintegrating tablet, Cyclodextrin, Direct compression, Wet granulation, Taste masking.

1. INTRODUCTION AND PURPOSES

The oral route is the recommended way of drug administration, and tablets are the most widely used dosage form currently due to their simplicity of self-administration, convenience and precision of dosing, and most significantly, patient compliance. Additionally, compared to liquid dosage forms, solid oral delivery methods are less expensive to develop and offer good drug stability. However, the tablets also have significant disadvantages, especially for those who are unable to swallow conventional oral dosage forms, like dysphagic patients, pediatric and geriatric patients, and patients with pathological conditions such as neurological disorders and Parkinson's disease. (Tafere, Yilma, Abrha, & Yehualaw, 2021).

Oral disintegrating tablets (ODTs), new dosage form that quickly disintegrates in saliva and can be simply taken without water, have been formulated to overcome these problems. This innovative dosage form offers many advantages over traditional dosage forms, and can be manufactured using either conventional or patented techniques. Additionally, taste-masking is an essential step toward improving orally disintegrating tablet (Pandey & Dahiya, 2016). ODT has developed for drugs which are poorly absorbed by the gastrointestinal system but are difficult to provide parenterally (Yasmeen, Revathi, & Monica, 2019). Perception of tastes is another essential factor to consider since it can be difficult to formulate bitter medications as ODT, therefore, taste-masking excipients are suggested to be used (Ghourichay, Kiaie, Nokhodchi, & Javadzadeh, 2021).

Enhancement of solubility of poorly-soluble drugs and taste masking are considered to be important and challenging aspect of ODT's drug manufacturing and formulation. Cyclodextrin (CD) complexation is one of various techniques used to enhance the solubility of such medications. The capacity of CDs to form inclusion complexes, which enhance pharmaceutical features including solubility, bioavailability, stability, and taste without altering their inherent lipophilicity or pharmacological capabilities, is one of their most essential properties (Vidyadhara, Sasidhar, Deepti, & Vikas, 2016).

In the present study, different formulations of oral disintegrating tablets containing flurbiprofen, as model drug, were studied by using different methods (direct compression and wet granulation), and different excipients (Ludipress, co-processed

superdisintegrant, cyclodextrin, sodium starch glycolate, and crospovidone) to examine effect on quality attributes and taste-masking of different excipients and methods. The characteristics and quality attributes of the tablets (diameter, thickness, friability, weight variation, content uniformity, wetting time, in vitro dissolution, and disintegration time, in addition to taste masking feature) have been tested, and the results were compared.

2. GENERAL INFORMATION

2.1. Oral Disintegrating Tablets

In 1998, the Nomenclature Standards Committee of the Center for Drug Evaluation and Research (CDER) introduced the concept of Oral Disintegrating Tablets (ODTs) as a type of solid dosage form containing medicinal ingredients that rapidly disintegrate, typically within a few seconds, when placed on the tongue. The United States Food and Drug Administration (FDA) recommends that ODTs be classified as solid oral preparations designed to disintegrate rapidly in the oral cavity, with an in-vitro disintegration time of approximately 30 seconds or less. This determination is based on the criteria outlined in the United States Pharmacopeia (USP) disintegration test method or alternative methods (Food and Drug Administration, 2008).

According to the European Pharmacopea (EP), ODTs are "uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed" and tablets should disintegrate within 3 min" (European Pharmacopoeia, 2019). ODTs are also known by the names orally disintegrating, fast-dissolving multiparticulate, orodispersing, mouth-dissolving, melt-in-mouth tablets, rapid dissolving, rapid-disintegrating tablets, fast-melting, fast-dissolving, freeze-dried wafers, quick-dissolve, and porous tablets in official documents and literature (Yapar, 2014).

Oral disintegrating tablets have been developed, and new ODT technologies assist the development of pharmaceutical and patient demands, from improved life-cycle management to simple dosing for dysphagic patients, pediatric and geriatric patients, and psychiatric patients (Arvapalli, Swamy, & Shyamala, 2019). Additionally, oral dispersible tablets are employed when a local effect in the mouth is preferred, such as with local anesthetics for toothaches, mouth ulcers, and cold sores (Nikam, Shete, & Khapare, 2020).

2.1.1. Distinctions Between Conventional Tablets and ODTs

Even if numerous attributes of ODTs are analogous to conventional tablets, notable discrepancies persist between the two (Comoglua & Ozyilmaza, 2019).The divergences are outlined in Table 2-1.

Tablo 2-1: Distinctions between conventional tablets and ODTs.

Features	Conventional tablets	ODTs
Disintegration time	Max. 15 min. for uncoated tablets	Max. 3 min.
Ease of use	Water is needed	Water is not needed
Bioavailability	Less	More
Packaging	More easy	More difficult
Stability	Less affected by environmental factors	More affected by environmental factors
Superdisintegrant	Not necessary	Necessary
Dose of active phamaceutical ingredient (API)	Found in higher doses	Found at max. 50 mg.
Taste of formulation	May have bitter taste	Should have a good taste

2.1.2. Advantages of ODTs

ODTs have many benefits that, in most situations, make them preferable for patients who cannot swallow conventional dosage forms. The advantages of ODTs can be outlined as follows (Nayak & Manna, 2011):

- Easy administration for patients who have difficulty swallowing tablets, such as geriatric, psychiatric, pediatric, paralyzed, and bedridden individuals.
- For pediatric populations, satisfactory mouthfeel holds particular significance, as taste-masking methodologies are employed to alleviate the bitter flavors of medicinal products.
- ODTs provide heightened safety and compliance during administration, as the risk of airway obstruction and choking upon swallowing is diminished owing to their rapid disintegration.
- In contrast to conventional tablet forms, ODTs don't require water to be swallowed.
- Drug bioavailability is enhanced because of absorption occurring through the oral mucosa, pharynx, and esophagus. This, in conjunction with lower

dosages, leads to improved clinical efficacy by mitigating potential side effects.

- With rapid dissolution and absorption through the oral cavity, the therapeutic effect promptly initiates.
- Tablets can be manufactured with minimal costs by employing conventional processing and packaging machinery.

2.1.3. Disadvantages of ODTs

Despite having numerous benefits, ODTs are also associated with specific challenges, as succinctly outlined by (Pandey & Dahiya, 2016).

- Due to often inadequate mechanical strength, conscientious handling is necessary for tablets.
- Insufficiently formulated tablets might result in an unfavorable taste and texture sensation in the oral cavity.
- Formulating drugs with high dosages can be present challenges.
- ODTs are not suitable for patients who are taking anti-cholinergic medications simultaneously.
- ODTs must be stored in a dry environment due to its hygroscopic nature.

2.1.4. Mechanisms of ODTs

To accomplish the required fast dissolving properties, ODTs use the following mechanisms (Arvapalli, Swamy, & Shyamala, 2019):

- To instantly disintegrate the tablet, water must immediately enter the matrix of the tablet.
- Incorporating appropriate disintegrating substances or excipients that are highly soluble in water into the formulation of the tablet.
- Mechanisms that cause the tablet to be broken up into small particles, which then produce a solution or suspension of the medicine, such as chemical reactivity, capillary action, and high disintegrating swell ability.

2.1.5. Properties of Ideal ODTs

Ideal properties that are essential for the success of ODTs should include (Yapar, 2014):

- Dissolving, dispersing, or disintegrating in the mouth cavity in a matter of seconds,
- High drug loading.
- Minimizing residual mountfeel and providing a mouth-pleasing sensation.
- The possibility to avoid tablet size expansion.
- Rapid onset of therapeutic action.
- Compatible with other excipients and taste masking.
- Sufficient mechanical strength to resist the demands of manufacturing and handling after manufacturing.
- Insensitive to environmental factors like humidity and temperature.

2.1.6. Challenges in the Formulations of ODTs

Numerous techniques have been explored in the pursuit of ODT development, notwithstanding the myriad challenges entailed in their formulation and production, which also outlined as below: (Badgujar & Mundada, 2011).

- To obtain inadequate mechanical strength for ODTs.
- Difficulty to accomplish the fast disintegration of tablet.
- The choice of polymer and its concentration for drug particle coating, as the dissolving profile is affected by the solubility of the coated polymer or the drug particle coating's thickening.
- Difficulty to obtain adequate taste masking for bitter active pharmaceutical ingredients (APIs).
- Problem to accomplish the optimal method for taste masking among various approaches.
- After swallowing, the presence of residual medication in the oral cavity, which can lead to patient noncompliance.

2.1.7. Characteristics of Ideal Drug Candicate for ODT Formulations

To be deemed suitable for an ODT formulation, a drug must possess the following attributes (Nayak & Manna, 2011):

- Not having a unfavorable taste.
- Minimum possible dose (<20 mg).

- Low to medium molecular weight (less than 500 Da).
- High solubility in saliva and water.
- Mostly non-ionized feature at the oral pH.
- The ability to distribute and separate into the epithelium of the upper gastrointestinal tract (log P >1, or ideally >2).
- Being able to penetrate through the oral mucosa.

2.1.8. Excipients Used in ODT Formulations

All of the excipients used in ODT formulations must meet certain criteria as follows (Nandhini & Rajalakshmi, 2018):

- Being inert physiologically.
- To be accepted by regulatory authorities and proving the regulatory criteria.
- Being chemically and physiologically stable.
- Not affecting the drug's bioavailability.
- Being readily available on the market in a form and purity that meets pharmaceutical requirements.
- Low cost.

Basically, ODT formulations consist of diluent, binder, superdisintegrant, taste-masking agent, and lubricant. Furthermore, superdisintegrant and taste-masking agents are the two most crucial excipients because disintegration time and taste-masking is characteristic properties of ODTs.

2.1.8.1. Superdisintegrants

Disintegrating substances are compounds that are frequently added to the formulation of tablets to help the compressed mass break down into separate particles. This process allows to effectively release or dissolve of active pharmaceutical content when a tablet becomes in contact with the surroundings fluid. Disintegrants also improve the tablet matrix's susceptibility to moisture and enhance its dispersion properties. The primary purpose of disintegrating agents is to overcome the effects of binders and mechanical forces applied during the compression, thereby promoting proper formation of the tablet structure.

In the case of solid dosage forms, superdisintegrants are commonly used at low concentrations, typically ranging from 1% to 10% by weight of the total weight of the dosage unit. These superdisintegrants usually have small, porous particles, which facilitate rapid tablet dissolution in the mouth without causing an unpleasant mouthfeel that can occur with larger particles or gelling agents. Effective superdisintegrants enhance compressibility and compatibility while having negligible effects on their mechanical properties of the formulations that includes high-dose medications (Pahwa & Gupta, 2011).

An ideal superdisintegrant should meet the following specific criteria (Pahwa & Gupta, 2011)

- Poor solubility.
- Insufficient gel formation.
- High hydration capacity.
- Favorable flow and molding characteristics.
- No potential to combine the drugs in complexes.
- Pleasant mouthfeel.
- Additionally, it should exhibit advantageous tableting properties and be compatible with the other excipients.

Superdisintegrants achieve their functionalities through the swelling, particle repulsive forces, deformation recovery, porosity and capillary action mechanisms. As outlined in Table 2-2, the mechanisms of superdisintegrants are also elaborated as follows (Badgujar & Mundada, 2011).

Swelling: The most frequently reported mechanism for tablet disintegrants is swelling. Upon contact with an appropriate medium, disintegrant particles undergo expansion, generating a swelling force that disrupts the tablet matrix. Tablets with high porosity tend to exhibit inadequate disintegration because of insufficient swelling forces, whereas those with low porosity demonstrate more effective disintegration driven by substantial swelling forces.

Porosity and capillary action (Wicking): Superdisintegrants that don't undergo significant swelling are thought to perform disintegration influence using capillary and porosity effect. The porosity of tablets creates channels through which fluids can enter

the tablets. Upon immersing the tablet in a suitable aqueous medium, the medium permeates the tablet, displacing the air that has adhered to the particles. This disruption weakens the intermolecular links, ultimately resulting in fragmentation of tablet into smaller pieces.

Particle Repulsive Forces: According to the principle of particle-particle repulsion, water enters tablets through hydrophilic pores, where it forms a constant starch network which may transfer water from a single particle to another, creating large fluid pressure. As a consequence, water permeates within starch particles due to their attraction to starch surfaces, disrupting hydrogen chemical bonds as well as other cohesive factors that maintain the tablet's structural integrity.

Deformation Recovery: According to the deformations recovery theory, the disintegrant particles' shape is altered during compaction and returns into their original shape after being wet. The increased size of the affected particles is what causes the disintegration of the tablet. This situation might be crucial to the mechanism of action of disintegrants with low swelling, like starch and crospovidone. (Pahwa & Gupta, 2011)

Table 2-2: Superdisintegrants commonly used in ODTs and their mechanisms (Badgujar & Mundada, 2011).

Superdisintegrant	Chemical structure	Physical properties	Mechanism of action
Crospovidone (Kollidon CL, Polyplasdone XL)	Synthetic homopolymer of cross-linked N-vinyl-2-pyrrolidone	Water insoluble, spongy in nature so gives a porous tablet, smoother mouth feel	Capillary action absorbs water leading to swelling
Croscarmellose sodium (Ac-Di-Sol®, Nymce ZSX®,Primellose®, Solutab®,Vivasol®)	Crosslinked form of sodium CMC	Swells in two dimensions, swells 4–8 folds in <10 sec	Swelling
Sodium starch glycolate (Explotab®, Primogel®, Vivastar P)	Sodium salt of carboxymethyl ether of starch	Swells in three dimensions and at high concentration, serves as sustained-release matrix, Insoluble in organic solvents, disperse in cold water	Water uptake followed by rapid and enormous swelling
Sodium alginate (Kelcosol, Keltone, Protanal)	Sodium salts of alginic acid	Hygroscopic in nature and slowly soluble in water	Swelling
Acrylic acid derivatives	Poly (acrylic acid) super porous hydrogel		Wicking

Soy polysaccharides (Emcosoy®)	Natural polysaccharide	Does not contain any starch or sugar	
NS-300 (Carmellose)	Carboxymethyl cellulose	Particle size 106 μm, disintegration time 20 sec	Wicking
ECG-505 (Carmellose calcium)	Calcium salt of CMC	Disintegration time 80 sec	Swelling
L-HPC (LH-11)	Low hydroxypropyl cellulose	Disintegration time 90 sec	Both swelling and wicking
Ion exchange resin (Indion414, Indion 234, Tulsion234, Tulsion 344, Amberlite IPR88)			Swelling
Gas evolving disintegrants (Citric acid, tartaric acid, sodium bicarbonate)	Effervescence substance	Evolution of CO_2 after contact with fluid	In contact with water liberates CO_2 that disrupts the tablet
Isphagula husk		*Plantago ovata* seed husk has high swellability and gives uniform and rapid disintegration	Swelling

In the preparation of ODT formulations, there are three techniques available for incorporating superdisintegrants into tablet formulations (Pahwa & Gupta, 2011).

i. ***Internal Addition (Intra-granular):*** In this technique, the superdisintegrant is mixed with other powdered ingredients before being wetted with the granulating fluid. This process leads to the integration of the disintegrant within the granules.

ii. ***External Addition (Extra-granular)***: In this approach the superdisintegrant is added into the specified granulation before compression stage.

iii. ***Partially Internal and External***- This method combines both internal and external addition of the disintegrant. This causes the tablet to immediately break up into previously compressed granules, and disintegrating agent in granules causes more erosion of granules into original powder particles.

2.1.8.2. Taste-Masking Agents

Taste masking is the assumed elimination of an unpleasant flavor that would be otherwise be detectable. In the development of the majority of ODTs, taste masking is a critical stage (Sohi, Sultana, & Khar, 2004).

There are available some techniques for taste masking in ODTs, which both efficacy of the process and quality of final product can be also influenced. These techniques are outlined below (Singh & Verma, 2016):

Physical taste masking: It encopasess the use of sweeteners (aspartame, sugar derivatives, dextrose, fructose, etc.) and flavors (vanilla, citrus oils, fruit essences, etc.) in the formulation. It is among the easiest methods for taste masking. Sweeteners slow the interaction of unfavorable API with taste buds because they are highly water soluble, dissolve in saliva, and coat the taste buds, while flavoring agents improve formulation and give it distinctive flavor. They should be included in addition to the main taste masking agent.

Using of some cooling flavorings such as menthol, suppress the taste receptors and slow the perception of bitter flavors. It is also possible to add other excipients, such as bitterness inhibitors (Singh & Verma, 2016).

Granulation: This technique involves the preparation of tablets using binding agents composed of polymers that are insoluble in saliva. This property enables the masking of the drug's bitter taste. Examples of substances utilized in drug granulation include alginic acid, sugar alcohol solutions, polycarbophil, microcrystalline solutions, castor oil, and various other compounds (Singh & Verma, 2016).

Complexation: Another alternative method to achieving taste masking is to utilize the polymers such as cyclodextrins, which form complexes with the drugs (Chinwala, 2020). The drug molecule enters into the host molecule's cavity, which acts as a complexing agent, forming stable complex. This process of complexation minimizes amount of drug particles that are exposed to taste receptors, which reduces sensation of bitterness. The complexing agent serves to disguise the bitter taste through mechanisms such as lowering the drug's oral solubility or limiting its interaction with taste receptors. β-cyclodextrin is commonly utilized as a complexing agent for taste masking due to its mild flavor and safe characteristics (Singh & Verma, 2016).

Ion Exchange Resins: Ion exchange resins are synthesized organic polymers that are inactive in nature, made up of a hydrocarbon chain to which insoluble groups are linked. These resins have the unique capacity to exchange their labile ions with ions present in the contacting solutions. They are classified as cation exchange resins or anion

exchange resins based on the charge of the functional groups they contain. Column method and batch method are both used to load the medicines onto the resins (Singh & Verma, 2016).

Coating: Microencapsulation is recognized as one of the most efficient strategies for masking the taste of bitter pharmaceutical ingredients. This technique can involve coating tablets that contain bitter active pharmaceutical ingredients (APIs) or even coating the bitter API particles themselves.

The selected polymers for the coating process should have the capability to inhibit the rapid release of the API in the oral cavity, enabling its release at the absorption site. There are three main categories of coating materials: lipids, polymers, and sugars. These materials can be employed individually or in combination, either as a single layer or through multiple layers, to effectively mask the bitter taste of medications. Hydrophobic polymers have been more commonly utilized than hydrophilic polymers for coating bitter-tasting drugs.

Microencapsulation is a comprehensive process that involves encasing the active component with a polymeric substance or film. Various techniques can be used for microencapsulation, including air suspension coating, coacervation phase separation, spray drying, spray congealing, solvent evaporation, pan coating, and interfacial polymerization (Singh & Verma, 2016). Eudragit® is an example of a polymeric substance that is used to encapsulate drugs in order to form microparticles that are then compacted or molded into ODTs (Chinwala, 2020).

Matrix Entrapment: In this method, drugs are encapsulated within a dense matrix. This matrix serves to delay their interaction with taste receptors. It can consist of various materials, such as polymers, resins, gelling agents, or lipids (Singh & Verma, 2016).

Prodrug Formation: Prodrugs are initially inactive compounds that, through biotransformation, convert into active substances. During prodrug formation, bitter sites undergo physicochemical modifications that prevent them from interacting with taste receptors, thereby masking the bitter taste (Singh & Verma, 2016)

Salt Formation: The solubility of the API in saliva is extended through salt formation, effectively delaying the perception of its taste. This technique involves the

formation of a salt compound that reduces the immediate taste perception of the API (Singh & Verma, 2016).

Adsorption: Through an adsorption process utilizing insoluble substances like silica gel, bentonite, and veegum, the drug solution is adsorbed, leading to the formation of adsorbates of bitter drugs. This approach aids in minimizing the interaction between the drug and taste receptors (Singh & Verma, 2016).

2.1.8.3. Diluents

The diluents are commonly incorporated into tablets to increase their volume for easier processing and handling. Ideally, a diluent should exhibit chemical inertness, non-hygroscopic property, hydrophilicity, a pleasant taste for oral formulations, and cost-effective.

The choice of diluent can affect the formability and various formulation qualities such as powder flowability, wet or dry granule formability, content homogeneity, disintegration, dissolution, tablet appearance, tablet hardness, friability, physical and chemical stability, and more. Notably, some diluents such as microcrystalline cellulose are commonly employed as dry binders due to their significant strength during the final tablet compression process.

Despite often being considered inert, diluents can impact the stability and bioavailability of the dosage form. For instance, one of the most widely used inorganic salts as a filler and binder for direct compression is dibasic calcium phosphate, available in anhydrous and dihydrate forms (Gad, 2008). Additionally, prior processing is frequently employed to enhance the flowability and compressibility of diluents in direct compression formulations, such as amorphous lactose. However, this may lead to reduced stability, especially in humid conditions where reverting to the crystalline form becomes more likely (Conway, 2008)

2.1.8.4. Binders

Binders are essential components in tablet manufacturing as they facilitate the adhesion of powder particles to one another. They play a crucial role in ensuring proper compactibility and maintaining free-flowing characteristics by promoting the aggregation and cohesiveness of granules. A binder should provide appropriate cohesiveness without slowing dissolution or disintegration.

Binders are classified as either solution binders (such as hydroxypropyl methylcellulose, gelatin, and polyvinylpyrrolidone) or dry binders (such as microcrystalline cellulose) based on how they are incorporated into tablet formulations. Addition of dry powder binders can be involved blending with other powders before agglomeration, dissolved in water or a solvent added during granulation, or added before compaction. While dry binders can also be applied prior to tablet compression, solution binders are generally more effective and can be sprayed, poured, or combined with the powder mixture for agglomeration (Gad, 2008). They are considered suitable materials for co-processing due to their capacity to modify the compressibility of tablet formulations, thereby improving the performance of excipients with low compressibility (Apeji, et al., 2019)

Gums such as acacia and sodium alginate, in combination with starch, gelatin, and sugars, are utilized between 2 and 10% w/w. Other materials used as dry binders include cellulose derivates and polyvinyl pyrrolidone (PVP) (Conway, 2008).

2.1.8.5. Lubricants

Lubricants are materials that are added to tablet and capsule formulations in extremely low concentrations (typically in the range of 0.25% and 5.0%, w/w) to enhance the formulations' powder processing capabilities (Li & Wu, 2014).

The ideal lubricants should exhibit weak cohesive tendencies in contrast to the shear line and low shear strengths. To reduce frictional forces at the point where a powder, granule, or tablet surface meets a die wall, lubricants in powder form are utilized. Numerous aspects of the manufactured tablets, including tablet weight, crushing strength, friability, disintegration time, and stability are affected by its type, concentration, incorporation method, time, and circumstances of mixing as well as efficiency of lubricant (Alebiowu & Adeagbo, 2009). As some lubricants may interact adversely when used in combination, careful selection of lubricants is required (Faldu & Zalavadiya, 2012).

