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College of Pharmacy

Preparation, Evaluation and Optimization of Easily Swallowed Tablets with Slippery Coating (Oroslippery Tablets) for Valsartan

A Thesis

Submitted to the Department of Pharmaceutics and the Committee of Graduate Studies of the College of Pharmacy/University of Al- Mustansiriya in Partial Fulfillment of the Requirements for the Degree of Master of Science in Pharmacy "Pharmaceutics"

By

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بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

أَلَمْ نَشْرَحْ لَكَ صَدْرَكَ ﴿١﴾ وَوَضَعْنَا عَنكَ وِزْرَكَ ﴿٢﴾ الَّذِي
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We, the examining committee, after reading this thesis, titled ***(Development, Evaluation and Optimization of Elastic Tablets with Slippery Coating (Oroslippery Tablets) for Valsartan)****, and examining the student (Zainab Hassan Mahdi) in its content, find it is adequate as a thesis for the degree of Master of Science in Pharmacy (Pharmaceutics).*

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Dedication

To my parents .....

Whose affection, encouragements, love and prays make me able to get through any difficulties.

To my brother (Ahmed) and sister (Ghada) .....

I am truly grateful for your support, inspiration, and Instigation.

To my marvelous husband (Hassan).....

Thank you for your continuous care, assistance, patience, and understanding.

To the little angel and precious treasure (Maryam) .....

You are really the delight of our life and God's gift to us.

I Dedicate My Thesis With Love

Zainab

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Abbreviations

Ang II	Angiotensin II
ANOVA	Analysis of variance
ARB	Angiotensin receptor blocker
CCS	Cross carmellose sodium
CP	Crosspovidone
DT	Disintegration time
f1 and f2	Difference factor and similarity factor respectively
FT-IR	Fourier transform infrared spectroscopy
GIT	Gastrointestinal tract
HCl	Hydrochloric acid
HPMC	Hydroxypropylmethyl cellulose
K	Degradation rate constant
kol.	Kollicoat IR
LES	Lower esophageal sphincter
MCC	Microcrystalline cellulose
Mg stearate	Magnesium stearate
ODT(s)	Orodispersible tablet(s)
OST(s)	Oroslippery tablet(s)
PEG	Polyethylene glycol
pH	Negative logarithm of hydrogen ion concentration
PVA	Polyvinyl alcohol

PVP	Polyvinylpyrrolidone
rpm	Round per minute
SD	Standard Deviation
SDL	Spray dried lactose
SL	Sublingual
SSG	Sodium starch glycolate
$t_{10\%}$	Time required for the drug to lose 10% of its potency
$T_{80\%}$	Time required for 80% release
T_g	Glass transition temperature
UES	Upper esophageal sphincter
USP	United States Pharmacopeia
UV	Ultraviolet
Xan.	Xanthan gum
λ max	Wave length with maximum absorbance
$\%D_{30min}$	Percent drug released in 30 minutes
θ	Angle of repose

Abstract

Swallowing difficulties (dysphagia) is a common problem in about 50% of the population that making tablet ingestion unpleasant experience for many people, especially pediatrics, geriatrics and patients who can't tolerate drinking water or in case of unavailability of water. Many tablet dosage forms were developed to overcome this problem such as buccal, sublingual and orodispersible tablet (ODTs), although these have certain restrictions such as limitations in drug and dose selection, taste masking difficulties, in addition to the friability, hygroscopicity and light sensitivity in ODTs.

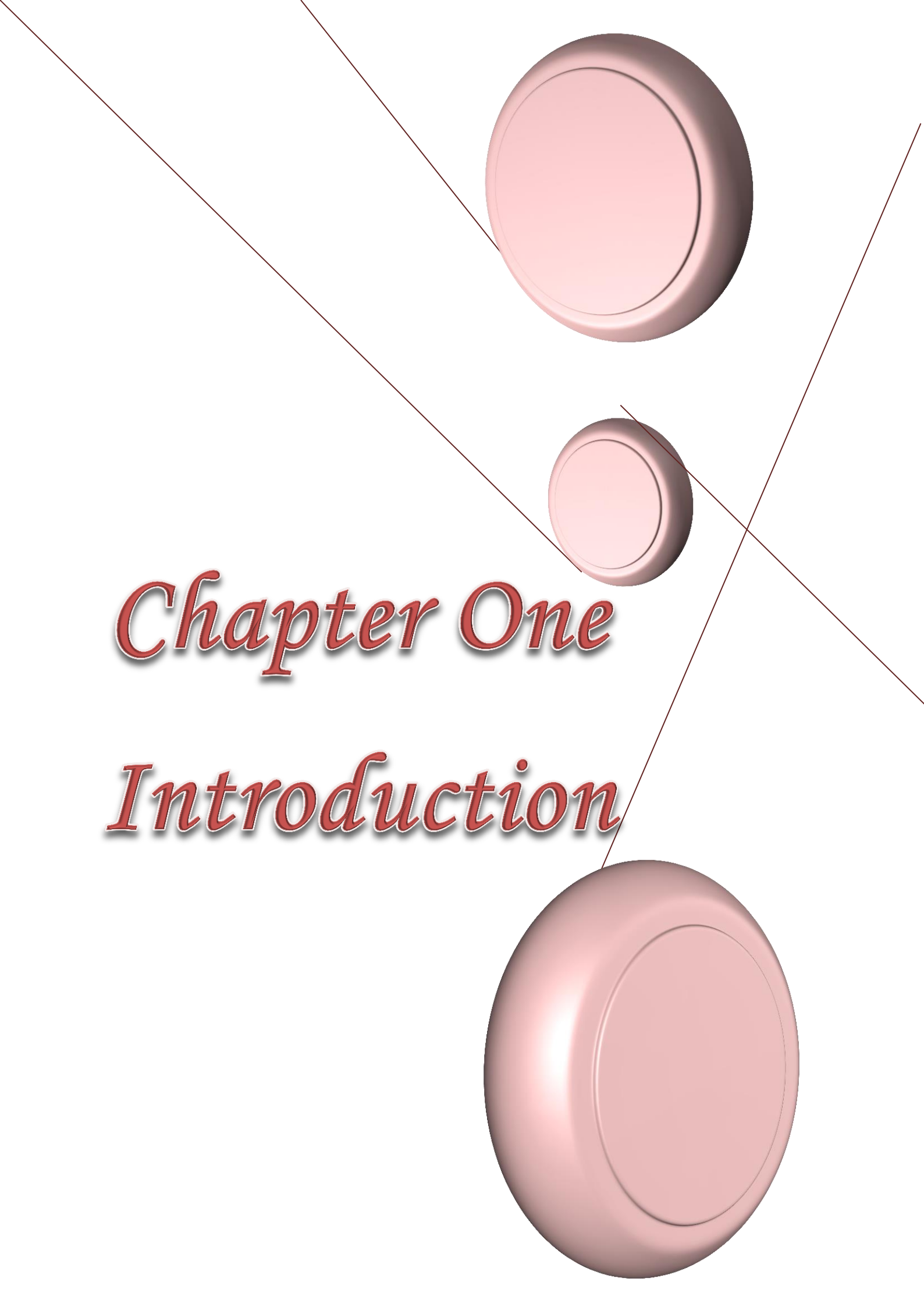
Therefore, in this study a new easily swallowed tablet of valsartan (160 mg); an antihypertensive drug with slightly bitter or metallic taste; was formulated by the application of a special coat on the tablet surface, which hydrates quickly upon contact with saliva offering an easy slipperiness of the tablet as intact form with good taste masking effect, without drinking water and without adversely affecting the immediate release profile of the drug in the GIT, these tablets was called an oroslippery tablets (OSTs).

For optimization; thirty-five valsartan OSTs formulas along with eight blank (drug free) OSTs formulas were prepared by dipping the core tablets in a coating dispersion containing a mixture of kollicoat IR (as a film former) and xanthan gum (as slipperiness inducer). The prepared OSTs were optimized for two types of variables; first variables related to the core tablets (including binder type and concentration, superdisintegrant type and concentration, diluent type and method of preparation), and second variables related to the coating dispersion (including kollicoat IR concentration, xanthan gum concentration and coating level).

Valsartan OSTs were evaluated for their physical properties, in-vitro disintegration and release in addition to the in-vivo evaluation of taste masking properties (time to feel bitterness), while the evaluation of in-vivo slipperiness (time required for swallowing) was performed on the prepared blank OSTs.