Examples of excipient groups and their functions are presented in Table 2-3.

Table 2-3: Examples of excipient groups used in ODT formulations (Nayak & Manna, 2011).

Excipients	Function	Examples
Super disintegrants	Facilitating tablet breaking when it meets water in oral cavity/gastrointestinal tract	Croscarmellose sodium, crospovidone, sodium starch glyconate (SSG), starch
Diluents	Making required bulk of tablet, improving cohesion, flowability, compatibility and stability	Lactose, spray dried lactose, microcrystalline cellulose, mannitol, sorbitol, dibasic calcium phosphate
Binders	Imparting cohesive qualities to powdered materials	Gelatin, glucose, lactose, methyl cellulose (MC), ethyl cellulose (EC), hydroxypropyl methylcellulose (HPMC), starch, povidone, sodium alginate, carboxymethyl cellulose (CMC), acacia
Lubricants	Preventing adhesion of tablet to surface of dies and punches, reducing inter particulate friction	Insoluble- steric acid, magnesium stearate, talc, paraffin, soluble- sodium lauryl sulfate, Sodium benzoate, polyethylene glycol (PEG)
Glidants	Improving flow characteristics of powder mixture	Colloidal silicon dioxide, corn starch, talc
Sweeteners	Producing a palatable dosage form	Sucrose, sucralose, saccharin, aspartame
Flavors	Improving taste of dosage form	Peppermint, vanilla, orange, banana, cinnamon, mango

2.1.9. Techniques for Preparation of ODTs

2.1.9.1. Conventional Techniques

Direct Compression (DC) Method

The direct compression method is a practical and cost-effective approach when the bulk powder exhibits adequate flowability and compressibility. Oral Disintegrating Tablet (ODT) formulations are specifically designed to dissolve rapidly in the mouth. Consequently, the primary excipient in these formulations is a disintegrant or superdisintegrant, often used in combination. In the market, there are ready-to-use ODT excipients such as Ludiflash®, Parteck ODT®, Disintequik™ ODT, and PROSOLV®

ODT G2, which include the disintegrant/superdisintegrant, binder, and filler components. These products possess excellent flow properties, making them suitable for direct compression. To manufacture tablets with the desired hardness and friability, while not compromising the rapid oral disintegration rate, it's crucial to optimize the compression force. By employing the direct compression technique, it is possible to efficiently produce ODTs with favorable mechanical strength and stability, all while keeping production costs in check (Akdağ, et al., 2020).

Granulation Methods

i. **Wet granulation:** Wet granulation involves adding a liquid to a powder in a vessel, with stirring to induce agglomeration or the formation of granules. This manufacturing process is widely utilized in tablet production and is enhanced through the creation of granulates. These granulates exhibit improved flowability, homogeneity, and compressibility compared to the original drug-containing powder blend. Wet granulation is a complex procedure that, like the majority of pharmaceutical processes, depends on a number of variables, including the binder employed and the processing environment, to determine the final granule's physical characteristics (Parkash, et al., 2011).

ii. **Dry granulation:** Slugging can be applied to generate granules when tablet ingredients possess adequate inherent cohesive or binding qualities but are sensitive to moisture or cannot resist high temperatures during drying. This technique is also reffered as dry granulation, dual compression, or precompressionn (Parkash, et al., 2011)

iii. **Melt Granulation:** In this process, binding agent with low melting/softening point is utilized, eliminating the need for solvents At typical temperatures, melted substances act as binder and harden to form stable dosage form. To produce granules, the waxy binder melts in the mixer, which are then dried in tray dryers. The granules are mixed with excipients and compressed into tablets after being sieved to obtain uniform granules. Melt granulation produces controlled-release particles that are also inexpensive (Ghourichay, Kiaie, Nokhodchi, & Javadzadeh, 2021).

Freeze Drying Method (FD)

In the freeze-drying method, compounds and proper excipients are dissolved or suspended to form stable suspension or solution. The resulting mixture is evenly divided among blisters and frozen at -20°C. Subsequently, to produce freeze-dried ODTs, the lyophilization technique is carried out at the appropriate pressure and temperature levels (0.44 mbar and -55°C). The critical characteristics of this approach are matrix-forming substances such as gelatin and sodium alginate, as well as antifoaming chemicals such as simethicone. The disintegration and consequently the dissolution characteristics of ODTs may differ depending on characteristics of excipients that form the matrix. Since the drug is dissolved or dispersed in the mixture, this method is well-suited for low-dose pharmaceuticals and drugs which are sensitive to heat. The freeze drying method yields with lower hardness and friability than the direct compression method but achieves satisfactory tablet strength in the final packaging. Moreover, in comparison to ODTs prepared using the direct compression method, those prepared using freeze drying method exhibit faster disintegration and a higher dissolving rate (Akdağ, et al., 2020).

Spray drying

The spray drying method is commonly utilized to produce solid dispersions and micronized drug/excipient particles for oral or inhalation delivery. To create a highly porous structure, an initial step involves atomizing and spraying a liquid mixture of materials into a heated chamber. These micro-sized particles are then mixed with mannitol and kneaded using distilled water before undergoing a two-hour drying process at 60°C. The resulting granules are subsequently sifted, blended with various excipients, and compacted into tablets using compression techniques. This process yields highly porous tablets that dissolve rapidly in the mouth. However, the primary drawbacks of this method are the fragility of the product and the high production costs, which make traditional packaging methods unsuitable for this dosage form. (Ghourichay, Kiaie, Nokhodchi, & Javadzadeh, 2021).

Molding

Molding can be classified into two main categories: Compression molding and heating molding, which also include wetting, dispersing, or dissolving, compressing tablets, and evaporating any residual solvents. Hydrophilic excipients are employed to

achieve optimal solubility. Due to the removal of solvents through drying, compression-molded tablets hexhibit an extremely porous structure and relatively low mechanical strength. This is attributed to the fact that the compression is carried out under low pressure conditions. In the case of heating molding, the drug is suspended with water-soluble sugars including xylitol, agar, mannitol, lactose, and sucrose. The blisters are subsequently filled with this mixture, which also contains agar solution as a binder. At room temperature, the agar solution undergoes a transformation into a gel form, which is then dried under vacuum at a temperature of around 30 °C (Akdağ, et al., 2020).

Phase Transition Method

ODTs can be manufactured by blending sugar alcohols with both low and high melting points, allowing for a phase transition during the production process. These ODTs are created by heating the mixture to a temperature that falls between the melting points of these sugar alcohols and subsequently cooling it. The inclusion of a low melting point sugar alcohol and the heating process can indeed influence ODT characteristics such as hardness and disintegration time. It's worth noting that the heating step tends to increase the tablets' hardness (Akdağ, et al., 2020).

Sublimation

The major reason for ODT's fast disintegration is the matrix of the tablet, which has a highly porous structure. Even though typical tablets contain ingredients that are extremely water soluble, they frequently fail to dissolve rapidly due to limited porosity (Parkash, et al., 2011). Water can transition directly from its solid state to vapor through a process known as sublimation. In the sublimation process, volatile substances such as urea, camphor, ammonium carbonate, ammonium bicarbonate, and hexamethylene-tetramine are frequently utilized to create a porous matrix. It is then blended with excipients and compacted using low pressure (Akdağ, et al., 2020).

Mass Extrusion

In this method, the powder blend is softened with water-soluble solvents such as polyethylene glycol (PEG) and methanol or ethanol before being sieved through the extrusion or syringe. Following extrusion, alcohol is eliminated by evaporation. A gel that has hardened into a string-like shape is the final result, and a mortar is subsequently used to grind it into granules. These granules are then blended with excipients, and

compressed to produce ODTs. To increase physical strength and disintegration, PEG stearate is used as binder. Moreover, the unfavorable taste of the drug could be masked by using coating method involving the materials such as Eudragit E 100, polyvinyl alcohol, and polyvinyl acetate (Ghourichay, Kiaie, Nokhodchi, & Javadzadeh, 2021).

Cotton candy process

This procedure gets its name from the unique rotating mechanism, it employs to create crystalline structures that resemble cotton buds and look like cotton candy. Flash melting and rotating are utilized to obtain a matrix of polysaccharides in this technique. After recrystallization, the candy floss matrix is milled, followed by blending it with the active pharmaceutical ingredients (APIs) and excipients. Subsequently, the resulting mixture is compressed to form Orally Disintegrating Tablets (ODTs). (Singh, Kaur, Singh, & Dhawan, 2021).

2.1.9.2. Patented Techniques

Zydis® Technology

Among ODTs, Zydis is the most widely used technique. When placed on the tongue, the tablet dissolves in oral cavity within seconds. Zydis tablets are prepared by freeze-drying drug within gelatin-based matrix. These tablets necessitate specialized blister packaging. Zydis ODTs offer the benefits such as improved solubility and enhanced bioavailability, but it is an expensive technology and has stability issues at elevated temperatures (Comoglua & Ozyilmaza, 2019).

Orasolv® Technology

In contrast to Zydis, OraSolv technology relies on a nearly imperceptible effervescence to disperse in saliva. OraSolv technology is most accurately described as tablets that dissolve rapidly, with the coated drug powder remaining once the tablet matrix dissolves in under a minute. Instead of only masking a drug's disagreeable flavor with sweeteners or flavors, OraSolv also coats the powdered substance with effervescence. OraSolv's low compaction ensures taste masking particle coating remains intact during processing. This technology is frequently employed in the manufacturing of over-the-counter preparations. However, the mechanical strength of the OraSolv formulation constitutes a significant drawback (Ghosh, Ghosh, & Prasad, 2011).

Durasolv® Technology

Because of utilization of higher compaction pressures during tablet manufacturing process, DuraSolv, which is manufactured in the manner similar to OraSolv, exhibits significantly more mechanical strength than its precursor. DuraSolv tablets have robust hardness and are manufactured using conventional tableting technology (with a friability less than 2 percent). DuraSolv is produced more quickly and cost-effectively. Due to its high durability, it can be put into vials, capsules, or even standard blister packaging. However, the its incompatibility in high dosages of APIs limits DuraSolv technique (Ghosh, Ghosh, & Prasad, 2011)..

Flashtab® Technology

A tablet in this technology contains an API in the form of microcrystal. Drugs can be produced in microgranules using conventional techniques, including co-precipitation, microencapsulation, and extrusion spheronization. The shear form matrix used to produce tablets is composed of fibrous polysaccharides, compressed to produce thin sugar fibers that quickly dissolve upon contact with saliva. The tablets, prepared by this technique, exhibit rapid disintegration due to their extensive surface areas. However, they possess characteristics of softness, fragility, and suspectibility to humidity (Jassem, 2022).

Oroquick® Technology

The formulation of OraQuick ODTs also employs an innovative taste-masking approach. Unlike other taste-masking methods, microsphere technology, known as MicroMask, significantly enhances mouthfeel. The absence of solvent usage in this flavor-masking technique makes production quicker and more productive. Moreover, OraQuick is well-suited for heat-sensitive drugs as it generates less heat compared to alternative ODT technologies. OraQuick offers improved taste masking and rapid disintegrating in just seconds (Jassem, 2022).

Wowtab® Technology

This method holds a patent from Yamanochi Pharmaceutical Company, and “WOW” stands for "WithOut Water." Specifically, it involves mixture of saccharides with high moldability, hardness (maltose, mannitol, and sorbitol) and low moldability (lactose, glucose, mannitol, and xylitol). They are compressed to form tablet formulation with the optimal values of hardness and rapid dissolution. With the use of a unique smooth

melt action, this technology creates a pleasant tongue sensation by using a flavor masking component. It takes less than 15 seconds to fully disintegrate (Jassem, 2022).

NanoCrystal™ Technology

In this method, blisters are filled with water-soluble GRAS materials and lyophilized after being filled with nanocrystal colloidal dispersions of drug. The resulting samples are extremely robust but rapidly disintegrate in even very small amounts of water. This method is particularly appealing when dealing with dangerous or very effective APIs because it avoids production processes (including granulation, mixing, and tableting) that produce significant amounts of aerosolized powder and pose a significantly higher risk of exposure. Small amounts of drug can also be turned into ODT dosage forms using the freeze-drying method because manufacturing losses are limited (Ghosh, Ghosh, & Prasad, 2011).

2.1.10. Recent Advancements in ODTs

In recent years, there have been available numerous studies about ODTs. They are summarized as described below.

The effectiveness of two novel co-processed excipients (mannitol and tapioca starch) as disintegrants in oral disintegrating paracetamol tablets was examined by (Adeoye & Alebiowu, 2014). The study concluded that the co-processing and disintegrant incorporation methods affected the disintegrants' performance. The study concluded that coprocessing and disintegrant incorporation methods influenced the disintegrants' performance. Furthermore, it was found that the novel disintegrant improved mechanical properties of tablets containing it reducing friability and increasing tensile strength. Additionally, the study highlighted that factors such as water absorption, disintegrant type, and incorporation method had an impact on paracetamol release.

ODTs containing levodopa and benzylhydrazine (L/B ODTs) were studied. The researchers found that optimum formulation with microcrystalline cellulose of 25.7 %, cross-polyvinylpyrrolidone of 6.22 %, and sodium starch glyconate of 5.36 % significantly decreased disintegration time and exhibited faster dissolution profile (Zhang, et al., 2020).

Jang et al. developed Eudragit® EPO-coated dextrin microcapsules of amlodipine using the spray-drying method and incorporated them into ODTs (Jang, Bae, & Oh,

October 2014). Interestingly, the dextrin-coated microcapsules remained intact during tablet compression process, unlike the uncoated ones. As a result, the authors concluded that an amlodipine ODT formulation should utilize dextrin microcapsules coated with Eudragit® EPO.

The development of ODTs represents one of the latest advancements in 3D printing technology. Through the use of selective laser sintering 3D printing, the researchers were able to produce ondansetron ODTs containing drug-cyclodextrin complexes and mannitol. Interestingly, these ODTs exhibited disintegration and drug release properties that were comparable to a commercial ODT product known as Vonau® Flash. The utilization of 3D printing technology for manufacturing dosage forms like ODTs not only offers technological advancements but also the potential for customized dosage forms tailored to individual patients (Allahham, et al., 2020).

Tanaka et al. prepared ODTs with powdered chafuroside A and chafuroside B using the microwave procedure (Tanaka, et al., 2016). When compared to tablets that had not been microwaved, it was found that these tablets' disintegration time was significantly faster (less than 20 seconds), and their chafuroside A and chafuroside B contents had increased 7- and 11-fold, respectively.

In order to increase piroxicam's saturation solubility and dissolution rate, ODTs of various piroxicam nanocrystal were produced. Poloxamer 188 was utilized as a stabilizer during the high-pressure homogenization methods used to produce piroxicam nanocrystals. To investigate their effect on the piroxicam dissolving properties, three different ODTs were produced utilizing the same nanosuspension and various excipients. It was observed that all piroxicam nanocrystal ODT formulations displayed greater drug dissolution rates than coarse piroxicam ODTs (Lai, et al., 2014).

Okuda et al. successfully utilized enteric-coated particles to develop ODTs of tamsulosin hydrochloride using RACTAB® technology by Towa in Osaka, Japan (Okuda, et al., 2014). These ODTs exhibited excellent friability (0.5%) and hardness (>50 N). Impressively, despite being compressed with at 9 kN of pressure, the tamsulosin ODTs dissolved rapidly in vivo, achieving dissolution within just 30 seconds. These results have clearly indicated that RACTAB® technology has hold great promise as a method for producing ODTs with enteric-coated particles.

Diphenhydramine, a bitter drug, was converted into a pleasant ODT product using an integrated crystal and particle engineering method. The solid-state characteristics of a diphenhydramine salt that contains acesulfame (Acs) as the sweetener were thoroughly discussed. Using the direct compression technique, the results have demonstrated that integrated crystal and particle engineering is a successful strategy to develop high-quality ODTs (Wang, Hu, & Sun, 2017).

Several researchers have explored the use of naturally occurring materials, such as Occimum gratissimum seeds (OGS), which have undergone various modification processes and have been used as a disintegrant in the wet granulation method to prepare ODTs. The wetting time, disintegration time, and dissolution rate of OGS were all optimized as a result of the swelling/milling process's completion of OGS modification. The modified OGS has demonstrated its potential as a viable material for ODT manufacturing, offering the advantages of cost-effectiveness, non-toxicity, and simplicity in the manufacturing process (Dang, Tran, & Tran, 2020).

Amphetamine extended-release ODTs (AMP XR-ODTs) have recently been produced as a novel treatment for attention-deficit/hyperactivity disorder. In this study, it was discovered that AMP XR-ODTs were well tolerated and exhibited a pharmacokinetic profile consistent with a once-daily dose in children with attention-deficit/hyperactivity disorder (Stark, Engelking, McMahen, & Sikes, 2017).

Tamsulosin hydrochloride-containing sustained-release microparticles were produced by Cho et al. as an ODT formulation (Cho, Min, Hwang, & Park, 2018). Utilizing a melt-adsorption technique, magnesium aluminom etasilicate (Neusilin®) was utilized as an adsorbent, while a lipid and ethylcellulose suspension (Surelease®) was used to delay drug release. Because of its superior mechanical strength, Beeswax was chosen as the lipid component. Surelease® to Beeswax ratio of 1:50 was discovered to produce the appropriate particle size distribution and modest burst release.. Additionally, the optimized microparticle-containing ODTs had an allowed tablet hardness and fast disintegration.

In the development of a freeze-dried oral disintegrating formulation for cetirizine hydrochloride, researchers have explored the use of cyclodextrins and ion exchange resins as potential taste-masking agents for the drug. The Zydis® oral lyophilizate, for instance, incorporates a pre-formed resinate of cetirizine hydrochloride along with several

cyclodextrins. During a human taste test, it was observed that 80% of the volunteers found the taste-masked formulation, which utilized beta-cyclodextrin in combination with a cherry/sucralose flavor, to be acceptable. (Preis, Grother, Axe, & Breitkreutz, 2015).

In another research study, it was shown that the incorporation of the disintegrant crospovidone resulted in the shortest disintegration time for orally disintegrating tablets (ODTs). Additionally, crospovidone was found to inhibit drug release in a pH 6.8 medium, while facilitating rapid release in a pH 1.2 medium. The authors of the study suggest that these findings indicate the potential value of crospovidone in formulating ODTs designed to prevent acetaminophen from dissolving in the oral cavity (Ikeuchi-Takahashi, et al., 2020).

2.2. Cyclodextrins

Cyclodextrins (CDs) are cyclic oligosaccharides that have minimum of six D-(+)-glucopyranose units, and are attached by α(1→4) glucoside linkages. The ring size and solubility are two characteristics that distinguish α, β, and γ cyclodextrins. They each contain a varying amount of glucose: 6, 7, or 8, respectively (Figure 2-1). Cyclodextrins are encountered as white, odorless, fine, crystalline powders having slightly sweet taste, while some types exist in the form of amorphous powders (Rowe, Sheskey, & Quinn, 2009)

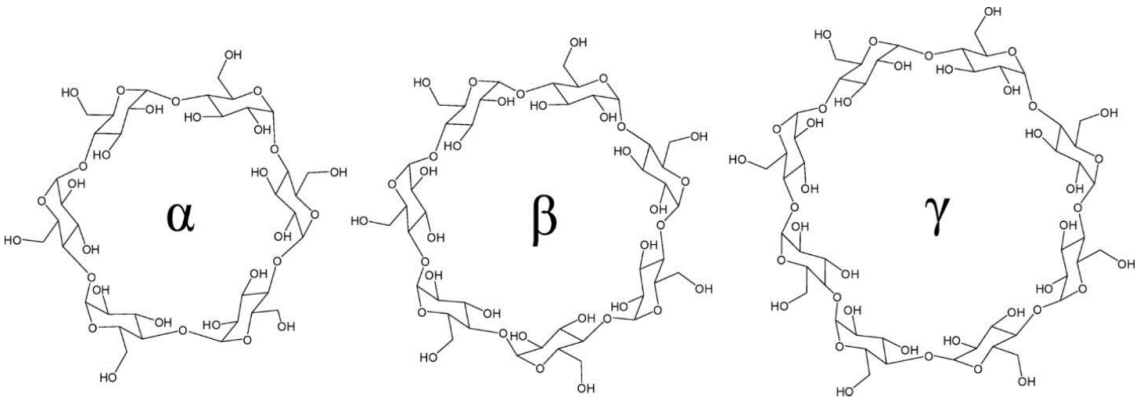


Figure 2-1: The common structure of the cyclodextrins

They possess a compressed cone-like structure, where the inner cavity is polar, and the outer surface of the cone exhibits a hydrophilic character due to the hydroxyl groups of glucopyranose units (Figure 2-2). The primary -OH groups at end of the cavity

are oriented in a way that reduces the cavity's size, while the secondary hydroxyls around the C2 and C3 carbon atoms of the glucose units are located towards the edges of the cavity, contributing to the truncated shape (Bülbül, Eleftheriadou, Okur, & Siafaka, 2020).

.

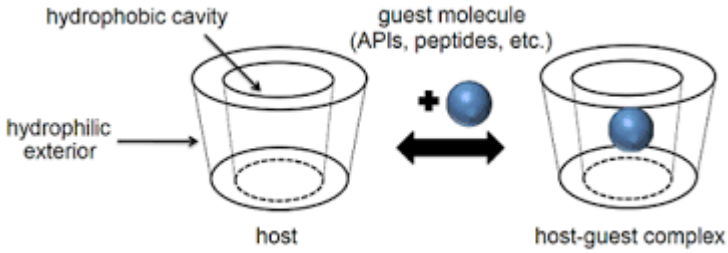


Figure 2-2: Structure and complexation procedure of cyclodextrin (host-guest complex)

One or two guest molecules can be held by up to three CDs, and the creation of the complexes can be quickly identified by phase solubility tests, which is the main characteristic of CDs (Bülbül, Eleftheriadou, Okur, & Siafaka, 2020).

2.2.1. Cyclodextrin Characteristics

Cyclodextrins possess robust stability under alkaline conditions and maintain their stability in water and various organic solvents. The natural CDs show pKa values between 12.1 and 13.5 (Poulson, et al., 2022). The hydrolysis rate of cyclodextrins follows the following order of: αCD > βCD > γCD. In acidic conditions, cyclodextrins hydrolyze more slowly than maltooligosaccharides. The γ- amylase is responsible for hydrolyzing the glycosidic bond of CDs. γ cyclodextrin has the highest rate of enzymatic hydrolysis of cyclodextrins, followed by β cyclodextrin and α cyclodextrin. CDs are stable in a nitrogen environment up to 250C (Kaid, 2021). The physical properties of α, β and γ cyclodextrins are outlined in Table 2-4.