Formulas F32 and F34 with cores containing 6% HPMC (F32) or 2% avecil (F34) as a binder, 6% crosscarmellose sodium as superdisintegrant and mannitol as a diluent which were prepared by direct compression method and double coated with (15% kollicoat IR+0.3% xanthan gum) were selected as the optimum formulas for valsartan OSTs, since they possessed adequate slipperiness (8±2.88 seconds) without liberation of the bitter taste (58±1.06 seconds) or disintegration (5.57±1.36 and 5.55±0.98 minutes for F32 and F34 respectively). In addition these selected OSTs possessed a similar immediate release profile to the marketed tablet Diovan®, with a similarity factor (f_2) more than 50 and difference factor (f_1) less than 15 in both phosphate buffer pH 6.8 and HCl pH 1.2. The expiration date were (3.28 and 3.18) years for F32 and F34 respectively.

The overall result of this study involves the provision of a new easily swallowed tablets of valsartan with a slippery property that can be used as an alternative to buccal, sublingual and orodispersible tablets where it offers a high flexibility in drug selection with high loading capacity, furthermore, these OSTs are coated with a special coat that do not dissolve or disintegrate in the oral cavity improving by that the taste masking property without affecting the immediate release pattern of the drug in the GIT. In addition, the presence of the outer coating layer makes this dosage form more resistant to shocks, light and humidity comparing to ODTs.



Chapter One

Introduction

1. Introduction

1.1 Oral solid dosage forms

Oral route had been known for decades as the most widely used route of drug administration with a wide acceptance up to (50-60%) among all other routes due to its ease of consumption, pain avoidance, versatility, and patient preference with no requirement of sterile conditions[1,2].

The term (oral solids) refers to the three major types of dosage forms, compressed tablets, capsules (hard and soft shell) and less frequently used powders. All together accounts 70% of all dispensed prescriptions encountered in worldwide. There are several reasons for the popularity of oral solids:-

- Employing oral route of administration, that is the most acceptable route.
- Permitting a high dose accuracy.
- Dose contained in relatively small volume which is more easier in packaging, transporting, storage and administration.
- All the three dosage forms are water free which reduce the loss of potency due to hydrolysis and enhance product stability[3].
- Encapsulating the medicine in a solid dosage form is the most efficient method to mask the bitter and/or irritative nature of many active ingredients[4].

1.2 Tablets as the preferred oral solid dosage form

From the three solid dosage forms that mentioned earlier tablet is the most commonly used followed by hard shell capsule and then the soft shell capsule, by the ratio being about 65:30:5[3].

Tablets are solid dosage forms which containing one or more active ingredients formulated with the aid of suitable pharmaceutical excipients. They are obtained by compressing uniform volumes of particles and are mainly intended for oral administration[5].

Tablets vary widely in shape, and with a weight ranging from 0.06 to 0.60 gm. Jean de Renou applied the Latin word tabella to a special type of troche in 1608, while Burroughs Wellcome & Co. coined the term ‘‘tablet’’ in 1878 to refer to its brand of compressed pills, a term that is derived from the French tablette, meaning ‘‘shelf’’ and the Latin tabula, meaning ‘‘board’’. The first rotary tablet machine was invented by Henry Bower in 1872, an employee of the Philadelphia drug manufacturer John Wyeth. After two years, Joseph A. McFerran received a patent for the invention of the first fully automatic tablet machine[6].

The preparation of virtually all tablets involves a compression step, during which a uniform volume of solid particles are poured into a die and compressed between two punches. The applied pressure brings the particles into close proximity so that the interparticulate force of attraction can cause cohesion, which eventually result in the formation of compacted mass having low porosity[3].

1.2.1 Classes of tablets

Tablets are classified according to the function or route of administration into:-

A. Oral Tablets for Ingestion[7,8]:-

These are designed to be swallowed as an intact form (except for the chewable tablet) including:

❖ Compressed tablets: This refers to the standard uncoated tablets which are usually intended to provide rapid disintegration and release.

❖ Multiple compressed tablets: Includes two types

1- Layered tablets.

2- Compression-coated tablets.

Both types usually undergo a light compression as each component is placed separately, with the main compression being the final one.

❖ Repeated-action tablets: Includes both multiple compressed tablet and sugar-coated tablet in which the core being coated with shellac or enteric polymer with an additional dose in the sugar coating, to give repeated action of the drug.

❖ Delayed-action and enteric-coated tablets: They are dosage forms which are aimed to release the a drug after a lag time, while the enteric coated tablets are the dosage form which remain intact in the stomach but quickly release the drug in the upper intestine.

❖ Sugar-coated and chocolate coated tablets: They are usually made to give an elegant, glossy, easily swallowed tablets but generally tedious, time-consuming and cause a pronounced increase in tablet weight and size.

❖ Film-coated tablets: Developed as an alternative to sugar coating to produce thinner film that retain the deposed marking on the tablet and cause a little increase in tablet weight, furthermore, it avoids the use of sugar, simpler and less time-consuming.

❖ Chewable tablets: These tablets are intended to be chewed in the mouth and not to be swallowed intact.

B. Tablets Used in Oral Cavity[9]:-

Tablets in this group are designed to release the active ingredient in the oral cavity providing a systemic or local effect.

❖ Buccal tablets and sublingual tablets: These two types are intended to be held in the mouth, as they release the medication for direct absorption via the oral mucosa.

❖ Troches and lozenges: These are intended to dissolve slowly in order to give a local effect in mouth or throat.

❖ Dental cones: Minor tablets that are designed to be placed in the remaining empty socket following the procedure of tooth extraction.

❖ Orodispersible tablets (ODTs): Tablets that designed to dissolve in the tongue upon contact with saliva rather than swallowed whole.

C. Tablets Administered by Other Routes[8,10]:-

❖ Implantation tablets: They are also called depot tablets and designed for subcutaneous implantation to give prolonged effect of the medication.

❖ Vaginal tablets: Ovoid to pear-shaped tablets designed to undergo slow dissolution in the vaginal cavity.

D. Tablets Used to Prepare Solutions[8,9]:-

❖ Effervescent tablets: They are formulated to give a solution rapidly after the addition of water with the simultaneous release of carbon dioxide.

❖ Dispensing tablets: They are designed to be added to a certain volume of water by the pharmacist or the patient to give a solution of certain medicament concentration.

❖ Hypodermic tablets: They are consist of one or more active ingredients with other water soluble ingredients and designed to be added to a sterile water for injection.

❖ Tablet triturates: They are small cylindrical, compressed or molded tablets with a potent drug, providing an extemporaneous method of preparation by the pharmacist.

1.2.2 Advantages and limitations of tablets

Tablets have the superiority over other solid dosage forms because:-

1- They are unit dosage form offering the highest dose precision and least content variability.
2- They possess the lower cost and higher production rate.
3- Tamper proof dosage forms, which is the major advantage over the capsule.
4- Easiest and cheapest product identification by employing an embossed or monogrammed punch face[8].
5- They may be formulated to contain more than one therapeutic agent that provide medicines to be administered via different routes in different forms.
6- They are a versatile drug delivery system which can be formulated to achieve immediate release products with the availability of various techniques that can modify the release of the active ingredient from them[11].

Although they are also possess some constrains like:-

1- Some drugs can't be compressed into dense compacts due to their amorphous nature or flocculent, low-density properties.
2- The absorption of the therapeutic agent and hence its bioavailability depends on physicochemical properties of the drugs in addition to the physiological factors e.g. gastric emptying rate[8,12].
3- Difficult to be swallowed specially for patient suffering from dysphagia (swallowing difficulties) mostly pediatrics, geriatrics, bedridden people or patient suffering from nausea and vomiting or allergic cough whom can't tolerate drinking water, in addition to travelling patient who don't have ready access to water[13,14].

From the previously mentioned limitation, difficulty in swallowing requiring a serious consideration since it is found that about 50% of the population suffering from dysphagia or swallowing difficulties[15], consequently, many patients do not take their medications as prescribed, which results in a high prevalence of patient noncompliance and inadequate therapy[16].

However, crushing or splitting tablet can improve patient acceptance in some cases but may cause dosing inaccuracies, GIT irritation, and impaired bioavailability as a result of chemical instability at varying gastrointestinal pH due to the possible destruction of their release properties[17], in addition to the liberation of the unpleasant taste or odor of some medications[18].

As a result, although tablets are the ideal solid dosage forms to be received by the patient orally, difficulties in their swallowing become an object of public attention.