Table 2-4: Physiochemical properties of α, β and γ cyclodextrins

Properties	α-CD	β-CD	γ- CD
Formula	$C_{36}H_{60}O_{30}$	$C_{42}H_{70}O_{35}$	$C_{48}H_{80}O_{40}$
Glucose units	6	7	8
Cavity diameter (Å)	4.7-5.3	6.0-6.5	7.0-8.3
Cavity height (Å)	7.9	7.9	7.9
Cavity volume (Å)	174	262	427
Crystal shape	Hexagonal lattice	Monocyclic par-allelograms	Guadratic prism
Solubility in water (25°C) g/100ml	14.5	1.85	23.2
Log P (oct/water)	-13	-14	-17
Molecular weight (g/mol)	973	1135	1297

2.2.2. Cyclodextrin Derivatives

CDs can be modified by altering various functional groups on primary and/or secondary surfaces of molecule. The ligands do not have to be linked to the same glucose unit for this substitution to take place at any glucosyl residue. The chemical and physical characteristics of cyclodextrins can be altered to serve various purposes, including the modification of enzymes and the catalysis of reactions involving molecules contained within the cavity. Modified CDs also exhibit the unique feature of chelating, which has been used in pharmaceuticals to enhance drug activity, increase bioavailability, and function as delivery systems. Becauuse of cost-effective nature of cyclodextrin synthesis and the diverse range of applications for modified CDs, encompassing areas like anti-HIV activity, food preservation, and enzyme mimicry, it is anticipated that their utilization will experience growth (Poulson, et al., 2022). Table 2-5 presents some examples of marketed products containig cyclodextrin.

Table 2-5: Some examples of marketed products containing cyclodextrin (Loftsson, Jarho, & Järvinen, 2005)

Drug	Formulation	Trade name	Company
α-Cyclodextrin			
Alprostadil (PGE_1)	Intravenous solution	Prostavasin	Ono (Japan)
Cefotiam hexetil HCI	Oral tablet	Pansporin T	Takeda (Japan)
β-Cyclodextrin			
Benexate HCI	Oral capsule	Ulgut	Teikoku Kagaku Sangyou (Japan)
Dexamethasone	Dermal ointment	Glymesason	Fujinaga (Japan)
Nicotine	Sublingual tablet	Nicorette	Pharmacia (Sweden)
Nitroglycerin	Sublingual tablet	Nitropen	Nihon Kayaku (Japan)
Piroxicam	Oral tablet	Brexin	Chiesi (Italy)
Tiaprofenic acid	Oral tablet	Surgamyl	Roussel - Maestrelli (Italy)
2-Hydroxypropyl -β-cyclodextrin			
Cisapride	Suppository	Propulsid	Janssen (Belgium)
Indomethacin	Eye drop solution	Indocid	Chauvin (France)
Itraconazole	Oral and intravenous solutions	Sporanox	Janssen (Belgium)
Mitomycin	Intravenous solution	Mitozytrex MitoExtra	SuperGen (USA) Novartis (Switzerland)
Randomly methylated β-cyclodextrin			
17β-Oestradiol	Nasal spray	Aerodiol	Servier (France)
Chloramphenicol	Eye drop solution	Clorocil	Oftalder (Portugal)
Sulfobutylether β-cyclodextrin			
Voriconazole	Intravenous solution	Vfend	Pfizer (USA)
Ziprasidone maleate	Intramuscular solution	Geodon, Zeldox	Pfizer (USA)
2-Hydroxypropyl -γ-cyclodextrin			
Diclofenac sodium	Eye drop solution	Voltaren ophtha	Novartis (Switzerland)

2.2.3. Preparation Methods for Inclusion Complexes

2.2.3.1. Kneading Method

In the kneading method, the guest molecule is dissolved in a solvent, The resulting mixture is then dried at room temperature. Subsequently, the complexes are obtained in solid form and subjected to vacuum drying. Through this technique, guest molecule is trapped in CD, resulting in formation of cyclodextrin complexes with altered physicochemical properties (Vikas, Sandeep, Braham, Manjusha, & Budhwar, 2018).

2.2.3.2. Physical Blending Method

For small-scale production of inclusion complexes, a straightforward approach involves grinding or triturating the drug with cyclodextrin in a mortar. For larger-scale production, the complexes are produced by meticulously blending the drug and cyclodextrin using a rapid mass granulator for a typical duration of 30 minutes (Kumar, K.Ashok, Brahmaiah, Nama, & Baburao, 2013).

2.2.3.3. Coprecipitation Method

Hydrophobic drugs can form complexes with cyclodextrin through a process called coprecipitation. In this method, the host molecules are dissolved in an aqueous phase, while the hydrophobic drugs or guest molecules are dissolved in an organic phase. By employing suitable stirring, the solution from the organic phase is gradually added to the solution in the aqueous phase. After the complex formation, these complexes are washed with an organic solvent and then dried at 50°C. This process is reiterated for purification and obtaining the desired cyclodextrin-drug complexes (Vikas, Sandeep, Braham, Manjusha, & Budhwar, 2018).

2.2.3.4. Solvent Evaporation Method

This technique entails dissolving the host and guest molecules separately in compatible solvents and then blending the solutions to create a molecular dispersion. After complete solvent evaporation under vacuum conditions at 45°C, solid powdered inclusion complexes are obtained. The resulting dry mass is then subjected to sieving for additional refinement. This method is known for its simplicity and cost-effectiveness, making it suitable for both industrial and laboratory applications. It is regarded as a highly efficient alternative to the spray drying method (Vikas, Sandeep, Braham, Manjusha, & Budhwar, 2018).

2.2.3.5. Freeze Drying (Lyophilization) Method

This technique, which is often used in large-scale production as well, is the most efficient method for forming cyclodextrin complexes, particularly for thermolabile drugs. In this process, both the drug and cyclodextrin are dissolved in a suitable solvent with thorough stirring, and subsequently, the solution is freeze-dried. As the solvent evaporates under vacuum conditions, high-quality cyclodextrin inclusion complexes are generated (Vikas, Sandeep, Braham, Manjusha, & Budhwar, 2018).

2.2.3.6. Spray Drying Method

In this method, host and guest molecules are dissolved in an identical solvent and dried using the spray drying method. By examining the size of the sprayer or injector as well as other factors such as sample feeding rate and temperature gradient, different sizes of inclusion complexes are achieved. This technique minimizes losses for volatile substances but is ineffective for highly volatile or thermolabile drugs (Vikas, Sandeep, Braham, Manjusha, & Budhwar, 2018).

2.2.4. Advantages of Cyclodextrin Complexes

The cyclodextrin complexes offer a variety of advantages to improve the physicochemical properties of drugs.

2.2.4.1. Enhancement of Solubility and Dissolution Rate

Cyclodextrins (CDs) enhance the solubility of many poorly water-soluble drugs by creating inclusion complexes with their nonpolar molecules or functional groups. The resulting complex positions the hydrophilic hydroxyl groups on the outer surface, making them accessible to the surrounding environment, while concealing most of the hydrophobic portions within the internal cavity of the CD. This interaction results in the formation of a water-soluble CD-drug complex (Devi, et al., 2010).

2.2.4.2. Enhancement of Bioavailability

The release of an orally administered drug from its dissolved formulation is a essential for its absorption. The complexing of the drug with CDs leads to an increased dissolution rate, subsequently enhancing its absorption. Furthermore, reducing the hydrophobicity of drugs through CD complexation offers an advantage in terms of improved transdermal or rectal absorption. By complexing individual drug molecules,

CDs not only increase solubility but also prevent the crystallization of APIs by preventing the molecules' ability to self-assemble into a crystal lattice (Devi, et al., 2010).

2.2.4.3. Improvement of Stability

The complexation involving cyclodextrins (CDs) finds extensive applications in improving the chemical, physical, and thermal stability of pharmaceuticals. When an active molecule is exposed to factors such as oxygen, water, radiation, or heat, it can undergo chemical reactions leading to degradation. However, when a molecule is encapsulated within the CD cavity, it becomes challenging for the reactive elements to diffuse into the cavity and interact with the protected guest, thereby preserving the stability of the compound (Devi, et al., 2010).

2.2.4.4. Irritation Reduction

The drugs that irritate the skin, eyes, or stomach can be encapsulated inside a CD cavity to lessen their irritancy. The local concentration of the free drug is lowered below the irritancy threshold by inclusion complexation with CDs. The drug is taken into the body as the complex progressively separates, and is released as a free drug, and its local free concentration is never above levels which could irritate the mucosa (Devi, et al., 2010).

2.2.4.5. Prevention of Incompatibility

In formulations, the drugs often interact with each other or with excipients. To prevent undesirable drug-drug or drug-excipient interactions, the drug can be encapsulated within a CD molecule. This approach stabilizes the formulation by physically isolating the components (Devi, et al., 2010).

2.2.4.6. Taste and Odor Masking

Drugs' unpleasant smell and bitter taste can be masked by complexing them with CDs. By encasing them inside the CD cavity, molecules or functional groups that produce unpleasant tastes or odors can be maintained out of reach of the sensory receptors. The produced complexes generally possess minimal to no taste or odor, thus rendering them more palatable and tolerable for patients (Devi, et al., 2010).

2.2.5. Pharmaceutical Applications of Cyclodextrin Complexes

2.2.5.1. Cyclodextrin in Oral Drug Delivery

The most difficult stage for scientists in the formulation and development of dosage forms is to improve the oral bioavailability of poorly water soluble drugs. Because of their unique structural composition and wide range of physicochemical properties, cyclodextrins play a pivotal role in enhancing the solubility, stability, and bioavailability of drugs in the gastrointestinal tract (Vikas, Sandeep, Braham, Manjusha, & Budhwar, 2018). CDs are instrumental in augmenting the quantity of free drug accessible at the absorption surface, primarily by enhancing mucosal drug permeability. Moreover, through cyclodextrin complexation, tablets have been formulated and developed to ensure rapid dissolution for sublingual and buccal administration (Kaid, 2021).

2.2.5.2. Cyclodextrin in Nasal Drug Delivery

Nasal drug delivery presents an improved approach for the systemic distribution of drugs by circumventing first-pass metabolism or degradation in the liver and gastrointestinal tract. Cyclodextrin complexes contribute to enhanced drug absorption through the nasal mucosa, which enhancing drug solubility. Methylated cyclodextrin derivatives, known as Me-CDs, have notably found to be useful excipients for nasal drug delivery systems (Vikas, Sandeep, Braham, Manjusha, & Budhwar, 2018).

In the context of nasal formulations that incorporate complexes of steroids and cyclodextrins, the influence of cyclodextrins (CDs) on nasal epithelial membranes appears to have limited significance in terms of enhancing absorption. This is because the capacity of CDs to interact with the membranes diminishes when their cavities are occupied by steroids. Furthermore, when administered nasally, CDs exhibit relatively minimal local toxicity. In separate research efforts, CDs have been investigated for their potential to enhance the transport of insulin across the nasal mucosa. These studies have involved CDs with a high loading content of insulin and have demonstrated in vivo reductions in blood glucose levels (Kaid, 2021).

2.2.5.3. Cyclodextrin in Topical Drug Delivery

The CDs improve the solubility and stability of drugs in topical preparations, enhance transdermal drug absorption, prolong drug delivery from the vehicle, and prevent unfavorable side effects related to drugs given topically. They improve drug distribution

through water diffusion barriers but not across the stratum corneum or other lipophilic barriers (Bhaskar, Ola, Patel, & Chalikwar, 2019).

The CDs vary in size and hydrophilic outer surface, limiting drug/cyclodextrin complex penetration through the lipophilic membrane. The drug molecules separated from the cyclodextrin complexes at the lipophilic barrier, and drug absorption from aqueous solutions are membrane and diffusion-controlled. Moreover, the CDs act as permeation enhancers, carrying the drug through the aqueous barrier (Vikas, Sandeep, Braham, Manjusha, & Budhwar, 2018).

2.2.5.4. Cyclodextrin in Ocular Drug Delivery

The lipophilic drugs achieve increased solubility in water when combined with cyclodextrin complexes, which also improve the drugs' capacity to pass through biological membranes without changing their chemical structure. By forming inclusion complexes, CDs serve as anti-irritants by either masking irritating potential of drugs or substituting irritating excipients in the formulation. To increase the permeability of drugs through biological membranes such as the cornea, the right mechanism of CDs involves the CD serving as a actual carrier. It transports hydrophobic/lipophilic drug molecules through the aqueous mucin layer to the surface of the ocular barrier. This allows the molecules to partition into the barrier while remaining in a soluble state (Bhaskar, Ola, Patel, & Chalikwar, 2019). In aqueous eye drop formulations, hydrophilic cyclodextrins, particularly 2-hydroxypropyl β-cyclodextrin and sulfobutyl β-cyclodextrin, are well tolerated and harmless to the eye (Vikas, Sandeep, Braham, Manjusha, & Budhwar, 2018).

2.2.5.5. Cyclodextrins in Peptide and Protein Delivery

The succesful utilization of therapeutic peptides and proteins faces various challenges, encompassing factors such as immunogenicity, limited absorption through biological membranes, rapid plasma clearance, and susceptibility to chemical and enzymatic instability (Bhaskar, Ola, Patel, & Chalikwar, 2019). Nevertheless, CDs can also interact with biological membranes, making them suitable carriers for facilitating the transport of proteins, peptides, and drugs, even oligonucleotides, due to their bioadaptive properties (Devi, et al., 2010).

2.2.5.6. Cyclodextrins in Gene delivery

The use of CDs in gene delivery vectors can increase the system's overall effectiveness. There is evidence that CDs lessen their associated toxicity. Currently, numerous effective gene delivery vectors are associated with side effects. Ongoing research is exploring the utilization of CDs for gene delivery, and as additional applications are discovered, the significance of the CD system continues to expand (Haley, Gottardi, Langer, & Mitchell, 2020).

2.2.5.7. Cyclodextrins in Brain Drug Delivery

In the management of neurological disorders, CDs play a significant role as both excipients and active pharmaceutical substances. Many commercially available medicines with central actions, such as antiepileptics, contain them as solubilizers. For drug delivery to the CNS, innovative and effective CD derivatives and CD nanoparticles are being developed (Vecsernyes, et al., 2014).

2.2.5.8. Cyclodextrins in Novel Delivery Systems

Cyclodextrins are capable of reducing the unwanted features of drug molecules in a variety of nanotechnology applications by forming inclusion complexes because of their bioadaptability and multifunctional properties. To prepare economically drug/cyclodextrin complexes with appropriate properties, knowledge of the various elements that can affect complex formation is required. Additionally, the capability of the drug carrier to deliver a drug into a specific site is the most desired feature. The D-drugs that have been conjugated with CD can be used to create a variety of novel drug delivery systems, including nanoparticles, liposomes, dendrimers, and carbon nanotubes (Rapolu, Aatipamula, Reddy, & Voruganti, 2012).

2.2.6. Excipients Used in the Study

2.2.6.1. Beta-Cyclodextrin and Hydroxy-Beta Cyclodextrin

Among all cyclodextrins, β-CD is the most widely used, inexpensive, and widely available. β-CD is a white crystalline powder which has a molecular weight of 1134.98 (Thermo Scientific, 2023). It has a cone-like structure and it has seven glucopyranose subunits, which are joined together by 1-4 glycosidic linkages. Its cavity size can hold the majority of drugs having molecular weights within 200 and 800 Daltons. The non-polar

cavity of β-CD is hydrophobic from the inside, making it soluble in water and able to encapsulate a variety of hydrophobic guest molecules. About 1-2% of β-CD is absorbed in the upper gastrointestinal tract without being metabolized, and the remaining portion is metabolized by colonic bacteria and caecum in the lower gastrointestinal tract (Fatima, Khalid, Liaqat, Zulfiqar, & Munir, 2023).

Some of the properties of β-CD include improving the water solubility of a variety of insolubile substances, increasing bioavailability and pharmacological impact, and reducing the therapeutic dose of the drug. It can be utilized to improve the stability of substances so that they can resist temperature, oxidation, degradation, and light. Carbohydrate-based surfactants enhance their effectiveness and application range when complexed with βCD, enhancing micelle concentration and surfactant solubility. βCD can also form inclusion complexes with antioxidants and UV filters, improving aqueous solubility and protecting against degradative variables. It can improve the stability, effectiveness, and controlled drug release profile of sunscreens, as well as their UV ray protection. βCD has the ability to mask both the color or colors of the substances as well as their unpleasant tastes and odors. Another function of βCD is to effectively turn liquid material into powders. They can be utilized in nanotechnology to create nanoparticles, nanosponges, nanomicelles, nanovesicles, etc., which have numerous uses in nanomedicine (Fatima, Khalid, Liaqat, Zulfiqar, & Munir, 2023).

Hydroxypropyl-β-CD (HP-β-CD) is a derivative of β-CD that is produced by replacing a number of hydroxyls at both ends of CD's molecule. This process decreases CD's crystallinity and enhances its water solubility, stability, absorption and toxicological profile (Ferreira, Campos, Veig, Cardoso, & Paiva-Santos, 2022).

As a result, it is frequently used in pharmaceutical products including excipients and solubilizers (Ahad, Bin Jardan , Raish, Al-Mohizea, & Al-Jenoobi, 2022). It is a white to light yellow powder which has a molecular weight of 1180.05 (Thermo Scientific , 2023).

HP-β-CD, which exhibits a good level of inclusion ability, offers significant therapeutic benefits in terms of increasing stability, promoting water solubility, maximizing bioavailability, regulating the release of active substances, and reducing drug toxicity, among other cyclodextrines. Clinically, HP-β-CD is utilized as a pharmaceutical excipient for drugs with low water solubilities such as posaconazole, sulconazole,

apiprazole, trimethoprim, daidzein, fluconazole, glabridin, telmisartan, miconazole, and curcumin to enhance their solubility (Kirimlioğlu, 2020). The marketed forms of HP-β-CD include oral, buccal, rectal, ocular, and intravenous preparations. Itraconazole, a broad-spectrum triazole antifungal drug, is typically present in oral and intravenous preparations that contain HP-β-CD. Additionally, HP-CyD has just received approval for the treatment of Niemann-Pick Type C disease (NPC), a condition characterized by abnormal lysosomal lipid storage (Yokoo, et al., 2015).

2.2.6.2. Ludipress® LCE

Ludipress® LCE is an odorless, neutral taste, white to slightly yellowish, and free-flowing powder, which is a granulated excipient. It mainly consists of 3.5% of Povidone K30 (Kollidon® 30) and 96.5 % of lactose monohydrate (Ludipress® LCE, 2017). (LCE, 2017). The characteristic values of Ludipress are presented in Table 2-6.

Table 2-6: The characteristic values of Ludipress

Angle of repose	29.58
Bulk density	0.56 ±0.6 g/cm^3
Hausner ratio	1.20 ±0.10
Particle size distribution	≤20%, <63 µm, 40–65%, <200 µm, ≤20%, <400 µm
Solubility	Soluble in water
Water content	≤6.0%

Ludipress® LCE has established as an addition to the BASF line of direct compression excipients for use in chewable tablets and lozenges, effervescent tablets, and as a bulking element in hard gelatin capsules. All other formulations are nevertheless appropriate when used in combination with Kollidon® CL-F or Kollidon® CL as a tablet disintegrant (Ludipress® LCE, 2017).

Advantages of using Ludipress are (Ludipress® LCE, 2017):

- Improving the production process in the direct tableting.
- Totally soluble in water.
- Remarkable binding ability.
- Excellent flowability and optimal particle size dispersion.

- Producing extremely hard tablets.

2.2.6.3. Lactose, Monohydrate

Lactose is an odorless, slightly sweet-tasting, white to off-white crystalline particle or powder. In comparison to sucrose, α-lactose is around 20% of sweeter, whereas ß-lactose is 40% of sweeter. In the solid stage, lactose can take on a variety of isomeric forms, including α-lactose monohydrate, β-lactose anhydrous, and α-lactose anhydrous, depending on the crystallization and drying circumstances. Lactose exists in three stable crystalline forms: α-lactose monohydrate, β-lactose anhydrous, and stable α-lactose anhydrous. α-Lactose monohydrate is a natural disaccharide derived from milk that has one galactose and one glucose component. According to USP32-NF27, α-lactose monohydrate can have its physical properties modified, and contains amorphous lactose in different amounts (USP32-NF27, 2008).

The chemical name of lactose monohydrate is O-β-D-Galactopyranosyl- (1→4)-α-D-glucopyranose monohydrate, and it is empirical formula and molecular weight are $C_{12}H_{22}O_{11}.H_2O$, and 360.31 g/mol, respectively (European Pharmacopoeia, 2019). The molecular formula of lactose monohydrate is illustrated in Figures 2-3.

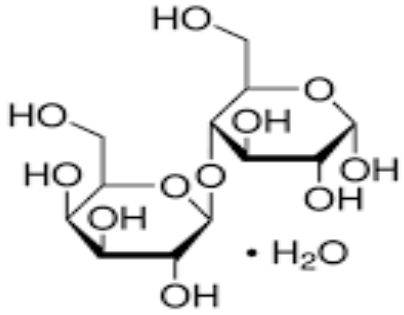


Figure 2-3: Molecular formula of lactose monohydrate

Lactose is commonly utilized as a filler and diluent in tablets and capsules, and to a limited extent in lyophilized formulations. Various commercial lactose grades are available, each with distinct physical characteristics such as particle size distribution and flow properties. Fine-grade lactose is often preferred for tablet manufacturing through the wet-granulation method or when milling is required during processing. Additionally, in

lyophilized products, lactose serves the purpose of increasing pore size and promoting cohesion. It is added to solutions that undergo freeze-drying, contributing to the overall structure and stability of the lyophilized product. Furthermore, lactose can be combined with sucrose, typically in a 1:3 ratio, to create sugar coating solutions for tablets or other pharmaceutical applications (Rowe, Sheskey, & Quinn, 2009).

2.2.6.4. Microcrystalline Cellulose (Avicel PH 102)

Microcrystalline cellulose is a purified, partially depolymerized form of cellulose that appears as a white, crystalline powder with no taste or smell, composed of porous particles. It is offered commercially in a variety of particle sizes and moisture grades, with different grades and uses.

Cellulose is the chemical name, $(C_6H_{10}O_5)_n$ refers to the empirical formula and has a molecular weight of 36000 g/mol. The molecular formula of microcrystalline cellulose is illustrated in Figure 2-4.

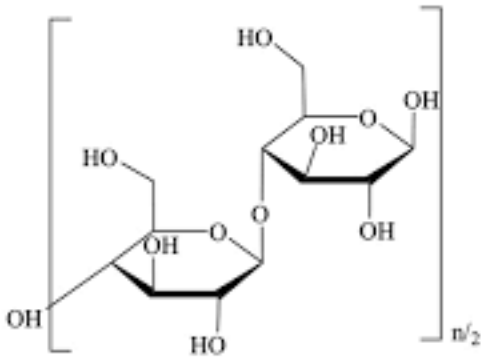


Figure 2-4: Molecular formula of microcrystalline cellulose

Microcrystalline cellulose is widely employed in the pharmaceutical industry, especially as a binder/diluent in oral tablet and capsule formulations, where it is used in both wet granulation and direct compression procedures. Additionally, it has certain lubricating and disintegrant effects that are advantageous for tableting (Rowe, Sheskey, & Quinn, 2009). Table 2-7 presents the concentrations used in each functional category.