1.3 Normal swallowing

1.3.1 The digestive system

The digestive system (Figure 1-A) consist from two types of organs: digestive organs and accessory digestive organs. The digestive organs together form the gastrointestinal tract (GIT) or also called digestive or alimentary tract and they include the oral cavity, pharynx, esophagus, stomach, small intestine and large intestine. These organs form a continuous duct from mouth to the anus and the contraction in the GIT wall pushes food from one organ to the next. The accessory digestive organs are extended from and connected to the GIT. They assist in the process of food digestion and include the tongue, teeth, salivary glands, liver, gallbladder and pancreas[19,20].

The GIT from the esophagus to the anal canal is composed of four layers (Figure 1-B): mucosa, submucosa, muscularis and serosa.

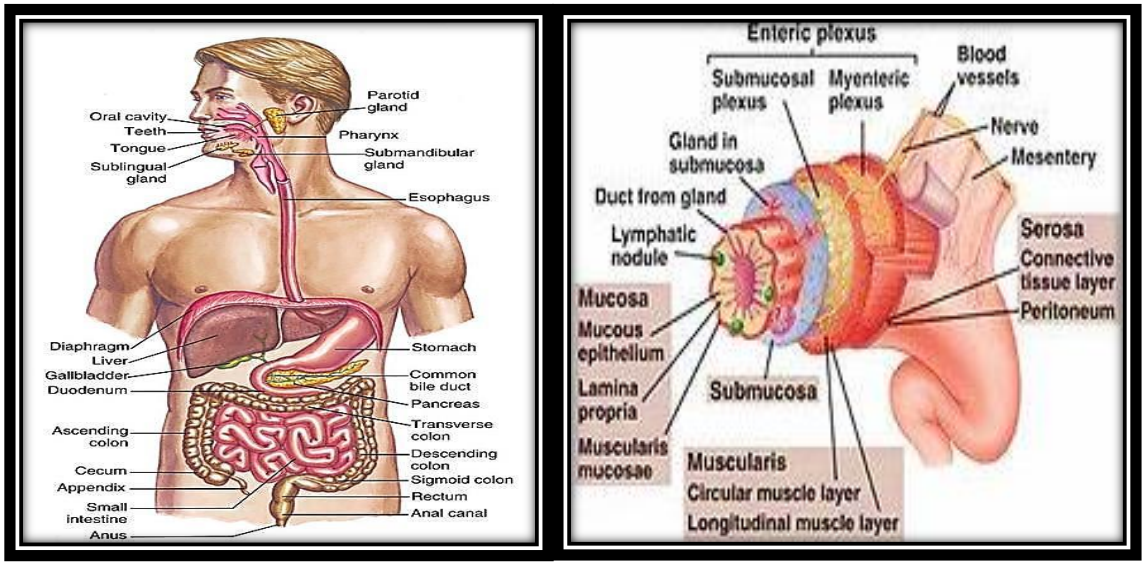
❖ Mucosa: Innermost mucosa consisting of three layers, epithelium, lamina properia and muscularis mucosa.

❖ Submucosa: Consisting of a thick layer of connective tissue with the submucosal nerve plexus (meissner's plexus).

❖ Muscularis: Consisting of inner circular smooth muscle and outer longitudinal smooth muscle with the myenteric nerve plexus in between, with the exception of upper esophagus which consist from striated muscle and the stomach that contain three layers of the smooth muscle.

❖ Serosa or adventitia: It is the outermost layer and consisting from the simple squamous epithelium, mesothelium and a small amount of connective tissue[21,22].

The submucosal and myenteric nerve plexus collectively constitute the enteric plexus which represent a pathway at which extrinsic nervous system (sympathetic and parasympathetic) and the intrinsic nervous system (enteric) act to control GIT movement and secretions[22].



-A- ***-B-***

Figure(1): A-Organs of digestive system[19], B- Layers of GIT [21]

1.3.2 Process of normal swallowing

Swallowing or deglutition is the process of moving the ingested material from the oral cavity to the stomach without forcing it into nasopharynx or trachea[20]. It is a complex behavior including a volitional and reflexive activities that is triggered by afferent impulses mainly in trigeminal, glossopharyngeal and vagus nerves[23]which are controlled by the medulla oblongata that function as swallowing center[19,24](Figure 2). This center is responsible for the coordination between upper digestive and respiratory systems that is essential for safe and efficient feeding and breathing process[25].

The swallowing process involves mainly three phases: oral phase, pharyngeal phase and esophageal phase (Figure 3). Of these three phases, only the oral phase is voluntary while the following two phases are involuntary[20,26].

A. Oral phase:-

During this phase the tongue push the food bolus back against the hard palate as the transverse palatine folds direct the bolus posteriorly toward the oropharynx[20], this phase involves the use of the cranial nerves V (trigeminal), VII (facial), and XII (hypoglossal)[27]. The duration of this phase ranges from a fraction of seconds to 10 seconds[28].

B. Pharyngeal phase:-

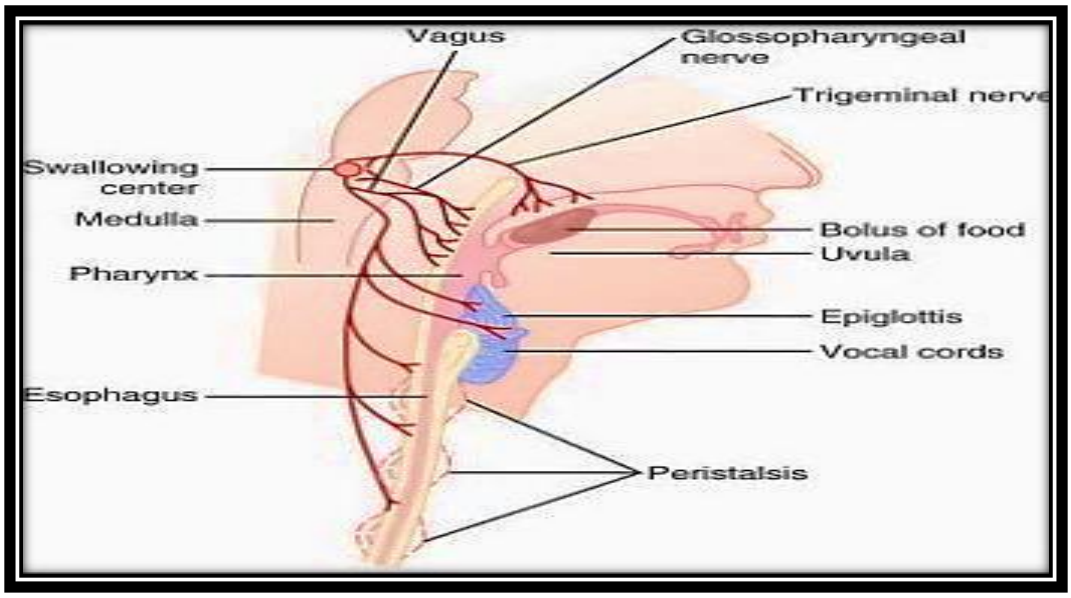
The appearance of food bolus in the beginning of oropharynx causing the sensory receptors to trigger a swallowing reflex that is controlled by the swallowing center in the medulla oblongata to inhibits the respiratory center, halting the respiration at any point for few seconds, to allow swallowing to proceed. All leading the bolus to pass involuntarily to the esophagus.