Table 2-7: The concentrations used in each functional category of microcrystalline cellulose

Use	Concentration (%)
Adsorbent	20–90
Antiadherent	5–20
Capsule binder/diluent	20–90
Tablet disintegrant	5–15
Tablet binder/diluent	20–90

2.2.6.5. Povidone

Povidone, also recognized under various names such as Kollidon, Plasdonem, poly[1-(2-oxo-1-pyrrolidinyl)ethylene], polyvidone, polyvinylpyrrolidone, Povidonum, Povipharm, and PVP, belongs to the family of 1-vinyl-2-pyrrolidinone polymers. Povidone is a finely textured, odorless, or nearly odorless, hygroscopic powder. Its color can range from white to creamy-white. The production of Povidone can involve different methods: spray-drying is used to produce Povidones with K values of 30 or less, resulting in spherical-shaped particles, while drum drying is employed to produce Povidones with K values of 90 or more, which typically take the form of plates or flakes. The viscosity of Povidone in an aqueous solution is characterized by its K-value, which is a measure of thermal conductivity in relation to that of water.

The chemical name of povidone is 1-Ethenyl-2-pyrrolidinone homopolymer. Its empirical formula and molecular weight are $(C_6H_9NO)_n$, and 2500–3000000 g/mol, respectively (Rowe, Sheskey, & Quinn, 2009). The molecular formula of povidone is illustrated in Figures 2-5.

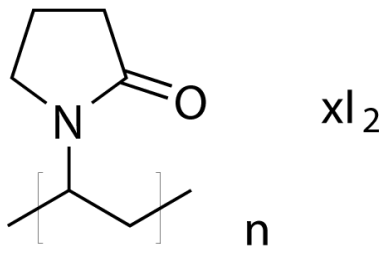


Figure 2-5: Molecular formula of Povidone

Povidone is primarily utilized in solid-dosage forms and various other pharmaceutical formulations as a dissolving enhancer, suspending agent, and tablet binder (Rowe, Sheskey, & Quinn, 2009), typically at the concentrations listed in Table 2-8.

Table 2-8: The concentrations used in each functional category of Povidone

Use	Concentration (%)
Carrier for drugs	10–25
Dispersing agent	Up to 5
Eye drops	2–10
Suspending agent	Up to 5
Tablet binder or coating agent	0.5–5

Povidone solutions are introduced in the dry form into the powder mixtures and granulated in situ by adding water, alcohol, or hydroalcoholic solutions during the tablet manufacturing process.

Povidone has been employed to improve the dissolution of poorly soluble drugs in solid dosage forms. It is also applied as a solubilizer in oral and parenteral formulations.

Povidone solutions may also be employed as coating agents when coating active pharmaceutical ingredients on a support, such as sugar pellets. Moreover, a number of topical, oral suspensions and solutions use the povidone as suspending, stabilizing, or viscosity-increasing agent (Rowe, Sheskey, & Quinn, 2009).

2.2.6.6. Crospovidone

Crospovidone is a finely dispersed, free-flowing powder that appears hygroscopic, with a color ranging from white to creamy-white. It is virtually tasteless and odorless. According to USP32-NF27, crospovidone is defined as a synthetic, crosslinked homopolymer of N-vinyl-2-pyrrolidinone, and it is insoluble in water. Because of its insolubility, obtaining an accurate determination of its molecular weight has proven to be challenging.

The crospovidone is utilized in the tablets prepared by direct compression and wet or dry granulation processes at the concentration of 2–5% as a water-insoluble disintegrant and solubility enhancer. It exhibits a strong capillary activity, substantial hydration capacity, and slightly gel-forming ability (Rowe, Sheskey, & Quinn, 2009). According to literature, the particle size of crospovidone significantly affects the dissolution rate of analgesic tablets, with larger particles leading to faster disintegration compared to smaller particles. The crospovidone can be employed to enhance a drug's solubility through the co-evaporation process (Rowe, Sheskey, & Quinn, 2009).

2.2.6.7. Sodium Starch Glycolate

Sodium starch glycolate is a highly hygroscopic powder that flows freely and is either white or nearly white in color. As per PhEur 6.0, when observed under a microscope, it consists of granules with irregular shapes, ovoid or pear-shaped, ranging in size from 30 to 100 mm, or rounded, measuring 10 to 35 mm in size. (Rowe, Sheskey, & Quinn, 2009).

Sodium starch glycolate is known by several names, including carboxymethyl starch, sodium salt, carboxymethylamylum natricum, starch carboxymethyl ether, and sodium salt. In accordance with USP32-NF27, it is described as the sodium salt of a carboxymethyl ether of starch or a crosslinked carboxymethyl ether of starch. The USP32-NF27 also outlines two distinct forms of sodium starch glycolate, namely Type A and Type B (USP32-NF27, 2008).

Three types of the sodium starch glycolate are described by the PhEur 6.0: A crosslinked, partially O-carboxymethylated potato starch is defined as having two types: Type A and Type B. Type C is defined as the sodium salt of a partially O-carboxymethylated starch that has been physically dehydrated to form crosslinkings. The pH and salt content help to distinguish between Types A, B, and C. A degree of substitution and crosslinking can be used to describe sodium starch glycolate (Rowe, Sheskey, & Quinn, 2009).

The molecular formula of sodium starch glyconate is illustrated in Figure 2-6. Its chemical name is sodium carboxymethyl starch, and it has a molecular weight typically of 5×10^{5} and 1×10^{6} g/mol.

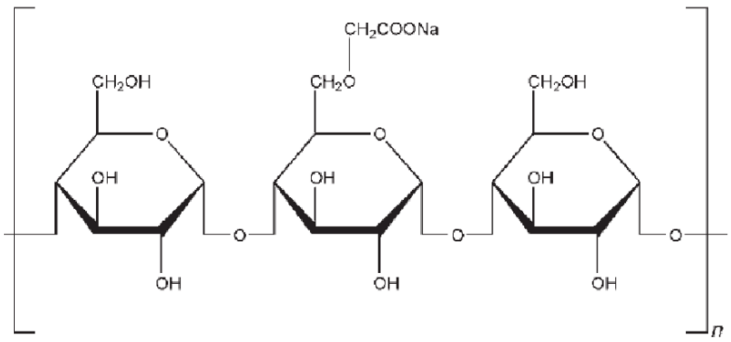


Figure 2-6: The molecular formula of sodium starch glycolate

Sodium starch glycolate is used as a disintegrant in oral pharmaceutical formulations of tablets prepared by wet-granulation or direct-compression methods and in capsules. The concentration ranges from 2% to 8%, with an optimum of 4%, the rapid water uptake leads to the disintegration and swelling (Rowe, Sheskey, & Quinn, 2009).

While hydrophobic excipients such as lubricants can reduce the efficacy of some disintegrants, sodium starch glycolate has no such bad impacts, and the disintegration time does not appear to be impacted by increasing tablet compression pressure either. Additionally, sodium starch glycolate has been researched as a potential suspending agent (Rowe, Sheskey, & Quinn, 2009).

2.2.6.8. Magnesium Stearate

Magnesium stearate is a finely powdered substance, typically appearing as a light white powder. It can be either precipitated or milled and has a greasy texture that readily adheres to the skin. It possesses a low bulk density, a faint stearic acid odor, and a distinctive taste (Rowe, Sheskey, & Quinn, 2009).

Magnesium stearate finds common usage in pharmaceuticals, food products, and cosmetics formulations. Its primary role is as a lubricant during the production of capsules and tablets, typically used at concentrations ranging from 0.25% to 5.0% w/w. (Rowe, Sheskey, & Quinn, 2009).

2.2.6.9. Talc

Talc is an extremely fine, odorless, impalpable, unctuous, crystalline powder that ranges from white to grayish-white. It readily sticks to the skin, feels smooth to the touch, and is not gritty.

Talc is defined as a hydrated, purified form of magnesium silicate with a chemical formula represented as $Mg_6(Si_2O_5)_4(OH)_4$. It might contain trace levels of iron and aluminum silicate. Talc is primarily used as a lubricant and diluent that is widely employed in oral solid dosage formulations but is now less frequently used. In the manufacturing of drugs with controlled releases, it is typically utilized as a dissolution inhibitor. Furthermore, talc serves as an adsorbent, a novel powder coating for extended release pellets, and a lubricant in tablet formulations, cosmetics and food products. Talc is also a dusting powder in topical preparations (Rowe, Sheskey, & Quinn, 2009). Table 2-9 presents the concentrations used in each functional category.

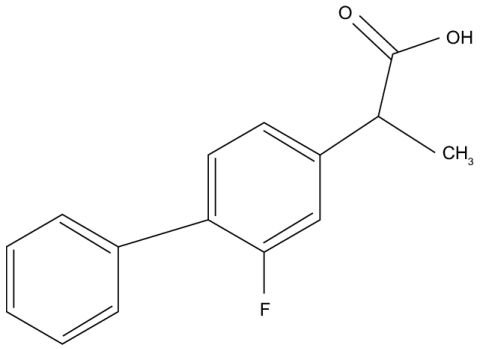
Table 2-9: The concentrations used in each functional category of talc

Use	Concentration (%)
Dusting powder	90.0–99.0
Glidant and lubricant	1.0–10.0
Diluent	5.0–30.0

2.3. Flurbiprofen

Flurbiprofen is a nonsteroidal anti-inflammatory drug (NSAID) commonly employed to alleviate pain and reduce inflammation. It is recommended for the treatment of various conditions including rheumatoid arthritis, degenerative joint disease, osteoarthritis, acute musculoskeletal disorders, and low back pain (Alkan & Yilmaz, 2014). Additionally, it finds use in the treatment of ocular gingivitis and postoperative ocular irritation. Recent reports have also highlighted the efficient antiplatelet activity of flurbiprofen and its potential applications in radio-protection, colon tumor prevention, pain management following foot surgery, and periodontal surgery, both topically and systemically (Abdel-Aziz, Al-Badr, & Hafez, 2012).

The empirical formula of flurbiprofen is $C_{15}H_{13}FO_2$, and its molecular weight is 244.26 g/mol. The molecular formula is illustrated in Figure 2-7.



2-(2-Fluoro-4-biphenylyl) propionic acid

Figure 2-7: The molecular formula of flurbiprofen

2.3.1. Physicochemical Properties

Flurpbirofen is a crystalline powder that is white or nearly white. Nearly insoluble in the water, freely soluble in ethanol (96%) and methylene chloride. It dissolves in alkali hydroxide and carbonate aqueous solutions (British Pharmacopeia 2020 pp 1094).

2.3.2. Mechanism of Action

The mechanism of action of flurbiprofen involves the inhibition of the enzyme cyclooxygenase (COX) to prevent the synthesis of prostanoid substances. COX is an enzyme known for its role in regulating processes like inflammation, fever, and pain. It catalyzes the oxidative conversion of arachidonic acid into prostaglandin H2, a critical element in the biosynthesis of prostaglandins, prostacyclins, and thromboxanes. These substances, in turn, play a pivotal role in controlling various physiological responses, both beneficial and pathological. Notably, current nonsteroidal anti-inflammatory drugs (NSAIDs) that function as COX inhibitors, including ibuprofen and flurbiprofen, have the capability to inhibit both COX-1 and COX-2 enzymes (Abdel-Aziz, Al-Badr, & Hafez, 2012).

2.3.3. Pharmacokinetics

Absorption

Following oral treatment, flurbiprofen is completely absorbed, reaching its peak plasma levels in one hour. The plasma peak concentration is about 12 μg/ml following 100 mg dose and reaches in 1.5 to 3 hours after ingestion (Maroof, Zafar, Ali, & Naveed, 2015).

Distribution

While flurbiprofen is known to be widely distributed throughout the body's tissues, there is no confirmed evidence of its accumulation in any specific tissue (Ishii, et al., 2008).

Metabolic Pathway

Flurbiprofen is metabolized mostly through oxidation and conjugation. 99 % of flurbiprofen is bound to the human serum albumin. Over 95% of an oral dosage is eliminated within 24 hours via kidney excretion. A daily oral dose is excreted in four different forms: 2-[2-fluoro-40-hydroxy-4-biphenylyl] propionic acid (40–47%), 2-[2-fluoro-30,40-hydroxy-4-biphenylyl]propionic acid (5%), 2-[2-fluoro-30,40-hydroxy-4-biphenylyl]propionic acid (20–30%), and the parent drug, flurbiprofen (20–25%) (Figure 2-8). The amount of flurbiprofen and its metabolites that are presented as glucuronide and sulfate conjugates ranges from 65% to 85% (Abdel-Aziz, Al-Badr, & Hafez, 2012).

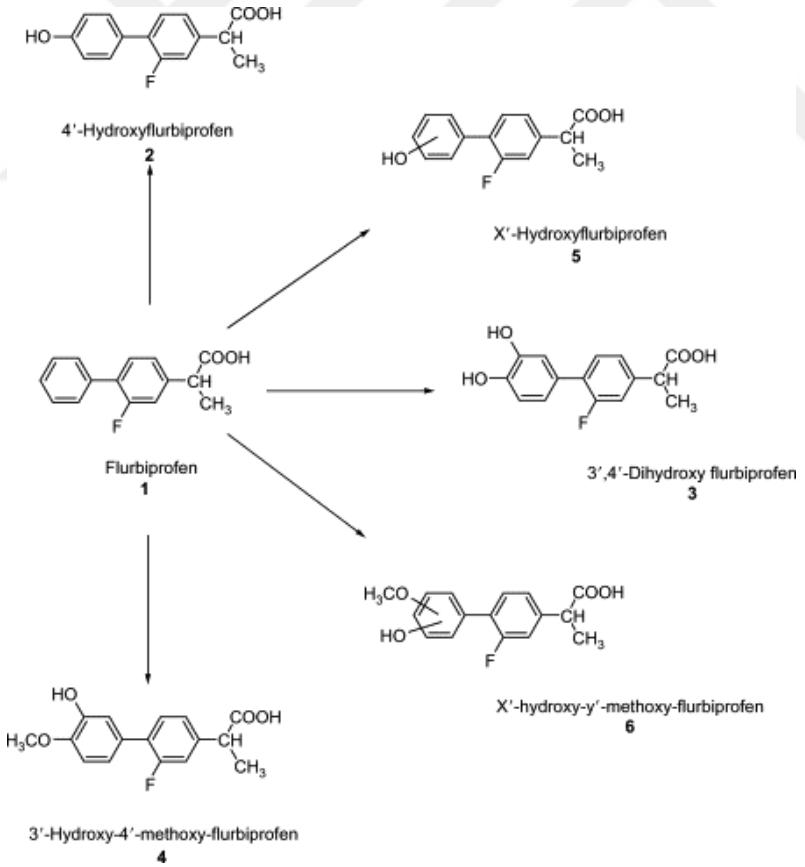


Figure 2-8: The chemical structures of Flurbiprofen and its metabolites

Elimination

Flurbiprofen undergoes significant biotransformation, resulting in the formation of glucuronide-conjugated metabolites, which are subsequently eliminated. Approximately 20% of flurbiprofen is excreted unchanged as conjugates in urine (Davies, 1995). The gastric emptying rate has been observed to be notably higher in the fed state, and the elimination half-life is around 3.5 hours following repeated doses (Maroof, Zafar, Ali, & Naveed, 2015).

2.3.4. Side Effects

Serious side effects, including ulcerations, burning sensations, cramping, nausea, and gastritis, are associated with the dosage of flurbiprofen. Long-term usage has also been linked to liver toxicity and gastrointestinal bleeding. Rash, tinnitus (ringing in the ears), and lightheadedness are rare side effects (WebMD, 2023).

2.3.5. Drug Interactions

- Fluconazole reduces the clearance of flurbiprofen by inhibiting the CYP2C9 enzyme that convert it to 4-hydroxy (OH)-flurbiprofen (Greenblatt, et al., 2006).
- Dapsone affects the CYP2C9 enzyme's cooperative activity, which may lead to a significant change in clearance, to influence flurbiprofen hydroxylation metabolism (Hutzler, et al., 2001).
- Flurbiprofen inhibits platelet release and extends the bleeding time when taken with warfarin (Stricker & Delhez, 1982).
- Flurbiprofen increases the serum level of lithium by inhibiting prostaglandin synthesis, which lowers renal blood flow and glomerular filtration rate (Aktepe, Özkorumak, & Kandil, 2007).
- Flurbiprofen and furosemide use simultaneously has also been linked to decreased urine volume, salt, and potassium concentrations (Symmons, Kendall, Rees, & Hind, 1983).

2.3.5.1. Spectrophotometric Methods

The first-order derivative spectrophotometry technique was developed to identify flurbiprofen in pharmaceutical formulations. Absorbance values were measured at 213,

233, and 260 nm. Tablet formulations were successfully employed using the described method, which featured a linear calibration curve, accuracy lower than 3.67%, within- and between-day precision values less than 4.95%, and a mean recovery value of 100.9% (Alkan & Yilmaz, 2014).

For the quantitative determination of flurbiprofen, novel and rapid spectrophotometric (UV) and reversed phase HPLC (LC) methods were provided. The detection limits for UV and LC methods were determined as 0.34 µg/ml and 15 ng/ml, respectively. Both techniques are directly and easily applicable to pharmaceutical compositions containing flurbiprofen, and they demonstrate equivalent levels of accuracy, sensitivity, precision, reproducibility, ruggedness, and durability. The LC method is effective for detecting very low levels (ng/ml), while the UV method is suitable for levels in the µg/ml range (Sajeev, Jadhav, RaviShankar, & Saha, 2002).

2.3.5.2. High-Performance Liquid Chromatography

A practical assay for flurbiprofen using high-performance liquid chromatography (HPLC) has been developed. This method was rapid, simple, sensitive, and specific. Gemini C_{18} column (5 µm, 4.6 x 250 mm), a mobile phase of disodium hydrogen phosphate solution (30 mM), pH 7.0, and acetonitrile (50:50) was used along with an isocratic flow rate of 1.0 ml/min, and the the detection wavelength was 247 nm. The reported HPLC method for flurbiprofen offers several advantages, including ease of use, high specificity, accuracy, and a rapid run-cycle time. (Akhlaq, et al., 2011).

A simultaneous analysis of two complementary drugs, flurbiprofen and ranitidine, incorporated into bilayer tablets, was performed using the HPLC method. For the separation of the drugs, a Gemini C_{18} column (ODS, 5 µm, 4.6 x 250 mm) was employed with a constant flow rate of 1 mL/min, at detection wavelength of 245 nm. The analysis was performed using an isocratic mobile phase composed of di-hydrogen potassium phosphate buffer solution (0.2 M) and acetonitrile in a 1:1 ratio (Hanif, et al., 2015).

To integrate and analyze the peaks in the chromatogram of the ternary complex comprising naproxen (NPX), flurbiprofen (FBP), and gamma-cyclodextrin (γCD), high-performance liquid chromatography (HPLC) analyses were conducted using a Shimadzu HPLC system equipped with a computer interface and software. The separation was carried out in a column oven maintained at a temperature of 40°C, utilizing a

SUPERIOREX ODS column (5 µm, 150 x 4.6 mm). The mobile phases used consisted of acetonitrile and a phosphate solution at pH 2.2, and the flow rate was held constant at 1 ml/min. Detection was performed at 245 nm, with retention times of 8.1 and 5.0 minutes, respectively, for the detection of FBP and NPX (Higashi, et al., 2010).

2.3.5.3. Gas chromatography-Mass Spectrometry

The determination of flurbiprofen concentration in human plasma was accomplished through chromatographic analysis. Separation was carried out using an Agilent Technologies HP-5 MS column with a film thickness of 0.25 µm (30 m x 0.25 mm inner diameter). Helium was used as the carrier gas at a flow rate of 1 mL/min. The injector and detector temperatures were set at 250°C. The settings for the Mass Spectrometry (MS) detector included an electron energy of 70 eV, a solvent delay of 3 minutes, and a transfer line temperature of 280°C. The quantitation ions for the internal standard were at m/z 73, while those for flurbiprofen were at m/z 180 (Yilmaz, Sahin, Akba, & Erdem, 2014).

2.3.5.4. Thin-Layer Chromatography

The lipophilicity of ibuprofen, naproxen, ketoprofen, and flurbiprofen was determined using a Thin-Layer Chromatography (TLC) separation method on HPTLC RP-18, F254s glass plates (10 cm). The mobile phase consisted of an acetonitrile and water solution (v/v), with acetonitrile content varying from 50% to 80% in 5% intervals. All experiments were conducted at a constant room temperature of 21 ± 1°C (Czyrski, 2019).

2.3.6. Pharmaceutical Preparations in Turkish Market

Flurbiprofen is generally available in the forms of 100 mg tablet and 200 mg capsule, as well as topical gel and sprey in Turkish Market. Table 2-10 outlines commercial preparations, dosage forms, strengths and manufacturers of flurbiprofen products in Turkish market.