This phase includes:-

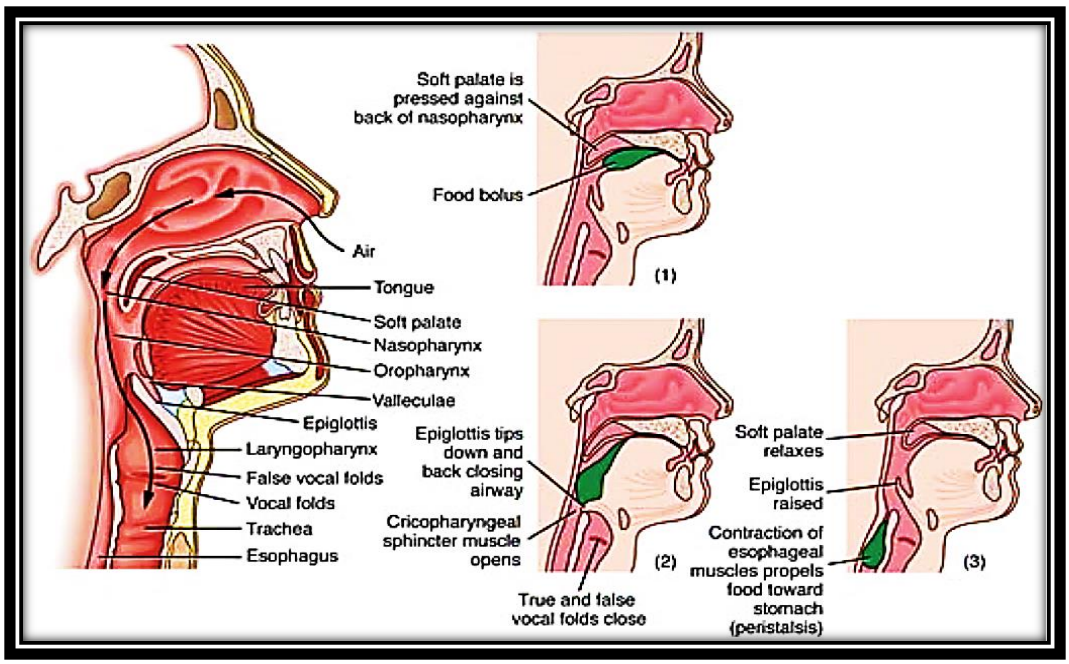
1. Elevation of the soft palate & uvula to block the space between nasopharynx and oropharynx.
2. Entry of the bolus to the oropharynx.
3. As the food approaches the esophagus the epiglottis is lowered and the glottis is slightly elevated to cover the larynx in order to prevent food from entering the trachea[29]. The duration of the pharyngeal phase is (1 to 2 seconds)[30]and involves the cranial nerves V (trigeminal), IX (glossopharyngeal), X (vagus), XI (accessory) and XII (hypoglossal)[27].

C. Esophageal phase:-

This phase begins as the upper esophageal sphincter (UES) relaxes allowing the bolus to pass to the esophagus followed by constriction of UES and stimulation of peristaltic contraction in order to transport the food down the esophageal tube, and at the time of bolus reaching the lower esophageal sphincter (LES), the sphincter is relaxed momentarily causing the food to easily entering into the stomach. Finally, the LES closes to prevent food reflexes back to the esophagus[30]. This phase duration is about (5-8 seconds) and involves the activity of both vagal nerve and ENS[24].



Figure(2): Major innervation in swallowing[24]



Figure(3): Mechanism of normal swallowing [26]

1.4 Dysphagia

Dysphagia is a medical term refers to difficulty in swallowing, or can be defined as the feeling of "food sticking" at the chest or throat. This term also indicates the difficulty in moving foods and liquids from the mouth to the stomach and it is originated from the Greek words dys, meaning "difficulty", and phagia, meaning "to eat"[31,32].

1.4.1 Classification and consequences of dysphagia

Anatomically dysphagia is classified as either oropharyngeal or esophageal dysphagia. The former is related to the problems in the passage of food bolus from the oropharynx to the esophagus, while the latter is related to the problems in passing food to the stomach resulting from abnormalities in esophageal peristalsis or in the LES[27,33]. The abnormalities in the LES are mostly represented by either achalasia (failure of the LES to

relax) or by gastroesophageal reflux disease (failure of the LES to contract)[23]. Consequently, dysphagia might cause several complications like dehydration, malnutrition, poor medication adherence, bronchospasm and airway obstruction, as well as aspiration pneumonia and chronic chest infection[30].

1.4.2 Common causes and management of dysphagia

Dysphagia occurs most commonly due to either mechanical obstruction (dysphagia for solids) or neuromuscular or motor disorder (dysphagia for both solid and liquid) along the area of food passage[34,27]. It is commonly associated with elderly persons, cerebrovascular diseases, malignancies, and dementia[35].

Depending on the cause of dysphagia, five aspects for the treatment of dysphagia are present: through medications, surgery, dilation, endoscopy and swallowing rehabilitation via dietary changes and swallowing therapy.

❖ Medications can be used to treat the underlying cause of dysphagia in addition to the medications that are given to treat the hyperacidity, prevent stomach acid from going back to the esophagus, or to treat infections. On the other hand, stopping and replacing any other medication causing dysphagia (e.g. drugs for insomnia and epilepsy).

❖ Surgery is advised when dysphagia is caused by obstruction such as diverticula or tumors and also can be used in achalasia treatment.

❖ Dilation is done with the use of a special device and is used to expand the narrowed parts of the esophagus.