Table 2-10: The commercial preparations, dosage forms, strengths, and manufacturers of flurbiprofen products in Turkish market

Preparation	Dosage Form	Strength	Manufacturer
ALGOPET	Film coated tablet	100 mg	İlko Pharmacuticals
ALGOPET SR	Micropellet capsules	200 mg	İlko Pharmacuticals
FIERA	Film coated tablet	100 mg	RDC Pharmaceuticals
FLUBI	Film SR capsules	200 mg	Biofarma Pharmaceutical
FLUBIMAK	Film tablet	100 mg	Akar pharma
FLUPEN	Film coated tablet	100 mg	Atayurt Pharmaceuticals
FLURFLEX	Film table	100 mg	Atabay Pharmaceutical
FLURIDIN	Gel	30 g	Exeltis Pharmaceuticals
FORTINE	Film tablet	100 mg	Bili Bilim Pharmaceuticals
FORTINE SR	Extended release capsules	200 mg	Bili Bilim Pharmaceuticals
FROLIX	Film tablet	100 mg	Ali Raif Pharmaceuticals
FROLIX SR	Mikropellet capsule	200 mg	Ali Raif Pharmaceuticals
MAJEZIK	Topical spray, solution	5 %	Sanovel Pharmaceuticals
MAJEZIK	Film tablet	100 mg	Sanovel Pharmaceuticals
MAJEZIK SR	Micropellet capsules	200 mg	Sanovel Pharmaceuticals
MAJEZIK	Topical gel	50 g	Sanovel Pharmaceuticals
MAPROFEN	Film tablet	100 mg	Nobel Pharmaceuticals
MAXALJIN	Film tablet	100 mg	Abdi İbrahim Pharmaceuticals
MAXALJIN	Capsule	200mg	Abdi İbrahim Pharmaceuticals
MAXIMUS	Film tablet	100 mg	Drogsan Pharmaceuticals
MERDEX	Micropellet capsules	200 mg	Aset Pharmaceuticals
NETFEN	Capsule	200 mg	Neutec Pharmaceuticals

PROJEZIK	Film tablet	100 mg	Vem Pharmaceuticals
UNIJEZIK	Film tablet	100 mg	Emkar Pharmaceuticals
ZERO-P	Film tablet	100 mg	Deva Pharmaceuticals
ZERO-P	Micropellet capsules	200 mg	Deva Pharmaceuticals

3. MATERIALS AND METHODS

3.1. Materials

- Flurbiprofen (Vem Pharmaceuticals)
- Ludipress (BASF)
- PVP K30 (BASF)
- Avicel PH-102 (Ali Raif Pharmaceuticals)
- Laktoz Monohydrate (Ali Raif Pharmaceuticals)
- Sodium Starch Glyconate (Ali Raif Pharmaceuticals)
- Kollidon CL(Crospovidon) (Ali Raif Pharmaceuticals)
- Beta-Cyclodextrin (Thermo Scientific)
- Hydroxypropyl-Beta-Cyclodextrin (Thermo Scientific)
- Magnesium Stearate (Sigma-Aldrich)
- Talk (Sigma-Aldrich)
- Rhodamine B (Sigma-Aldrich)
- Potassium Dihydrogen Phosphate (Sigma-Aldrich)
- Dipotassium Hydrogen Phosphate (Merck)
- Sodium Chloride (Merck)
- Sodium Hydroxide (Sigma-Aldrich)
- Phosphoric Acid (Sigma-Aldrich)
- Ethanol (Merck)

3.2. Equipments

- Electronic Balance (Denver Instrument, TB-Series)
- Eppendorf Micropipette (0,5-10 µl l, 20-200 µl,10-100µl, 100-1000 µl,)
- Heating Magnetic Stirrer (IKA RT 15 Power)
- Orbital Shaker (Thermo Electron Corporation)
- Lyophilizer (Leybold Heraeus Lyovac GT2)
- pH meter (Hanna HI 2020 Edge)
- Ultra-Pure Water Device (Millipore, MiliQ)
- Ultrasonic Water Bath (Bersonic Ultrasonic Cleaner)
- UV-Spectrophotometer (UV-1601, Shimadzu)
- Cubic Mixer (Yener Enginering)
- Tapped Density Analyzer (Yener Enginering)
- Friability Test Apparatus (Aymes Company)
- Hardness Test Apparatus (Sotax Corporation)
- Single Punch Tablet Machine (Zhejiang Leadtop Pharmaceutical Machinery Corporation)
- Thickness Vernier Calipers
- Disintegration Apparatus (DT2, Sotax Corporation)
- Dissolution Apparatus (AT2, Sotax Corporation)

3.3. Methods

3.3.1. Ultraviolet (UV) Spectrum

To assess the suitability of flurbiprofen as the active pharmaceutical ingredient for in vitro dissolution rate and quantity determination studies, its UV spectrum was examined. 10 mg of Flurbiprofen was dissolved in etanol and made up with 50 ml of ethanol to obtain final concentration of 200 µg/ml. By making an appropriate dilution of this solution phosphate buffer (pH 6.8), a solution with concentration of 5 µg/ml was prepared. This solution was analyzed in range of 200 and 400 nm using a UV-VIS spectrophotometry, and wavelength at which maximum absorbance was observed was recorded.

3.3.2. Quantification of Flurbiprofen by Spectrophotometry Method

In the content uniformity, taste-masking and in vitro dissolution rate studies of flurbiprofen, UV spectrophotometric method was employed for quantity determination. This method was conducted using the maximum wavelength.

3.3.3. Validation of Spectrophotometry Method of Flurbiprofen

The method validation has conducted to ensure that an analytical method is precise, accurate, and reproducible over the range that an analyte will be examined. The validation process encompassed various parameters, including the assessment of linearity, accuracy, precision, stability, and specificity for the analysis of flurbiprofen (Gandhimathi, Vijayaraj, & Jyothirmaie, 2012).

3.3.3.1. Specificity

The specificity refers to the ability to accurately and specifically measure the target analyte, even in the presence of other substances that would be predicted to be present in the drugs. It assesses the degree of interference from factors such as other active ingredient drugs, excipients, impurities, and degradation products, ensuring that a peak response is solely attributable to the active ingredient drug (Gandhimathi, Vijayaraj, & Jyothirmaie, 2012). Flurbiprofen was dissolved in ethanol, both individually and in combination with the other excipients. The spectrum was then recorded and analyzed to determine whether the concentration of flurbiprofen λ_{max} was affected (Kaid, 2021).

3.3.3.2. Linearity

The linearity refers to method's ability to generate test results which exhibit a direct proportionality to analyte's concentration within a specified range, as known by the variance. To assess linearity, the stock solution was initally prepared by dissolving 10 mg of Flurbiprofen with 50 ml of ethanol to obtain a final concentration of 200 µg/ml. By making an appropriate dilution (phosphate buffer (pH 6.8), of the stock solution, a calibration curve was constructed using seven data points (1, 2, 3, 5, 7, 8, and 10 µg/mL) by plotting the absorbance spectrum against the concentration of flurbiprofen. The performance of the calibration curve was further evaluated using its correlation coefficient, as outlined in the study by Yılmaz and Alkan (Yilmaz & Alkan, 2015).

3.3.3.3. Accuracy

The accuracy serves an indicator to assess the precision of an analytical method, measuring how closely the obtained value aligns with an accepted reference value, which can be a conventional standard or a recognized reference value (Gandhimathi, Vijayaraj, & Jyothirmaie, 2012). To validate the accuracy of the presented method, recovery studies were conducted at three distinct levels: 1, 5, and 10 µg/mL of the standard concentration. At each concentration level, the quantity of flurbiprofen and the percentage recoveries were calculated, following the methodology described by Lasure, Ansari, and Kalshetti (2020) (Lasure, Ansarı, & Kalshettı, 2020).

$$Accuracy = \frac{C_f - C_a}{C_a} \times 100$$

Where;

C_f represents the average concentration calculated using the regression equation

C_a is known theorical concentration.

3.3.3.4. Precision

The precision is expressed in terms of the absorbance's relative standard deviation (Lasure, Ansarı, & Kalshettı, 2020). The assessment of precision involves both repeatability (intra-day) and intermediate precision (inter-day) of the analytical method. The repeatability (intra-day) was determined at three different concentrations, three times daily, while intermediate precision (inter-day) was assessed by analyzing the sample

concentrations once daily for three days. The precision was determined by using the RSD of the reported concentrations obtained from the regression equation, following the methodology described by Yilmaz and Alkan (Yilmaz & Alkan, 2015).

$$Precision = \frac{\sigma}{\mu} \times 100$$

Where;

σ represents the standard deviation of the three individually measurements

μ denotes the average of these three individually measurements

3.3.3.5. Stability

5 μg/mL of the standard concentration were analyzed at different time intervals (0, 6, 24, 48, and 72 hours) to assess the stability of flurbiprofen. These measurements were compared to the measurements of 0^{th} hour to evaluate the results, and the deviations were expressed as a percentage (Alkan & Yilmaz, 2014).

3.3.3.6. Limit of Detection (LOD) and Limit of Quantification (LOQ)

To determine the active pharmaceutical ingredient's LOD and LOQ, at least three calibration curves' slopes or standard deviations of intercepts are utilized (Kaid, 2021). In this study, for the same purpose, slopes of three calibration curves were calculated, and the following formulas were employed to calculate the LOD and LOQ.

The limit of detection (LOD) = 3.3 x σ / S

The limit of quantification (LOQ)= 10 x σ /S

Where;

σ is the standard deviation values of the calibration curve slopes

S is the average of calibration curve slopes

3.3.4. Preparation of Flurbiprofen-Cyclodextrin Inclusion Complexes

3.3.4.1. Effect of Complexation Period, Cyclodextrin Amount, pH and Temperature in Preparation of Flurbiprofen-Cyclodextrin Inclusion Complexes

a. Complexation Period and Cyclodextrin Amount

To assess the time required for complexation to reach equilibrium and optimal cyclodextrin amount, separate solutions of 5 mM and 15 mM β-CD and HP-β-CD were stirred with 10 mg of flurbiprofen in 10 ml of pure water on the orbital shaker and maintained at 37˚C for various periods (1 day, 2 days, and 3 days). Following the conclusion of the complexation periods, the mixture was filtered using a 0.45 μm syringe filter membrane (Millipore LCR, 13 mm, 0.45 μm). The appropriate dilutions of Flurbiprofen-Cyclodextrin inclusion complexes were prepared, and flurbiprofen concentration was subsequently determined using UV-VIS spectrophotometer (Doile MM, 2008).

b. Temperature and pH

To investigate the influence of pH and temperature on the complexation, 5mM solutions of both β-CD and HP-β-CD were stirred with 10 mg of flurbiprofen in 10 ml of various mediums (pure water, pH 1.2, pH 4.5, and pH 6.8) on the orbital shaker and maintained at 25˚C and 37˚C for 2 days. Following 2 days, the mixture was filtered using a 0.45 μm syringe filter membrane (Millipore LCR, 13 mm, 0.45 μm). The appropriate dilutions of Flurbiprofen-Cyclodextrin inclusion complexes were prepared, and flurbiprofen concentration was subsequently determined using UV-VIS spectrophotometer (Kaid, 2021).

3.3.4.2. Preparation of the Flurbiprofen-Cyclodextrin Inclusion Complexes

Both 5 mM of β-CD (56.75 mg) and HP-β-CD (70.00 mg) were accurately weighed, and then each was individually dispersed in 10 mL of pure water. Flurbiprofen was then added to the aqueous solutions of β-CD and HP-β-CD in an equimolar ratio (1:1). Following that, the mixture was stirred on the orbital shaker for 48 hours at 37˚C. The 0.45 um syringe filter was utilized to filter the mixture, which was subsequently frozen at -20°C for 24 hours. The frozen solution was lyophilized for 72 hours at the pressure of 0.005 mBar. The lyophilized Flurbiprofen-Cyclodextrin inclusion complexes were sieved through an 80-mesh sieve before being blended with the excipients to

produce the direct compression tablets. The final product was stored in desiccators placed on top of silica gel until further characterization (Verma, Naik, & Mokale, 2014)

3.3.5. Determination of Tablet Powder Blend Characteristics

The tablet powder blends were assessed for physicochemical parameters such as angle of repose (flow properties), bulk density, tapped density, compressibility index, and Hauser's ratio.

3.3.5.1. Angle of Repose

The angle of repose (θ) was determined using a recommended method outlined in USP 44 (USP44-NF39, 2021). The precisely measured powder blend was allowed to flow freely onto the graph paper through a funnel, which was positioned approximately 2-4 cm away from the highest point of the powder heap and secured in a funnel holder. Subsequently, the angle of repose was calculated by measuring the height (h) and radius (r) of the formed powder cone and substituting these values into following the equation (Dawadi, et al., 2020)

$$\theta = tan - 1\ \frac{h}{r}$$

3.3.5.2. Bulk Density

The bulk density is the ratio of a powder's total mass to its bulk volume. For each specific formulation, a 25 ml graduated cylinder was filled with the weighed powder. Following that, the powder was gently leveled without compacting it, and nearest graduated unit was noted as the unsettled apparent volume (V_0) (Pavankumar, et al., 2021) . The bulk density was calculated in g/ml using the following equation:

Bulk density =W/V_0

Where, W is the weight of the powder.

3.3.5.3. Tapped Density

The tapped density is the fraction of the powder's total mass to its tapped volume. The test sample with the known weight of all the formulations was transferred into a 25 ml graduated cylinder. The mechanical tapped density tester was employed to perform the procedure, with tap counts of 10, 500, and 1250. The equivalent volumes V10, V500, and V1250 were recorded to the nearest graduated unit. V1250 (referred to as Vf) was defined to as the tapped volume when the difference between V500 and V1250 is 1 mL

or less. The following equation was utilized to calculate the tapped density in g/ml (USP 44-NF 39 2021).

Tapped density $=W/V_f$

Where, W is the weight of the powder.

3.3.5.4. Compressibility Index (Carr's Index)

To determine the compressibility index of the powder mixture, Carr's index was calculated, utilizing the bulk density and tapped density. It serves as a percentage-based measure of a material's flowability and is calculated as follows (Pavankumar, et al., 2021):

Carr's index $= 100x(V_0 - V_F)/V_0$

Where;

V_0 is unsettled apparent volume,

V_F is the tapped volume for V1250

3.3.5.5. Hausner's Ratio

The Hausner's Ratio is a parameter associated with the flowability of a powder. It is determined by calculating the ratio of tapped density to bulk density (Pavankumar, et al., 2021).

Hausner's ratio = Tapped density/Bulk density

3.3.6. Preparation of ODT Formulations

As the formula presented in Table 3-1, the ODTs were manufactured through two different methods: direct compression, and wet granulation. Furthermore, in order to examine effects of different manufacturing methods and drug-cyclodextrin inclusion complexes on bitter taste-masking and tablet characterization were prepared ODTs with Ludipress as control group for granulation method, and ODTs with drug-cyclodextrin physical mixtures as control groups for ODTs with drug-cyclodextrin inclusion complexes.

Table 3-1: The theorical contents and codes of ODT formulations (per tablet)

Components (mg)	F1	F2	F3	F4	F5	F6	F7
Flurbiprofen	50	50	50	2.17	3.98	-	-
Ludipress	75	-	-	75	75	75	75
Avicel PH-102	25	25	25	25	25	25	25
Lactose Monohydrate	-	69.75	69.75	-	-	-	-
Sodium Starch Glycolate	-	5	-	-	-	-	-
PVP K30	-	2.625	2.625	-	-	-	-
Kollidon CL (Crospovidon)	2.375	-	5	2.375	2.375	2.375	2.375
β-CD	-	-	-	47.83		-	-
HP-β-CD	-	-	-	-	46.02	-	-
Flurbiprofen-CD Inclusion Complex	-	-	-	-	-	50	50
Mg Stearate	1.56	1.56	1.56	1.56	1.56	1.56	1.56
Talk	2	2	2	2	2	2	2
Tablet Weight	155.935	155.935	155.935	155.935	155.935	155.935	155.935

3.3.6.1. Direct Compression Method

The direct compression method was employed in the production of flurbiprofen containing ODTs (F1, F4, F5, F6 and F7). Initially, flurbiprofen/Flurbiprofen-Cyclodextrin inclusion complexes and the excipients (excluding talc and magnesium stearate) were accurately weighed using an electronic balance. These components were then blended for 15 minutes in a Cubic Powder Mixer to ensure a homogeneous mixture. After that, talc and magnesium stearate after sieving were added as lubricant and glidant, and the mixture was only stirred for 5 minutes. The complete powder blends were assessed for various pre-formulation parameters before proceeding to tablet manufacturing. Finally, the resulting blend was directly compressed into approximately 155 mg tablets using 8-mm round flat punches at 600 psi of compression force on a single-station rotary tablet machine (Hyma & Kaveri, 2022).

3.3.6.2. Wet Granulation Method

Flurbiprofen, Avicel PH 102, and Crospovidon (or Sodium Starch Glycolate) were weighted and mixed for 5 minutes after passing through an 80-mesh sieve (Yasmeen, Revathi, & Monica, 2019). The wet granules were formed by wetting the mixture with PVP K30 solution as a granulating fluid and passed through an 80-mesh sieve. The wet granules were dried for 30 minutes in a hot-air oven at 50˚C before being sieved through an 80-mesh sieve to eliminate lumps. The dried granules were completely blended with an intergranular disintegrant (Crospovidon/ Sodium Starch Glycolate) for 10 minutes in a cubic mixer. Finally, talk and magnesium stearate were added to the mixture, blended for 5 minutes, and then compressed into approximately 155 mg tablets using 8-mm round flat punches at 600 psi of compression force on a single-station rotary tablet machine (Chen, Feng, Li, Du, & Weng, 2017).

3.3.7. Characterisation of ODT Formulations

The prepared tablets underwent a series of tests, including measurements of weight variation, thickness, hardness, friability, wetting time, drug content uniformity, disintegration test, dissolution test, and taste masking evaluation.

3.3.7.1. Weight Variation

Twenty tablets were randomly selected and weighed individually on the electronic balance, then the average weight was determined. The weight variance of the tablets was then calculated by comparing the specific weights of each tablet to the average weight (Hyma & Kaveri, 2022).

$$\text{Deviation \%} = (\text{Average tablet weight} - \text{Individual tablet weight}) / \text{Average tablet weight} * 100$$

3.3.7.2. Thickness and Diameter

Twenty tablets were randomly selected and measured with Thickness Vernier Calipers to determine the average thickness and diameter of ODTs. The thickness and diameter of the tablets was averaged.

3.3.7.3. Hardness

The breaking strength of ODTs was assessed using the Hardness Test Apparatus (Sotax Corporation). The crushing strength of tablets (measured in kilo Newtons, kN)

was recorded after placing the tablet in the designated space. This process were performed for 10 tablets (Tafere, Yilma, Abrha, & Yehualaw, 2021).

3.3.7.4. Friability Test

The tablet friability was assessed using the Friability Test Apparatus. Twenty pre-weighed tablets were placed in a friability tester, which was rotated at 25 rpm for 4 minutes. After dedusting and reweighing the tablets, the friability percentage was calculated using the below equation (Tafere, Yilma, Abrha, & Yehualaw, 2021).

$$\%F = (W_1-W_2)/W_1 \times 100$$

Where;

W_1 and W_2 represent the initial and final weights of the tablets, respectively.

3.3.7.5. Wetting Time

A straightforward and direct procedure was employed to determine the wetting time of the tablets. A circular tissue paper was placed in a petri dish with a 5 cm diameter. The petri dish was filled with five milliliters of water containing the water-soluble red dye, Rhodamin B (1%). Three tablets from each formulation were subjected to evaluation. The tablet was placed carefully at the top of the tissue paper. The wetting time was defined as the duration it took for water to fully wet the tablet's upper surface (Rahangdale, et al., 2020).

3.3.7.6. Content Uniformity

Ten tablets were were randomly selected, and then individually weighed. The tablet was placed into the 50 mL of volumetric balonjoje (Tafere, Yilma, Abrha, & Yehualaw, 2021). After completion with 0.1N NaOH, the mixture was stirred continuously for an hour using a magnetic stirrer. The sample was then filtered using a 0.45 µm syringe filter (Millipore LCR, 13 mm, 0.45 µm). 50 µL of clear filtrate (for F1, F2, and F3) were transferred to a 10 mL volumetric flask and diluted to volume with 0.1 N NaOH. For F4, F5, F6, and F7, 500 µL was diluted with 0.1 N NaOH in a 10 ml volumetric flask. The flurbiprofen concentration was subsequently determined using UV-VIS spectrophotometer, and % content uniformity were calculated using theorical and practical flurbiprofen amount per ODT (Shaheen & Zaman, 2018).

3.3.7.7. In Vitro Taste-Masking

To evaluate the in vitro taste masking test, three tablets were dispersed in pH: 6.8 phosphate buffer solution that was kept at 37±0.5°C. Each tablet was individually weighed before being placed into 50 ml buffer solution, and left undisturbed for 60 seconds. Subsequently, a 5 ml sample was taken and filtered through 0.45 μm syringe filter (Millipore LCR, 13 mm, 0.45 μm). In the case of F1 and F2, 0.5 ml of the filtered solution was diluted to a volume of 10 ml using phosphate buffer solution, while F3, F4, F5, F6, and F7 were examined directly without dilution. The flubiprofen concentration were then analyzed using UV spectrophotometer at λmax of 247 nm (Khan, Iqbal, Ibrahim, Nasir, & Ullah, 2015).

3.3.7.8. Disintegration Time

The test that described in USP 44- NF 39 was conducted on six tablets from each formulation. One tablet was placed in each tube, and the basket was then immersed in the disintegration medium, which consisted of 1000 ml distilled water that set at 37 ºC ±2 ºC. The time for tablet to become completely disintegrate without any remaining palatable mass was recorded in seconds (Dawadi, et al., 2020).

3.3.7.9. In-Vitro Dissolution Study

The in vitro dissolution test of ODTs was conducted using the USP Apparatus II paddle method. The paddle's rotational speed was set to 50 rpm. The dissolution medium consisted of 900 ml of phosphate buffer (pH 6.8), and was maintained at 37±0.5°C. At predefined time intervals (1, 2, 4, 6, 8, 10, 15, 20, 30, and 45 minutes), 5 mL samples were withdrawn from each vessel and immediately replaced with an equal volume of fresh dissolution medium. After being filtered and appropriately diluted with dissolving solution, the samples were analyzed spectrophotometrically at λ_{max} of 247 nm to determine flurbiprofen concentration. % Flurbiprofen release were calculated for 45 minutes and dissolution profiles were plotted % Flurbiprofen release versus the time (Tafere, Yilma, Abrha, & Yehualaw, 2021).

3.3.8. Statistical Analyses

The findings were expressed as mean ± SD. The obtained data were evaluated using Student's t-test or analysis of variance (ANOVA) followed by the Bonferroni test,

utilizing GraphPad Prism 5.04 software program. The significance level was expressed as $p < 0.05$.

4. RESULTS

4.1. The Results of Flurbiprofen

4.1.1. Ultraviolet (UV) spectrum

The solution of flurbiprofen prepared at a concentration of 5 µg/ml in phosphate buffer (pH 6.8) was scanned on UV spectrophotomery between 200-400 nm, and the wavelength at which the maximum absorbance was observed was found to be 247 nm (Figure 4-1).

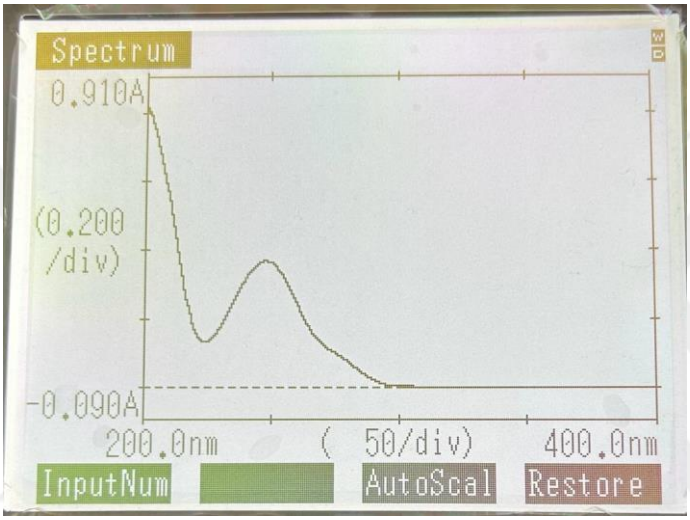


Figure 4-1: The UV spectrum of flurbiprofen in phosphate buffer (pH 6.8)

4.1.2. Quantification of Flurbiprofen by Spectrophotometric Method

UV spectrophotometer was used for the determination of flurbiprofen quantity, and measurements were taken at the maximum wavelength specified in Section 3.3.2, which was 247 nm.

4.1.3. Validation of Spectrophotometric Method of Flurbiprofen

The results obtained from the validation studies of the UV spectrophotometric method used for content uniformity, taste-masking and dissolution rate determination are presented under the following headings.

4.1.3.1. Specificity

The selectivity was performed as described in Section 3.3.3.1 of the validation studies. When absorbance values were evaluated in the solutions with excipients, there were no other peaks seen close to the flurbiprofen λ_{max}, which is 247 nm.

4.1.3.2. Linearity

In the method validation, linearity was examined as described in Section 3.3.3.2. The linear equation was found to be y = 0.0767x - 0.0029, with a slope of 0.0767 and an R^2 of 0.9991. The results are detailed in Table 4-1, and the linearity plot is shown in Figure 4-2.

Table 4-1: The results of the linearity study (n=3)

Concentration µg/mL	Mean absorbance	SD	RSD%
1	0.072	0.001	1.989
2	0.157	0.002	1.467
3	0.207	0.002	1.213
5	0.384	0.006	0.771
7	0.528	0.009	0.997
8	0.606	0.007	1.155
10	0.755	0.0122	0.627

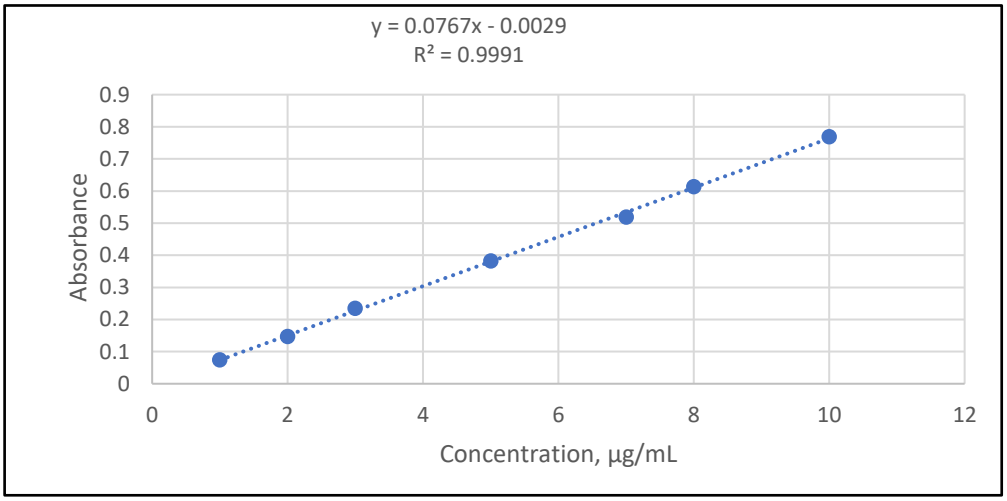


Figure 4-2: The flurbiprofen calibration curve obtained from the linearity study

4.1.3.3. Accuracy

The results of the accuracy study are presented in Table 4.2, as specified in Section 3.3.3.3.

Table 4-2: The results of accuracy study (n=3)

Theorical concentration (Mean, µg/mL)	Practical concentration (Mean, µg/mL)	Recovery (%)	SD	RSD (%)
1	1.014	101.374	0.008	0.774
5	4.975	99.505	0.095	1.913
10	10.008	100.080	0.012	1.690

SD: Standard deviation, RDS: Relative standard deviation

4.1.3.4. Precision

The precision parameter was evaluated in two ways: repeatability (intra-day) and intermediate precision (inter-day) studies. The study was conducted as described in Section 3.3.3.4. The results of the study are detailed in Table 4.3 for repeatability and Table 4.4 for intermediate precision.

Table 4-3: The results of repeatability (intra-day precision) study (n=3)

	Theorical concentration (Mean, µg/mL)	Absorption for n1	Absorption for n2	Absorption for n3	Mean Absorbance	SD	RSD (%)
Intra-day	**1**	0.056	0.056	0.0563	0.056	0.0001	0.308
	5	0.362	0.354	0.362	0.359	0.004	1.285
	10	0.737	0.741	0.725	0.734	0.008	1.133

Table 4-4: The results of intermediate (inter-day) precision study (n=3)

	Theorical concentration, (Mean, µg/mL)	1st Day	2nd Day	3rd Day	Mean Absorbance	SD	RSD (%)
Inter-day	**1**	0.058	0.057	0.0563	0.057	0.0008	1.496
	5	0.366	0.364	0.371	0.367	0.003	0.982
	10	0.721	0.739	0.725	0.728	0.009	1.297

4.1.3.5. Stability

In the method validation, the stability study was conducted as described in Section 3.3.3.5. The percent change in concentrations of the solutions at 6, 24, 48 and 72 hours is presented in Table 4-5.

Table 4-5: The results of stability study (n=3)

Time (Hours)	Theoretical Concentration of Flurbiprofen (µg/mL)	Practical Concentration of Flurbiprofen (µg/mL)
0	5	4.72
6	5	4.64
24	5	4.73
48	5	4.75
72	5	4.67
	Average	4.707
	SD (±)	0.044
	RSD%	0.942

4.1.3.6. Limit of Detection (LOD) and Limit of Quantification (LOQ)

By working as described in section 3.3.3.6., the data obtained, and the formulas used resulted in LOD value of 0.031 µg/mL and an LOQ value of 0.095 µg/mL.

4.2. The Results of Flurbiprofen-Cyclodextrin Inclusion Complexes

4.2.1. Complexation of Flurbiprofen-Cyclodextrin: Complexation Period, pH and Temperature Effect

a) Complexation Period and Cyclodextrin Amount

To determine optimal complexation period and cyclodextrin amount, this experiment were performed as described in section 3.3.4.1.a. Table 4-6 presents the complexation period of two cyclodextrin amounts (5 mM and 15 mM, β-CD and HP-β-CD) for 1 day, 2 days and 3 days.

Table 4-6: The complexation period of two cyclodextrin amounts (5 mM, 15 mM, β-CD and HP-β-CD) for 1 day, 2 days and 3 days (n=3)

	β-CD		HP-β-CD	
Days	**5mM**	**15mM**	**5mM**	**15mM**
	Concentration of Flurbiprofen in Inclusion Complex (µg/mL)			
1	5.08	3.90	13.98	17.45
2	5.31	4.22	14.89	18.47
3	3.97	3.46	12.49	15.80

b) pH and Temperature

To increase solubility of flurbiprofen in the inclusion complexes, pH and temperature were opitimized as described in section 3.3.4.1.b. Table 4-7 presents effect of pH and tempereature on the formation of the inclusion complexes.

Table 4-7: Effect of pH and temperature on the complexation of flurbiprofen with βCD and HPβCD (5 mM, n=3)

	β-CD				HP-β-CD
	pH 1.2	**pH 4.5**	**pH 6.8**	**Pure Water**	**Pure Water**
	Concentration of Flurbiprofen in Inclusion Complex (µg/mL)				
25˚C	2.18	4.12	17.71	1.716	10.89
37˚C	2.61	6.32	19.16	2.316	12.49

4.3. Characterisation of Tablet Powder Blends

The studies were conducted as described in the subsections of Section 3.3.5. The results of the studies are presented in Table 4-8.

Table 4-8: The characteristics of powder blends for ODT formulations (n=3)

Formulation	Angle of repose (θ)	Bulk Density (g/ml)	Tapped Density (g/ml)	Hausner ratio	Carr's Index (%)
F1	31.50 ±0.58	0.488 ±0.010	0.626 ±0.01	1.28±0.04	22.04±2.76
F2	24.92 ±2.08	0.438±0.001	0.489±0.001	1.11±0.001	10.42±2.88
F3	27.37 ±1.08	0.544±0.001	0.605±0.02	1.11±0.04	9.95±3.26
F4	29.15 ±4.30	0.501±0.008	0.681±0.02	1.35±0.05	26.35±2.94
F5	27.88 ±1.40	0.450±0.010	0.563±0.01	1.25±0.02	20.31±0.99
F6	26.45 ±0.64	0.293±0.011	0.402±0.01	1.37±0.03	27.14±1.33
F7	20.46 ±0.28	0.350±0.007	0.460±0.001	1.31±0.02	24.02±1.64

4.4. Characterization of ODT Formulations

4.4.1. Weight Variation

The studies were conducted as described in the Section 3.3.7.1. The weight deviation values of ODTs are presented in Table 4-9.

Table 4-9: The weight deviation values of ODTs (n=20)

Formulation	Weight variation (mg) (Mean±SD)	RSD (%)
F1	155.92±2.62	1.68
F2	133.14±2.94	2.21
F3	137.88±3.37	2.44
F4	161.91±0.99	0.61
F5	142.96±4.22	2.95
F6	89.14±2.23	2.50
F7	115.19±3.91	3.39

SD: Standart deviation, RSD: Relative standart deviation

4.4.2. Thickness and Diameter

The studies were conducted as described in the Section 3.3.7.2. The thickness and diameter values of ODTs are presented in Table 4-10.

Table 4-10: The thickness and diameter values of ODTs (n=20)

Formulation	Thickness (mm) (Mean±SD)	Diameter (mm) (Mean±SD)
F1	2.626±0.012	7.047±0.020
F2	2.421±0.018	7.027±0.009
F3	2.444±0.014	7.059±0.053
F4	2.726±0.070	7.039±0.007
F5	2.655±0.050	7.060±0.011
F6	2.358±0.030	6.995±0.047
F7	2.568±0.020	7.040±0.011

SD: Standart deviation

4.4.3. Hardness

The studies were conducted as described in the Section 3.3.7.3. The hardness values of ODTs are presented in Table 4-11.

Table 4-11: The hardness (n=10) and friability (n=20) values of ODTs

Formulation	Hardness (N) (Mean±SD)	Friability (%)
F1	62.1±8.21	0.72
F2	31.2±8.67	0.92
F3	60.8±8.38	0.34
F4	106.9±14.60	0.11
F5	50.6±15.27	0.49
F6	ND	27.75
F7	18.5±1.26	1.66

SD: Standart deviation, ND: Not determined

4.4.4. Friability

The studies were conducted as described in the Section 3.3.7.4. The friability (%) values of ODTs are presented in Table 4-11.

4.4.5. Wetting Time

The studies were conducted as described in the Section 3.3.7.5. The wetting time values of ODTs are presented in Table 4-12. Moreover, the digital photos of wetted ODTs are depicted in Figure 4-3.

Table 4-12: The wetting time values of ODTs (n=3)

Formulation	Wetting Time (s) (Mean±SD)
F1	18.33±3.21
F2	76.00±12.53
F3	202.00±58.03
F4	52.00±3.00
F5	549.33±71.06
F6	7.11±0.72
F7	126.00±16.97

SD: Standard deviation

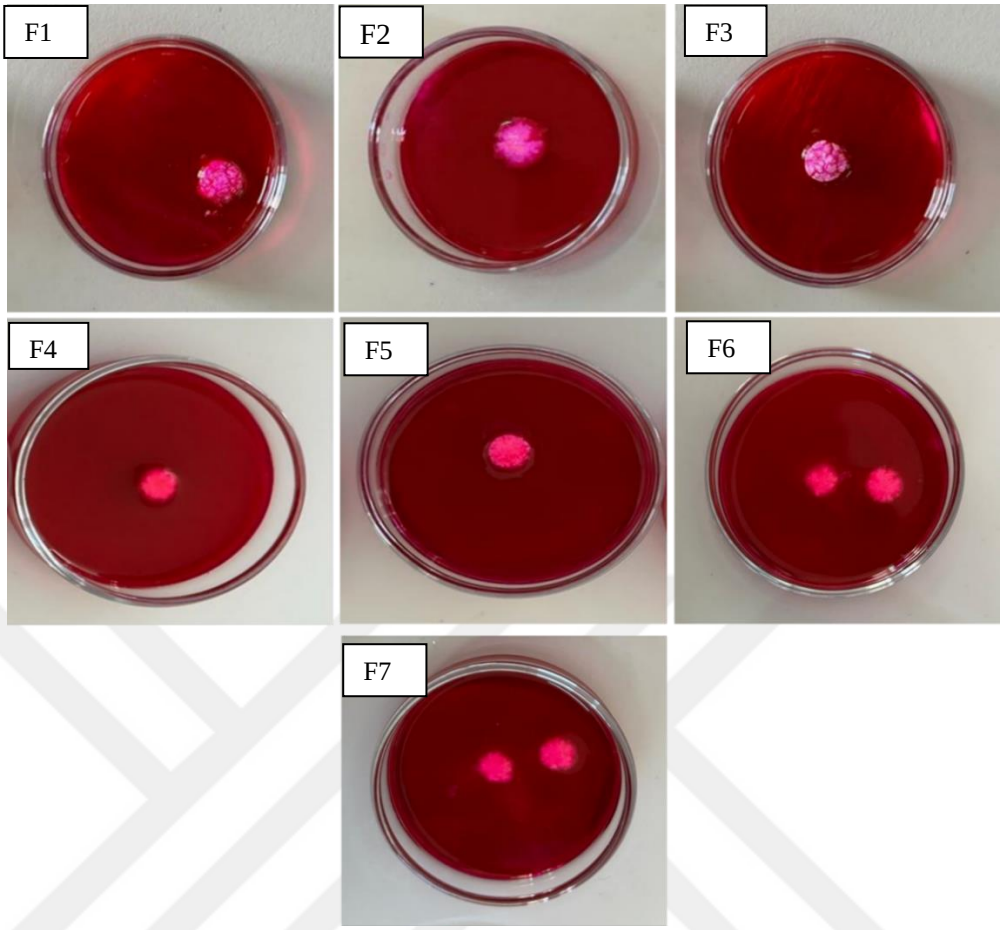


Figure 4-3: The digital photos of wetted ODT.

4.4.6. Content Uniformity

The studies were conducted as described in the Section 3.3.7.6. The content uniformity values of ODTs are presented in Table 4-13.

Table 4-13: The content uniformity values of ODTs (n=10)

Formulation	Content uniformity (%) (Mean±SD)
F1	101.04±3.77
F2	100.59±2.73
F3	98.50±2.89
F4	101.47±0.99
F5	99.28±2.96
F6	100.67±3.75
F7	98.71±2.62

SD: Standard deviation

4.4.7. In vitro Taste-Masking

The studies were conducted as described in the Section 3.3.7.7. The in vitro taste masking values of ODTs are presented in Table 4-14.

Table 4-14: The in vitro taste masking test values of ODTs (n=3)

Formulation	Drug release (%) (Mean±SD)
F1	2.532± 0.071
F2	0.851±0.154
F3	0.147±0.067
F4	1.264±0.480
F5	1.186±0.552
F6	3.255±0.233
F7	3.202±0.189

SD: Standard deviation

4.4.8. Disintegration Time

The studies were conducted as described in the Section 3.3.7.8. The disintegration time values of ODTs are presented in Table 4-15.

Table 4-15: The disintegration time values of ODTs (n=6)

Formulation	Disintegration time (s) (Mean±SD)
F1	36.17±13.18
F2	35.00±9.70
F3	104.00±22.83
F4	183.83±16.24
F5	223.17±18.94
F6	10.67±3.50
F7	19.33±4.23

SD: Standard deviation

4.4.9. In Vitro Dissolution Study

The studies were conducted as described in the Section 3.3.7.9. The dissolution rate results of ODT formulations are presented in Table 4-16-Table 4-23. The dissolution profiles of ODTs are depicted in Figure 4-4 and Figure 4-5.

Table 4-16: The dissolution rate results in F1 formulation.

Time (minutes)	Flurbiprofen release (%)								
	1st tablet	2nd tablet	3rd tablet	4th tablet	5th tablet	6th tablet	Mean	SD	RSD (%)
1	39.6942	33.3965	30.1304	27.2332	37.4426	41.8399	34.9561	5.6812	16.2525
2	62.4905	69.8395	61.8321	54.6584	68.0319	67.5549	64.0679	5.6073	8.7521
4	74.4586	87.4915	80.8432	80.9866	83.6207	86.9169	82.3863	4.8021	5.8288
6	87.2815	89.1499	88.2962	84.8262	84.6207	87.9412	87.0193	1.8789	2.1592
8	87.5665	91.1054	91.6042	88.3914	86.2679	88.7320	88.9446	2.0571	2.3128
10	92.1258	94.8940	94.9416	91.9567	92.7387	89.9422	92.7665	1.9132	2.0623
15	96.97	100.5882	96.0148	94.6992	95.6800	92.1560	96.0180	2.7771	2.8923
20	100.3894	96.6022	98.2202	98.813	100.0919	95.6902	98.3012	1.8729	1.9053
30	99.5346	102.0117	102.0795	104.5723	100.6802	97.8079	101.1144	2.3371	2.3114
45	101.2443	99.4493	100.9768	99.91	98.3271	98.1105	99.6697	1.3060	1.3103

SD: Standard deviation, RSD: Relative standard deviation

Table 4-17: The dissolution rate results in F2 formulation.

Time (minutes)	Flurbiprofen release (%)								
	1st tablet	2nd tablet	3rd tablet	4th tablet	5th tablet	6th tablet	Mean	SD	RSD (%)
1	52.0962	45.8984	38.963	64.1195	46.1454	34.2264	46.9082	10.4757	22.3323
2	88.5925	65.6551	69.7951	76.9897	69.348	67.6594	73.0066	8.5454	11.7050
4	93.9523	85.75298	86.8215	88.1122	90.4384	92.2296	89.5512	3.2025	3.5761
6	99.6154	94.6415	95.8195	94.6618	97.1845	100.4164	97.0565	2.4880	2.5634
8	101.3351	97.9419	98.762	98.5481	99.5754	102.7997	99.8270	1.8707	1.8740
10	101.4846	102.8884	101.9215	102.7245	100.9594	101.5994	101.9296	0.7483	0.7341
15	100.9694	101.6645	100.5461	100.6491	102.4591	99.0048	100.8822	1.1660	1.1558
20	101.5671	100.9411	100.9782	100.9721	100.1928	100.9789	100.9384	0.4372	0.4331
30	100.1389	98.3782	102.1431	99.1254	98.6919	101.0037	99.9135	1.4616	1.4628
45	102.5591	100.2624	99.6823	99.3612	100.1821	102.9412	100.8314	1.5273	1.5147

SD: Standard deviation, RSD: Relative standard deviation

Table 4-18: The dissolution rate results in F3 formulation.

Time (minutes)	Flurbiprofen release (%)								
	1st tablet	2nd tablet	3rd tablet	4th tablet	5th tablet	6th tablet	Mean	SD	RSD (%)
1	13.4125	3.9784	12.7648	12.4631	16.5046	10.6	11.6206	4.2078	36.2100
2	41.2906	27.0112	20.9125	17.4719	31.7021	38.226	29.4357	9.4297	32.0350
4	88.0639	74.5725	61.0475	56.6584	62.4012	72.158	69.1503	11.5189	16.6578
6	97.6664	88.9306	85.4906	78.4614	85.8055	86.5716	87.1544	6.2314	7.1499
8	99.525	97.9044	95.7924	98.7912	94.0122	102.1864	98.0353	2.8725	2.9300
10	100.6478	104.4852	99.6737	99.3805	99.7872	103.9881	101.3271	2.2983	2.2682
15	100.9134	103.0015	100.4916	100.1974	100.1569	102.4859	101.2078	1.2309	1.2162
20	99.5616	100.6416	99.4897	100.99	100.1287	100.9789	100.2984	0.6760	0.6740
30	100.6548	101.4912	100.4971	99.1529	99.6978	101.8915	100.5642	1.0369	1.0311
45	102.6481	101.9431	100.1213	100.1567	101.9748	100.9136	101.2929	1.0518	1.0384

SD: Standard deviation, RSD: Relative standard deviation

Table 4-19: The dissolution rate results in F4 formulation.

Time (minutes)	Flurbiprofen release (%)								
	1st tablet	2nd tablet	3rd tablet	4th tablet	5th tablet	6th tablet	Mean	SD	RSD (%)
1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	-	-	-
2	23.9963	35.3147	37.3203	54.0191	21.67797	26.8805	33.2015	11.9355	35.9488
4	55.1454	65.035	62.7398	66.1388	52.23468	51.6844	58.8297	6.5626	11.1553
6	63.221	83.1002	77.1826	73.0643	64.91859	64.3747	70.9769	8.1276	11.4510
8	70.7199	85.4312	77.7603	77.6497	72.41363	71.2967	75.8786	5.6132	7.3976
10	75.3346	88.345	81.8043	81.6418	78.75559	75.9114	80.2988	4.7976	5.9747
15	77.6419	90.676	83.5375	83.4526	82.21484	81.6797	83.2004	4.2484	5.1062
20	84.5639	91.5498	87.0037	85.7611	86.25063	82.8334	86.3271	2.9453	3.4118
30	88.1592	93.5897	87.5815	84.0297	87.40372	84.5639	87.5546	3.4112	3.8961
45	91.6454	95.338	88.1592	84.6069	90.28643	85.7176	89.2923	3.9772	4.4542

SD: Standard deviation, RSD: Relative standard deviation, n.d: not determined

Table 4-20: The dissolution rate results in F5 formulation.

Time (minutes)	Flurbiprofen release (%)								
	1st tablet	2nd tablet	3rd tablet	4th tablet	5th tablet	6th tablet	Mean	SD	RSD (%)
1	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	-	-	-
2	25.661	24.3173	28.327	25.2128	27.616	37.2673	28.0669	4.7521	16.9313
4	47.2218	45.1812	53.5146	47.3544	47.0841	54.1742	49.0884	3.7744	7.6890
6	68.0758	68.9229	71.0364	61.9965	71.5996	77.5562	69.8646	5.0899	7.2854
8	84.6883	74.6784	84.1778	79.1383	79.8916	85.1104	81.2808	4.1178	5.0661
10	86.1021	78.6354	84.9079	85.2094	85.2994	89.7868	84.9902	3.5994	4.2351
15	87.6416	85.4701	88.9233	86.2808	90.7072	90.5062	88.2549	2.1706	2.4595
20	88.9712	86.1896	89.2883	90.2091	92.5098	90.8659	89.6723	2.1228	2.3673
30	90.697	80.6791	89.6534	94.5591	92.8703	91.2257	89.9474	4.8579	5.4008
45	91.4039	96.9812	94.7639	98.423	94.3124	92.3048	94.6982	2.6766	2.8264

SD: Standard deviation, RSD: Relative standard deviation, n.d: not determined

Table 4-21: The dissolution rate results in F6 formulation.

Time (minutes)	Flurbiprofen release (%)								
	1st tablet	2nd tablet	3rd tablet	4th tablet	5th tablet	6th tablet	Mean	SD	RSD (%)
1	37.8972	33.0416	47.2069	40.6096	43.118	34.9801	39.4756	5.2616	13.3288
2	64.6196	36.825	48.4759	41.8328	60.0016	52.9494	50.7841	10.5961	20.8649
4	71.9075	70.8755	71.318	69.966	83.3788	74.5124	73.6597	5.0027	6.7917
6	80.6161	92.3147	81.47	83.421	91.1712	80.5022	84.9159	5.4028	6.3625
8	90.9781	92.3147	87.815	84.6442	92.4699	86.4919	89.1190	3.2718	3.6713
10	91.342	95.6664	89.084	91.9833	93.7687	88.8878	91.7887	2.6429	2.8793
15	92.5566	97.3592	92.891	94.4296	97.6649	92.4817	94.5638	2.3921	2.5296
20	97.4152	98.6203	95.4291	98.0992	98.9636	93.6796	97.0345	2.0663	2.1294
30	99.8445	99.8815	99.2361	99.6791	100.1512	97.5496	99.3903	0.9510	0.9568
45	101.3471	100.5969	103.9901	102.1597	104.1585	98.4714	101.7873	2.1550	2.1171

Table 4-22: The dissolution rate results in F7 formulation.

Time (minutes)	Flurbiprofen release (%)								
	1st tablet	2nd tablet	3rd tablet	4th tablet	5th tablet	6th tablet	Mean	SD	RSD (%)
1	21.286	20.6171	48.1856	23.4943	33.0868	25	28.6116	10.5828	36.9877
2	50.3572	46.6387	50.6643	51.8666	56.5774	50.4065	51.0851	3.2160	6.2954
4	63.1683	58.6487	67.5193	67.2972	69.0724	69.7155	65.9036	4.2247	6.4104
6	66.6174	67.1557	74.4597	70.7815	72.0712	72.2561	70.5569	3.0838	4.3707
8	69.0811	76.6636	76.4426	73.768	72.571	74.7968	73.8872	2.8253	3.8238
10	72.5302	78.6653	83.3829	80.2389	77.0692	77.6446	78.2552	3.6042	4.6057
15	74.0084	79.1657	84.3744	80.7367	78.0688	80.8943	79.5414	3.4508	4.3384
20	74.5011	80.1597	85.8616	82.23	83.0668	81.9106	81.2883	3.8129	4.6906
30	76.472	82.1682	88.3403	85.2165	85.6421	84.9594	83.7998	4.0920	4.8830
45	78.443	84.1699	89.8275	86.2121	87.0652	86.9919	85.4516	3.8850	4.5464

SD: Standard deviation, RSD: Relative standard deviation, n.d: not determined.

Table 4-23: The comparative dissolution rate results of ODTs

Time (minutes)	Flurbiprofen release (Mean, %)						
	F1	F2	F3	F4	F5	F6	F7
1	34.9561	46.9082	11.6206	n.d.	n.d.	39.4756	28.6116
2	64.0679	73.0066	29.4357	33.2015	28.0669	50.7841	51.0851
4	82.3863	89.5512	69.1503	58.8297	49.0884	73.6597	65.9036
6	87.0193	97.0565	87.1544	70.9769	69.8646	84.9159	70.5569
8	88.9446	99.8270	98.0353	75.8786	81.2808	89.1190	73.8872
10	92.7665	101.9296	101.3271	80.2988	84.9902	91.7887	78.2552
15	96.0180	100.8822	101.2078	83.2004	88.2549	94.5638	79.5414
20	98.3012	100.9384	100.2984	86.3271	89.6723	97.0345	81.2883
30	101.1144	99.9135	100.5642	87.5546	89.9474	99.3903	83.7998
45	99.6697	100.8314	101.2929	89.2923	94.6982	101.7873	85.4516

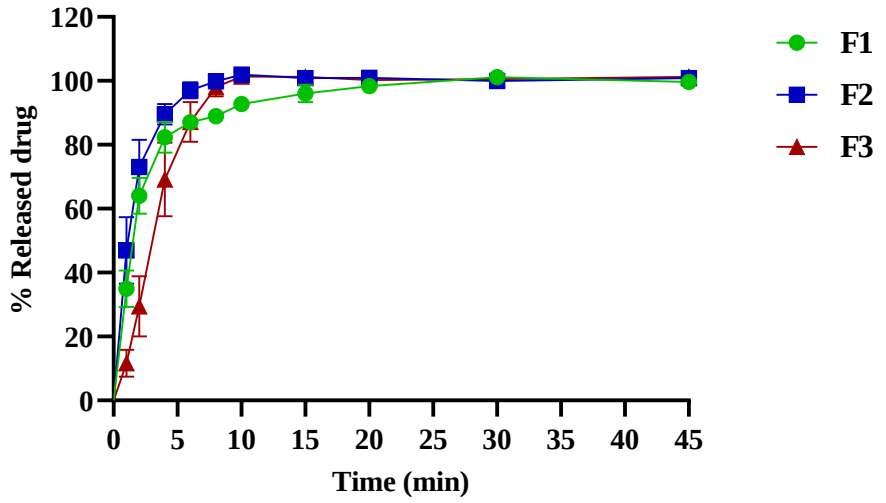


Figure 4-4: The dissolution profiles of F1, F2 and F3 formulations

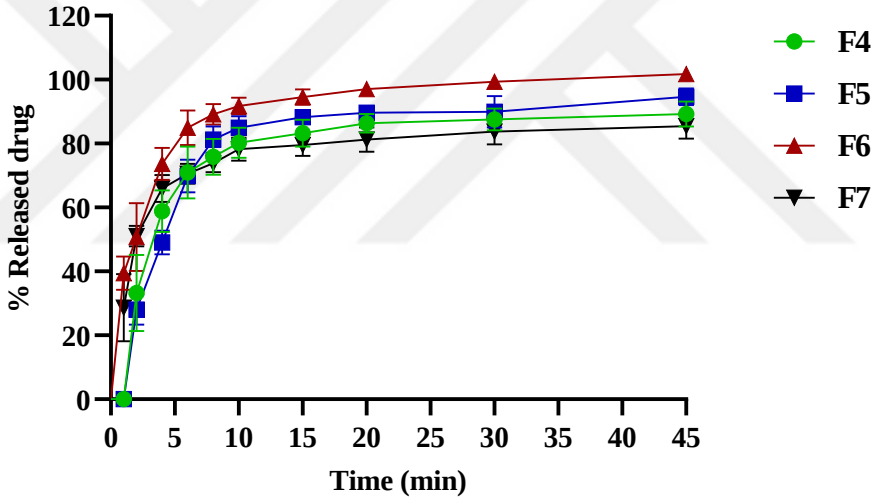


Figure 4-5: The dissolution profiles of F4, F5, F6 and F7 formulations

5. DISCUSSION

Oral drug administration is one of the most common methods of taking the drug among individuals. However, approximately 50% of people who take the drugs orally report difficulties in swallowing conventional dosage forms when they cannot find water, are immobile, or are experiencing conditions such as allergies, colds, or bronchitis accompanied by coughing fits. Furthermore, certain patient profiles, including pediatric, geriatric, disabled, psychiatric, and bedridden patients, may struggle to swallow traditional tablets and capsules. As a result, they may have difficulty adhering to treatment regimens and may receive ineffective or incomplete treatment. In recent years, various dosage forms designed for oral administration have been developed to address these issues. One of the dosage forms frequently studied in research is oral disintegrating tablets (ODTs). ODTs do not require water or chewing to be swallowed and rapidly disintegrate in the mouth. These tablets aim to improve patient compliance by making it easier for patients to take their medication. This, in turn, enhances the effectiveness and bioavailability of the drug (Kaur, Bala, Kanojia, Nagpal, & Dhingra, 2014) (Solanki & Dahima, 2011). This innovative dosage form offers many advantages over traditional dosage forms, and can be manufactured using either conventional or patented techniques. Additionally, taste-masking is an essential step toward improving oral disintegrating tablets (Pandey & Dahiya, 2016). Cyclodextrin (CD) complexation is one of the various techniques to mask bitter taste without altering their inherent lipophilicity or pharmacological capabilities in ODTs (Pandey & Dahiya, 2016).

In the present study, different formulations of oral disintegrating tablets containing flurbiprofen, as model drug, were studied by using different methods (direct compression and wet granulation,), and different excipients (Ludipress, co-processed superdisintegrant, cyclodextrin, sodium starch glycolate, and crospovidone). The characteristics of powder (angle of repose, Hausner ratio, and compressibility index), and quality attributes of the tablets (weight variation, diameter, thickness, hardness, friability, content uniformity, wetting time, in vitro dissolution, and disintegration time, in addition to taste masking feature) have been tested, and the results were compared to examine effect on quality attributes and taste-masking of different excipients and methods.

Before initiating formulation studies, the UV spectrum of flurbiprofen was obtained. It serves to determine whether the substance maintains its stability during the

formulation production process and subsequent testing. Additionally, it gives information its purity. The wavelength at which the maximum absorbance of flurbiprofen was observed is 247 nm, in accordance with the reported monograph (Yilmaz & Alkan, 2015) (Figure 4-1). This value has played a crucial role in numerous quantitative determination studies of the active compound, highlighting its importance.

UV-spectrophotometric method was employed for the quantification analysis of flurbiprofen, and the validation studies were performed to demonstrate the suitability and reliability of the analytical method. These validation studies were conducted in accordance with the guidelines outlined by the International Conference on Harmonisation (ICH) Q2(R1) (CPMP/ICH/381/95) recommended by the European Medicines Agency (EMA). Within this framework, parameters such as linearity, accuracy, precision, stability, and selectivity were evaluated (ICH Q 2 (R1) (CPMP/ICH/381/95), 1995).

The high determination coefficient (r^2, 0.9991) was obtained through the calibration curve in the linearity study (Figure 4-2), and the % RSD values at each concentration point being less than 2% (Table 4-1) confirmed the establishment of analytical method linearity in the concentration range of 1 µg/ml and 10 µg/ml. The limit of detection (LOD) of 0.0312 µg/mL and the limit of quantification (LOQ) of 0.0948 µg/mL were determined using three calibration curves' slopes.

There was no λ_{max} (247 nm) deviation for cyclodextrins, and other tablet excipients in the flurbiprofen spectra in mixture of ethanol and phosphate buffer solution (pH 6.8, PBS), indicating good specificity of the analytical method.

The accuracy parameter demonstrates the closeness of the results obtained from the analytical method to the true values. The accuracy results for three different concentrations (1, 5 and 10 µg /ml) were in the range of 99.505% to 101.374%, which enabled the validation requirements (Table 4-2).

The precision study was conducted under two subheadings. The first study was the repeatability (intra-day precision) study, where three series of the API solutions' at the predetermined concentrations (1, 5 and 10 µg /ml) were measured within the same day to assess intra-assay precision. The second study, which was the intermediate precision (inter-day) study, was conducted on different days. In both studies, the % RSD

values were less than 2% (Table 4-3, Table 4-4). Based on the results of the precision studies, the analytical method's precision was deemed satisfactory.

In the stability studies of flurbiprofen, the prepared solution was stored at room temperature (25°C) for up to 3 days. The percentage change values in the concentrations of the solution were found to be less than 2% (Table 4-5). Thus, it was observed that the prepared flubiprofen solution remained stable at room temperature for 72 hours.

Conclusionly, the data of validation studies have demonstrated that the UV spectrophotometric method used for the quantification of flurbiprofen. It has been determined that the analytical method is suitable for use in the tests.

To determine optimal conditions for the formation of Flurbiprofen-Cyclodextrin inclusion complexes, β-CD and HP-β-CD were investigated individullay at two different concantrations (5 mM and 15 mM) over a span of three days (1, 2 and 3 days). The results revealed that, for both cyclodextrin concentrations and types, a 2-day complexation period yielded the highest concentration of flurbiprofen within the inclusion complexes (Table 4-6). In subsequent studies, 5 mM concentration of cyclodextrin was selected due to its lighter total mass, a crucial factor in tablet manufacturing. Similarly, pure water was chosen for complexation due to the same consideration, despite phosphate buffer solution (PBS, pH: 6.8) resulting in a higher flurbiprofen concentration within the inclusion complexes (Table 4-7). Furthermore, the temperature of 37°C was significantly found to be more suitable for complexation than 25°C ($p<0.05$), as previously reported in the literature (Cirri, Rangoni, Maestrelli, Corti, & Mura, 2008).

The Flurbiprofen-Cyclodextrin inclusion complexes, which were produced through a 2-day complexation process at the temperature of 37°C using pure water and 5 mM cyclodextrin concentration, were identified as the optimal samples.

The characteristics of the powder blends in the formulations were evaluated through various parameters including angle of repose, bulk density, tapped density, compressibility index, and Hausner ratio, with the results presented in Table 4-8. The angle of repose ranged from 20.46±0.28 to 31.50 ±0.58, indicating for excellent to good flow properties according to (Vemula & Veerareddy, 2011). The bulk density values fell within the range of 0.293±0.011 to 0.544±0.001, while the tapped density ranged from 0.402±0.01 to 0.681±0.02. The compressibility indexes for all formulations ranged from

9.95 to 27.14. The Hausner ratio values spanned from 1.11±0.15 to 1.37±0.03. Assessment based on the Hausner ratio and Carr index (%) derived from bulk and tapped densities revealed the flowability that ranged from excellent to poor.

The formulations produced using the wet granulation method (F2 and F3) significantly displayed excellent compressibility and flowability characteristics compared to those prepared using the direct compression method ($p < 0.05$). These comprehensive results indicated generally acceptable compression levels for the powder blends for excluding F4 and F6. Therefore, it can be concluded that β-CD may negatively impact the compressibility and tabletability of the powder blends. Similarly, the data in line with our findings were reported by Khirwadkar et al. (Khirwadkar & Dashora, 2015).

The tablets generated from each formulation underwent evaluation for parameters such as weight variation, thickness and diameter, hardness, friability, wetting time, content uniformity, disintegration time, taste masking, and in vitro dissolution.

According to the United State Pharmacopeia (USP 44-NF 39, 2021), the weight variation test is considered successful if no more than 2 tablet weights deviate from the average weight by more than 7.5%. All tablet formulations passed the weight uniformity test, as the average percent deviation for all formulations was found to be below the specified limit (Table 4-9). Furthermore, it should be noted that there was variability in the tablet weights among all formulations, despite the manufacturing parameters being identical. This could be attributed to the flowability and bulk density characteristics of the powder blends (Table 4-8).

In the determination of thickness and diameter, the average values ranged from 2.358±0.030 to 2.726±0.070 mm and 6.995±0.047 to 7.060±0.011 mm, respectively (Table 4-10). The slight variations in diameter and thickness among the tablets can be attributed to the use of different types, quantities of excipients in the formulations and the manufacturing method. These obtained values indicate that the tablets exhibit good homogeneity, suitable for use in the tests.

As ODTs are expected to disintegrate rapidly, their hardness is ideally lower compared to conventional tablets. Tablet hardness is an indicator of the physical strength of ODTs and should be in the range of 30–80 N. Ideally, the hardness of ODTs should be at least 25 N. The hardness can influence disintegration rate and can also affect friability.

Therefore, prepared ODTs are expected to have the desired disintegration rate while also meeting appropriate hardness and friability values (Akdag, et al., 2020). In the produced tablets, the lowest hardness value was 18.5±1.26 N, observed in formulation F7, while the highest hardness value was 106.9±14.60 N, associated with formulation F4 (Table 4-11). The hardness values of the F1, F2, F3, and F5 formulation comply with the desired standards for ADTs, whereas those of F4, F6, and F7 are not suitable. It should be noted that the tableting strength was intentionally kept constant to compare the formulations containing cyclodextrin with the formulations that did not. The lower hardness observed in formulations F6 and F7 can be attributed to the porous structure of Flurbiprofen-Cyclodextrin inclusion complexes resulting from lyophilization, a phenomenon previously reported by Akdağ et al. (Akdag, et al., 2020).

All formulations exhibited the friability values below 1%, in compliance with pharmacopeial guidelines (USP 44 - NF 39 , 2021), except for F6 and F7, which were produced by Flurbiprofen-Cyclodextrin inclusion complexes (Table 4-11). The increased porosity of the tablets in F6 and F7 may account for the friable nature of these formulations.

The wetting time serves as a critical indicator of the effectiveness of a superdisintegrant in preventing excessive swelling when exposed to water (Vemula & Veerareddy, 2011). The wetting time data, ranging from 7.11±0.72 sec to 549.33±71.06 sec, are presented in Table 4-12. The wetting time can be affected by both the type of superdisintegrant and the manufacturing method of ODTs. Notably, despite F1 and F3 formulations having similar compositions, they exhibited significantly different wetting times, with values of 18.33±3.21 sec and 202.00±58.03 sec, respectively ($p<0.05$). Furthermore, F2 (76.00±12.53 sec) and F3 (202.00±58.03 sec) formulations exhibited significant differences in wetting time values despite employing different superdisintegrant types (sodium starch glyconate and Crospovidone) within the same manufacturing method, which was wet granulation. ($p<0.05$) Additionally, the presence of cyclodextrin and the type of cyclodextrin in the formulation might also affect the wetting time. In this study, the inclusion of β-CD in the formulation had significantly impact with shorter time on wetting time compared to HP-β-CD (Table 4-12).

In the determination of content uniformity (%), the average content of flubiprofen ranged between 98.50±2.89 % and 101.47±0.99 % (Table 4-13). The uniformity of

content in the tablets was found to be appropriate, as also described in pharmacopeial limits (USP 44-NF 39, 2021).

The results of taste masking are presented in Table 4-14 and vary from 0.147±0.067 s to 3.255±0.233 s. The formulations prepared through wet granulation method (F2 and F3) exhibited lower flurbiprofen concentration within 60 seconds, yielding favorable results. However, contrary to expectations, the presence of cyclodextrin in the formulation (either in free or inclusion complex form) resulted in an increased release of flurbiprofen concentration within 60 seconds. This effect can be attributed to the improved solubility of flurbiprofen when complexed with cyclodextrins and/or presence of the formulation, as previously described in the literature (Khan, Iqbal, Ibrahim, Nasir, & Ullah, 2015).

ODTs need to possess sufficient hardness to maintain physical stability during storage and transportation. However, they should also exhibit a degree of friability to dissolve or disperse into small pieces, ensuring comfortable swallowing for the patient. The determination of disintegration is among the most critical parameters in the development of ODTs, as these tablets are expected to rapidly disintegrate upon placement in the mouth. According to the European Pharmacopoeia (EP 8.0) (European Pharmacopoeia, 2019), the disintegration time for ODTs should be less than 3 minutes. Ideally, ODTs should disintegrate within 60 seconds (Akdag, et al., 2020). In the study, the acceptance limit was met by all formulations except for F4 and F5. Based on these data, it could be concluded that the physical presence of cyclodextrin in the formulation tended to increase disintegration time, whereas its inclusion complexes was not. Additionally, the type of superdisintegrant used and the presence of cyclodextrin in the formulation were observed to influence disintegration time, as evidenced by the differences between crospovidone (F3) and sodium starch glyconate (F2), as well as β-CD (F4) and HP-β-CD (F5) formulations (Table 4-15).

The dissolution studies were performed with phosphate buffer solution (pH=6.8), maintaining sink condition. In these studies, formulations without cyclodextrin (F1, F2, and F3) exhibited the dissolution of more than 85% of flurbiprofen within 6 minutes (Table 4-23). In the contrast, formulations containing cyclodextrin (whether in free or inclusion complex form) extended the dissolution time, reaching up to 15 minutes for F5 and 45 minutes for F7. (Khirwadkar & Dashora, 2015) revealed that the cyclodextrin

inclusion complexes contributed to slower dissolution of ODTs. However, in the case of F6, this phenomenon was not considered as its hardness was out of the acceptance limit, which resulted in more rapid dissolution.

Conclusionly, it has been observed that the manufacturing method and the excipients used significantly impact the quality characteristics and taste masking of ODTs, which compressed with the same parameters.

REFERENCES

Abdel-Aziz, A. A.-M., Al-Badr, A. A., & Hafez, G. A. (2012). Flurbiprofen, Comprehensive Profile. In *Profiles of Drug Substances, Excipients and Related Methodology* (pp. 81-11). Riyadh, Kingdom of Saudi Arabia: Elsevier.

Adeoye, O., & Alebiowu, G. (2014). The study evaluated two novel coprocessed excipients (with two methods) as disintegrants in an orally disintegrating paracetamol tablet formulation. *Acta Poloniae Pharmaceutica-Drug Research*, 71 (5): 803-811.

Ahad, A., Bin Jardan , Y., Raish, M., Al-Mohizea, A., & Al-Jenoobi, F. (2022). Hydroxypropyl-β-Cyclodextrin for delivery of sinapic acid via inclusion Complex prepared by solvent evaporation method. *Processes*, 10: 2046.

Akdag, Y., Gulsun, T., Izat, N., Cetin, M., Oner, L., & Sahin, S. (2020). Evaluation of preparation methods for orally disintegrating tablets. *Medicine Science International Medical Journal*, 9(1): 265-269.

Akdag, Y., Gulsun, T., Izat, N., Cetin, M., Oner, L., & Sahin , S. (2020). Characterization and comparison of deferasirox fast disintegrating tablets prepared by direct compression and lyophilization methods. *Journal of Drug Delivery Science and Technology*, 57:101760.

Akhlaq, M., Khan, G. M., Abdul Wahab, Hussain, A., Nawaz, A., & Abdelkader, H. (2011). A simple high-performance liquid chromatographic practical approach for determination of flurbiprofen. *Journal of Advanced Pharmaceutical Technology & Research*, 2(3): 151–155.

Aktepe, E., Özkorumak, E., & Kandil, S. (2007). Lithium interaction with flurbiprophen: A Case report. *Bulletin of Clinical Psychopharmacology*, 17: 83-86.

Alebiowu, G. & Adeagbo, A.A. (2009). Disintegrant properties of a paracetamol tablet formulation lubricated with co - processed lubricants. *Farmacia*, 57(4): 500-510.

Alkan, E. & Yilmaz, B. (2014). Determination of flurbiprofen in pharmaceutical preparations by first-order derivative spectrophotometry method. *International Journal of Pharmacognosy*, 7: 130-137.

Allahham, N., Fina, F., Marcuta, C., Kraschew, L., Mohr, W., Gaisford, S., Goyanes, A. (2020). Selective laser sintering 3D printing of orally disintegrating printlets containing ondansetron. *Pharmaceutics*, 12(2): 110.

Apeji, Y. E., Olayemi, O. J., Anyebe, S. N., Oparaeche, C., Orugun, O. A., Olowosulu, A. K., & Oyi, A. R. (2019). Impact of binder as a formulation variable on the material and tableting properties of developed co-processed excipients, *SN Applied Sciences*, 1: Article number 561.

Arvapalli, S., Swamy, D., & Shyamala. (2019). Oral disintegration tablets – An updated review. *Indo American Journal of Pharmaceutical Sciences*, 6(3): 6926-6934.

Badgujar, B.P. & Mundada, A.S. (2011). The technologies used for developing orally disintegrating tablets: A review. *Acta Pharm*, 61(2): 117-139.

Bhaskar, R., Ola, M., Patel, R., & Chalikwar, D. (2019). Cyclodextrin in drug delivery application: A Review. *Journal of Drug Discovery and Therapeutics*, 7(4): 01-10.

Brniak, W., Maślak, E., & Jachowicz, R. (2015). Orodispersible films and tablets with prednisolone microparticles. *European Journal of Pharmaceutical Sciences*, 75(30): 81-90.

Bülbül, E. Ö., Eleftheriadou, K., Okur, N. Ü. & Siafaka, P. (2020). An update on cyclodextrins as drug vehicles for antimicrobial applications. *Journal of Pharmaceutical Technology*, 1(1): 18-24.

CD Formulation. (n.d.). Retrieved from https://www.formulationbio.com/products/diluent-excipients.html

Chen, Y., Feng, T., Li, Y., Du, B., & Weng, W. (2017). Formulation and evaluation of a montelukast sodium orally disintegrating tablet with a similar dissolution profile as the marketed product. *Pharmaceutical Development and Technology*, 22(2): 168-172.

Chinwala, M. (2020). Recent formulation advances and therapeutic usefulness of orally disintegrating tablets (ODTs). *Pharmacy (Basel)*, 8(4): 186.

Cho, C.H., Min, J.H., Hwang, K.M., & Park, E.S. (2018). Development of sustained-release microparticles containing tamsulosin HCl for orally disintegrating tablet using melt-adsorption method. *Drug Delivery and Translational Research*, 8: 552–564.

Cirri, M., Rangoni, C., Maestrelli, F., Corti, G., & Mura, P. (2008). Development of fast-dissolving tablets of flurbiprofen-cyclodextrin complexes. *Drug Development and Industrial Pharmacy*, 31(7): 697-707.

Comoglua , T., & Ozyilmaza, E. D. (2019). Orally disintegrating tablets and orally disintegrating mini tablets – Novel dosage forms for pediatric use. *Pharmaceutical Development and Technology*, 24(7): 902–914.

Conceição, J., Adeoye, O., Cabral-Marques, H., Concheiro, A., Alvarez-Lorenzo, C., & Lobo, J. (2020). Orodispersible carbamazepine/Hydroxypropyl-β-Cyclodextrin tablets obtained by direct compression with five-in-one co-processed excipients. *AAPS PharmSciTech*, 21(2):39.

Conway, B. R. (2008). Solid dosage forms. In S. C. Gad, *Pharmaceutical manufacturing handbook: production and processes (Vol. 5)* (pp. 235-265). Canada: John Wiley & Sons.

Czyrski, A. (2019). Determination of the lipophilicity of ibuprofen, naproxen, ketoprofen, and flurbiprofen with thin-layer chromatography. *Journal of Chemistry,* 3407091.

Dang, Y., Tran, P., & Tran, T. (2020). Development of the modified ocimum gratissimum seeds for orally disintegrating tablets. *Recent Patents on Drug Delivery & Formulation*, 14(1): 40–47.

Davies, N. (1995). Clinical pharmacokinetics of flurbiprofen and its enantiomers. *Clin Pharmacokinet*, 28(2):100-114.

Dawadi, S., Pandey, B., Nepal, S., Gurau, Y., Shahi, R., Gautam, B., Mahat, C. A. (2020). Formulation and evaluation of orally disintegrating tablet of metoclopramide hydrochloride. *World Journal of CurrentMedicaland*, 322–329.

Dehghani, H., Taheri, A., & Homay, A. (2017). Design, optimization and evaluation of orally disintegrating tablet of meloxicam using its menthol based solid dispersions. *Current Drug Delivery*, 14(5): 709-717.

Devi, N. D., Rani, A., Kumar, K., Kaushik, J., & Sowjanya, V. (2010). Cyclodextrins in pharmacy- An overview. *Pharmacophore*, 1(3): 155-165.

Doile, M.M., et. al. (2008). Physicochemical properties and dissolution studies of dexamethasone acetate-β-cyclodextrin inclusion complexes produced by different methods. *AAPS PharmSciTech.*, 9(1): 314–321.

European Pharmacopoeia. (2019). In *European Pharmacopoeia* (pp. 937-939). France: European Directorate for the Quality of Medicines & Health Care of the Council of Europe (EDQM).

Faldu, B., & Zalavadiya, B. (2012). Lubricants: Fundamentals of tablet manufacturing. *International Journal of Research in Pharmacy And Chemistry*, 2(4): 921-925.

Fatima, N., Khalid, S., Liaqat, K., Zulfiqar, A., & Mcekr, R. (2023). Beta-Cyclodextrin: A Cyclodextrin derivative and its various applications. *Polymer Science*, 4(5): *On the print.*

Ferreira, L., Campos, J., Veig, F., Cardoso, C., & Paiva-Santos, A. (2022). Cyclodextrin-based delivery systems in parenteral formulations: A critical update review. *European Journal of Pharmaceutics and Biopharmaceutics*, 178: 35–52.

Food and Drug Administration. (2008, December). Retrieved from Guidance for industry: orally disintegrating tablets: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/orally-disintegrating-tablets

Gad, S. C. (2008). *Pharmaceutical manufacturing handbook: production and processes.* Canada: John Wiley & Sons.

Gandhimathi, R., Vijayaraj, S., & Jyothirmaie, M. (2012). Analytical process of drugs by ultraviolet (uv) spectroscopy-A review. *International Journal of Pharmaceutical Research & Analysis*, 2(2): 72-78.

Ghosh, T., Ghosh, A., & Prasad, D. (2011). A review on new generation orodispersible tablets and its future prospective. *International Journal of Pharmacy and Pharmaceutical Sciences*, 3(1): 1-7.

Ghourichay, M. P., Kiaie, S., Nokhodchi, A., & Javadzadeh, Y. (2021). Formulation and quality control of orally disintegrating tablets (ODTs): Recent Advances and Perspectives. *BioMed Research International*, 6618934.

Greenblatt, D., Lisa , L., Moltke, v., Perloff, E. S., Luo, Y., Harmatz, J. S., & Zinny, M. A. (2006). Interaction of flurbiprofen with cranberryjuice, grape juice, tea, and fluconazole: In vitro and clinical studies. *Clinical Pharmacology and Therapeutics*, 79(1): 125–133.

Haley, R., Gottardi, R., Langer, R., & Mitchell, M. (2020). Cyclodextrins in drug delivery: Applications in gene and combination therapy. *Drug delivery and translational research*, 10: 661-677.

Hanif, M., Nazer, N., Chaurasiya, V., & Zia, U. (2016). Simultaneous determination of famotidine and flurbiprofen by high performance liquid chromatography. *Tropical Journal of Pharmaceutical Research*, 15(3): 605-611.

Hanif, M., Nazir, N., Chudhary, B. A., Abbas, G., Rana, S. J., & Zaman, M. (2015). Development of high performance liquid chomatography method for

determination of flurbiprofen and ranitidine in bilayer tablets. *Latin American Journal of Pharmacy*, 34(9): 1737-1742.

Higashi, K., Ideura, S., Waraya,, H., Limwikrant, W., Moribe, K., & Yamamoto, K. (2010). Simultaneous dissolution of naproxen and flurbiprofen from a novel ternary γ-cyclodextrin complex. *Chemical and Pharmaceutical Bulletin*, 58(5): 769-772.

Hutzler, J., Frye, R., Korzekwa, K., Branch, R., Huang, S., & Tracy, T. (2001). Minimal in vivo activation of CYP2C9-mediated flurbiprofen metabolism by dapsone. *European Journal of Pharmaceutical Sciences*, 14(1): 47–52.

Hyma, P., & Kaveri, A. (2022). Formulation and evaluation of orodispersible tablets of aceclofenac by direct compression method. *Journal of Advanced Scientific Research*, 13(2): 142-148.

ICH Q 2 (R1) (CPMP/ICH/381/95). (1995, June). Retrieved from Validation of analytical prrocedures: definitions and methodology: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-2-r1-validation-analytical-procedures-text-methodology-step-5_en.pdf

Ikeuchi-Takahashi, Y., Ito, S., Itokawa, A., Ota, M., Onuki, Y., Hidaka, S., & Onishi, H. (2020). Preparation and evaluation of orally disintegrating tablets containing taste masked microparticles of acetaminophen. *Pharmazie*, 75(1): 2-6.

Ishii, Y., Sakai, Y., Masumoto, S., Inoue, M., Fujii, T., & Kobayasbi, H. (2008). Absorption, distribution, excretion and anti-inflammatory effects of flurbiprofen in animals after rectal administration. *Current Medical Research and Opinion*, 3(4): 31-38.

Jang, D.-J., Bae, S. K., & Oh, E. (October 2014). Coated dextrin microcapsules of amlodipine incorporable into orally disintegrating tablets for geriatric patients. *Biomedicine & Pharmacotherapy*, 68(8): 1117-1124.

Jassem, N. A. (2022). Orodispersible tablets: A review on recent trends in drug delivery. *International Journal of Drug Delivery Technology*, 12(1): 432-436.

Kaid, N. (2021). *Studies on cyclodextrin complexation of a poorly water soluble anti-hyperlipidemic drug, tablet formulation and characterization.* Istanbul: T.C. Yeditepe University.

Kaur, L., Bala, R., Kanojia, N., Nagpal, M., & Dhingra, G. A. (2014). Formulation development and optimization of fast dissolving tablets of aceclofenac using natural superdisintegrant. *International Scholarly Research Notices*, 242504.

Khan, A., Iqbal, Z., Ibrahim, M., Nasir, F., & Ullah, Z. (2015). Prediction of the effect of taste masking on disintegration behavior, mechanical strength and rheological characteristics of highly water soluble drug (itopride HCl); An application of SeDeM-ODT expert system. *Powder Technology*, 284: 411-417.

Khirwadkar, P., & Dashora, K. (2015). Flurbiprofen β-cyclodextrin formulations: an improved method for fast dissolving tablet. *Indian Journal of Research in Pharmacy and Biotechnology*, 3(5): 2320 – 2347.

Kirimlioğlu, G. Y. (2020). Host-guest inclusion complex of desloratadine with 2-(hydroxy)propyl-β-cyclodextrin. *Journal of Research in Pharmacy*, 24(5): 693-707.

Kumar, A., K.Ashok, Brahmaiah, B., Nama, S., & Baburao, C. (2013). the cyclodextrins: a review. *International Journal of Pharmaceutical Research and Bio-Science*, 2(2): 291-304.

Lai, F., Pini, E., Corrias , F., Perricci, J., Manconi , M., Fadda , A. M., & Sinico, C. (2014). Formulation strategy and evaluation of nanocrystal piroxicam orally disintegrating tablets manufacturing by freeze-drying. *International Journal of Pharmaceutics*, 467(1–2): 27-33.

Lasure, A., Ansarı, A., & Kalshettı, M. (2020). UV spectrophotometric analysis and validation of acyclovir in solid dosage form. *International Journal of Current Pharmaceutical Research*, 12(2): 100-103.

Li, J., & Wu, Y. (2014). Lubricants in pharmaceutical solid dosage forms. *Lubricants*, 2(1): 21-43.

Loftsson, T., Jarho, P., & Järvinen, T. (2005). Cyclodextrins in drug delivery. *Expert opinion on drug delivery*, 2(2): 335-351.

Ludipress® LCE. (2017). Retrieved from BASF Pharma: https://pharma.basf.com/products/ludipress-lce

Maroof, K., Zafar, F., Ali, H., & Naveed, S. (2015). Flurbiprofen: A Potent Pain Reliever. *Journal of Bioequivalence & Bioavailability*, 7(1): 56-58.

Mayur, A.C. & Senthilkumaran, K., (2012). Cyclodextrin in drug delivery: A review. *Research and Reviews: Journal of Pharmacy and Pharmaceutical Sciences*, 1(1): 19-29.

Mustarichie, R., Gozali, D., & Priambodo, D. (2020). Dissolution profile of ambroxol hcl tablet with additional variations of ludipress® and lactose using the direct press method. *International Journal of Applied Pharmaceutics*, 12(3): 62-66.

Nagar, P., Singh, K., Chauhan, I., Verma, M., Yasir, M., Khan, A., Gupta, N. (2011). Orally disintegrating tablets : formulation, preparation techniques and evaluation. *Journal of Applied Pharmaceutical Science*, 1(4): 35-45.

Nandhini, J., & Rajalakshmi, A. N. (2018). Dispersible tablets: A review. *Journal of Pharmaceutical Advanced Research*, 1(3): 148-155.

Nayak, A., & Manna, K. (2011). Current developments in orally disintegrating tablet technology. *Journal of Pharmacetical Education Research*, 2(1): 21-34.

Nikam, V. K., Shete, S. K., & Khapare, J. P. (2020). Most promising solid dispersion technique of oral dispersible tablet. *Beni-Suef University Journal of Basic and Applied Sciences*, 9: Article number 62.

Okuda, Y., Okamoto, Y., Irisawa, Y., Okimoto, K., Osawa, T., & Yamashita, S. (2014). Formulation design for orally disintegrating tablets containing enteric-coated particles. *Chemical and Pharmaceutical Bulletin*, 62(5): 407-414.

Pahwa , R., & Gupta, N. (2011). Superdisintegrants in the development of orally disintegrating tablets: A review. *International Journal of Pharmaceutical Sciences and Research*, 2(11): 2767-2780.

Pandey, P., & Dahiya, M. (2016). Oral disintegrating tablets: A review. *International Journal of Pharma Research & Review*, 5(1): 50-62.

Parkash, V., Maan, S., Deepika, Yadav, S. K., Hemlata, & Jogpal, V. (2011). Fast disintegrating tablets: Opportunity in drug delivery system. *Journal of Advanced Pharmaceutical Technology & Research*, 2(4): 223–235.

Pavankumar, K., Krishna, T. S., Madhusudhan, C., Srikanth, K., Reddy, S., & Shivaram, C. (2021). Formulation and Evaluation of Taste masking Lornoxicam oral disintegrating tablets. *International Journal of Pharmaceutical Sciences Review and Research*, 58(2): 157-162.

Poulson, B. G., Alsulami, Q. A., Sharfalddin, A., El Agammy, E. F., Mouffouk, F., Emwas, A.-H., & Jaremko, L. (2022). Cyclodextrins: Structural, Chemical, and Physical Properties, and Applications. *Polysaccharides*, 3: 1–31.

Preis, M., Grother, L., Axe, P., & Breitkreutz, J. (2015). In-vitro and in-vivo evaluation of taste-masked cetirizine hydrochloride formulated in oral lyophilisates. *International Journal of Pharmaceutics*, 491(1–2): 8-16.

Rahangdale, K., Dongaewar, A., Neware, P., Gondane, A., Barbate, A., Humane, A., Damahe, A. (2020). Formulation, evaluation and validation of orally disintegrating rizatriptan benzoate tablet. *International Journal of Creative Research Thoughts (IJCRT)*, 23202882.

Rapolu, K., Aatipamula, V., Reddy, K. J., & Voruganti, S. (2012). Cyclodextrins: nanocarriers for novel drug delivery. *International Journal of Pharmaceutics*, 2(1): 109-116.

Rowe, R., Sheskey, P., & Quinn, M. (2009). *Handbook of Pharmaceutical Excipients.* USA: Pharmaceutical Press.

Sajeev, C., Jadhav, P. R., RaviShankar, D., & Saha, R. (2002). Determination of flurbiprofen in pharmaceutical formulations by UV spectrophotometry and liquid chromatography. *Analytica Chimica Acta*, 463(2): 207-217.

Shaheen, N., & Zaman, S. (2018). Development of fast dissolving tablets of flurbiprofen by sublimation method and its in vitro evaluation. *Brazilian Journal of Pharmaceutical Sciences*, 54(4).

Singh, H., Kaur, L., Singh, G., & Dhawan, R. (2021). Orodispersible tablets: A new trend in drug delivery. *International Journal of Pharmaceutical Sciences Review and Research*, 69(1): 127-131.

Singh, S., & Verma, N. (2016). Taste masked orodispersible tablets: a highly patient complaint dosage form. *Asian Journal of Pharmaceutical and Clinical Research*, 9(3): 1-7.

Sohi, H., Sultana, Y., & Khar, R. (2004). Taste masking technologies in oral pharmaceuticals: Recent developments and approaches. *Drug Development and Industrial Pharmacy*, 30(5): 429–448.

Solanki , S. S., & Dahima, R. (2011). Formulation and evaluation of aceclofenac mouth-dissolving tablet. *Journal of Advanced Pharmaceutical Technology & Research*, 2(2): 128–131.

Stark, J. G., Engelking, D., McMahen, R., & Sikes, C. (2017). Pharmacokinetics of a novel amphetamine extended-release orally disintegrating tablet in children with attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology*, 27(3): 216–222.

Stricker, B., & Delhez, J. (1982). Interactions between flurbiprofen and coumarins. *British medical journal (Clinical research ed.)*, 285(6344): 812–813.

Symmons, D., Kendall, M., Rees, J., & Hind, I. (1983). The effect of flurbiprofen on the responses to frusemide in healthy volunteers. *International journal of clinical pharmacology, therapy, and toxicology*, 21(7): 350–354.

Tafere, C., Yilma, Z., Abrha, S., & Yehualaw, A. (2021). Formulation, in vitro characterization and optimization of taste-masked orally disintegrating co-trimoxazole tablet by direct compression. *PLoS ONE*, 16(3): e0246648.

Tanaka, H., Iwao, Y., Izumikawa, M., Sano, S., Ishida, H., Noguchi, S., & Itai, S. (2016). Preparation of orally disintegrating tablets containing powdered tea leaves with enriched levels of bioactive compounds by means of microwave irradiation technique. *Chemical & pharmaceutical bulletin*, 64(9):1288-1297.

Thermo Scientific. (2023). Retrieved from Thermo Fisher Scientific : https://assets.thermofisher.com/chem-specs pdf/retrievePdf?rootSku=29756&sku=297565000

Thermo Scientific. (2023). Retrieved from Thermo Fisher Scientific: https://assets.thermofisher.com/chem-specs-pdf/retrievePdf?rootSku=40600&sku=406005000

USP 44 - NF 39 . (2021). Retrieved from Tablet friability: https://online.uspnf.com/uspnf/document/1_GUID-BE725528-5F2D-4F87-8184-2EACA45448F9_1_en-US

USP 44-NF 39. (2021). Retrieved from Uniformity of dosage units: https://online.uspnf.com/uspnf/document/1_GUID-BA3755E4-77AA-4DEB-8FE2-4FC78C587E9E_1_en-US

USP32-NF27. (2008). *United states pharmacopeia*. Retrieved from Lactose Monohydrate: https://www.usp.org/sites/default/files/usp/document/harmonization/excipients/e24_current_webpage_stage_6_monograph_14_oct_2011.pdf

USP44-NF39. (2021). *United States Pharmacopeia.* Retrieved from Powder flow: https://online.uspnf.com/uspnf/document/1_GUID-D48AA926-0912-4F7D-8B2B-3A022A1196FE_1_en-US

Vecsernyes, M., Fenyvesi, F., Bacskay, I., Deli, M., Szente, L., & Fenyvesi, E. (2014). Cyclodextrins, bloodebrain barrier, and treatment of neurological diseases. *Arch Med Res*, 45(8): 711–729.

Vemula, S. K., & Veerareddy, P. R. (2011). Fast disintegrating tablets of flurbiprofen: Formulation and characterization. *Latin American Journal of Pharmacy*, 30(6): 1135-1141.

Verma, U., Naik, J., & Mokale, V. (2014). Preparation and Characterisation of the inclusion complex of famotidine with (2-Hydroxy Propyl) –β-Cyclodextrin & PVP K-30: Effects on solubility and bitter taste mask. *Conference: Int. Conf. on Advances in Chemical Engineering and Technology, ICACE TKMCE '14*, 63–67.

Vidyadhara, S., Sasidhar, R., Deepti, B., & Vikas, S. (2016). Formulation of fast dissolving tablets for olmesartan using hydroxy propyl β-Cyclodextrins. *Scholars Research Library*, 8 (13): 115-125.

Vikas, Y., Sandeep, K., Braham, D., Manjusha, C., & Budhwar, V. (2018). Cyclodextrin complexes: An approach to improve the physicochemical properties of drugs and applications of cyclodextrin complexes. *Asian Journal of Pharmaceutics*, 12(2): S394.

Wang, C., Hu, S., & Sun, C. C. (2017). Expedited development of diphenhydramine orally disintegrating tablet through integrated crystal and particle engineering. *Molecular Pharmaceutics*, 14(10): 3399–3408.

WebMD. (2023). Retrieved from Flurbiprofen-uses, side effects, and more: https://www.webmd.com/drugs/2/drug-13459/flurbiprofen-oral/details

Yapar, E. A. (2014). Orally disintegrating tablets: An Overview. *Journal of Applied Pharmaceutical Science*, 4(2):118-125.

Yasmeen, G., Revathi, G. A., & Monica, M. (2019). Formulation and in-vitroevaluation of orodispersible tablets of telmisartan. *Journal of Drug Delivery and Therapeutics*, 9: 53-55.

Yilmaz, B., & Alkan, E. (2015). Spectrofluorometric and UV Spectrophotometric Methods for the Determination of Flurbiprofen in Pharmaceutical Preparations. *Research & Reviews: Journal of Pharmaceutical Analysis*, 4(4): 1-8.

Yilmaz, B., Sahin, H., Akba, V., & Erdem, A. F. (2014). Determination of flurbiprofen in human plasma by gas chromatography with mass spectrometry and its pharmacokinetics. *Journal of AOAC International*, 97(4): 1061-1066.

Yokoo, M., Kubota, Y., Motoyama, K., Higashi, T., Taniyoshi, M., Tokumaru, H., Kimura, S. (2015). 2-Hydroxypropyl-β-Cyclodextrin acts as a novel anticancer agent. *PLOS ONE*, 10(11): e0141946.

Yu, J., Shan , X., Chen, S., Sun, X., Song , P., Zhao , R., & Hu, L. (2020). Preparation and evaluation of novel multi-channel orally disintegrating tablets. *European Journal of Pharmaceutical Sciences*, 142: 105108.

Zhang, Y., Li, Z., Tang, H., Ren, W., Sun, Y., Zhao, Q., Liu, J. (2020). Development and optimization of levodopa and benzylhydrazine orally disintegrating tablets by direct compression and response surface methodology. *Drug Development and Industrial Pharmacy*, 46(1):42-49.

SUPPLEMENTARY

FORMS

THE FIRST PAGE OF PLAGIARISM REPORT