❖ Endoscopy aside from diagnosis, endoscopy can also be used in the treatment of dysphagia as it is used for the removal of the object that has been stuck at the esophagus.

❖ Swallowing rehabilitation via diet changes and swallowing therapy. Diet changes may reduce choking problems by the administration of thickened liquids or soften foods to make them easier to swallow[31]. Swallowing therapy on the other hand, can teach the patient different ways of swallowing by using different head and body positions in addition to different training exercises to strengthen the muscles that help swallowing or via sensory stimulation by the use of chemical, thermal, and tactile stimulation through changing the volume, taste, temperature, and even additional pressure on the tongue with a spoon can be used effectively to modulate the swallowing behavior[27].

Recently, it was found that hot and cold perception can be evoked by chemical agent (e.g. menthol induce cold perception) by stimulation of trigeminal nerve that significantly improves the swallowing reflex which facilities the swallowing process[36].

1.5 Tablet dosage forms applied to overcome swallowing difficulty

They include buccal, sublingual (SL) and orodispersible tablets (ODTs) in which drugs are introduced into the oral cavity without the need of chewing or prior dispersion or dissolution in water in order to produce a systemic effect[37]. These tablets are important for patients whom chewing is difficult or painful and also for patients suffering from dysphagia such as elderly, children, uncooperative, nauseated, and people who are suffering

from allergic bronchitis or mentally retarded patients and in case of in availability of water in travelling patient[38].

1.5.1 Buccal and sublingual tablets

They are flat, oval tablets intended to be dissolved slowly in the buccal pouch for buccal tablets or rapidly beneath the tongue for SL tablets for absorption via the oral mucosa. They are useful for medications that are adversely affected by the gastric juice and/or poorly absorbed from the GIT, for emergency, and for patients suffering from dysphagia[39].

Buccal and SL tablets have certain drawbacks like:-

1. Drug administration via the buccal mucosa may have many problems such as pH stability problems, low permeability, in addition, drugs which are irritant to oral mucosa, having bitter or unpleasant taste and odor cannot be administered by this route[40,41].
2. Overhydration may lead to disruption of the structural integrity of the formulation by the hydration & swelling of the bioadhesive polymer[41].
3. high dose drugs are often difficult to be administered.
4. Restricted eating and drinking until the end of drug release.
5. Limited surface area for absorption & unpredicted bioavailability[42,43].
6. Saliva washes away drugs.
7. Possible chewing or swallowing of the dosage form by the patient[44].

1.5.2 Orodispersible tablets

Orodispersible tablets (ODTs) are solid dosage forms that dissolve or disintegrate quickly (within few seconds) in the oral cavity, resulting in a

solution or suspension without the need of water[45]. They also called fast disintegrating tablets, mouth melting tablets or mouth dissolving tablets[46].

ODT also have certain limitation like:-

1. Suitable for only small doses preferably less than 50 mg[47].
2. They may cause unpleasant taste and/or grittiness in the mouth if not suitably formulated.
3. They are hygroscopic in nature, and should be kept in dry places[48,49].
4. Not suitable for patients who have recently taken anticholinergic drugs.
5. Unsuitable candidates for medications with frequent dosing, short half-life and those who require controlled or sustained release[50].
6. Special handling and packaging requirement due to its friability and weak mechanical strength[46,51].
7. ODT's may be unsuitable for light-sensitive medications where there is no option for film coating[52].
8. The drug should possess ideal properties of low to moderate molecular weight, good salivary and water solubility, partially non-ionized property at the oral pH and capability to permeate oral mucosa[53].

1.5.3 Development of the oroslippery tablets

Generally the process of tablet swallowing might be difficult for many people and this mainly resulted from both physical and psychological barriers for tablet ingestion[54]. Physical barriers are mainly attributed to tablet size, shape, taste and surface[51,55], which may cause the tablet to scratch or irritate the esophagus during its passage, while psychological barriers are attributed to patient resistance or previous experience with a tablet sticking in the esophagus. As a result, these factors collectively make

the swallowing of tablets an uncomfortable experience to the patient, and this might consequently lead to noncompliance[54].

It is generally reported that the easiest swallow tablet size is (7-8 mm)[56], and oblong/oval tablets with arched endings pass better than circular tablets. While, The rough surface and the bad taste of the tablet can be resolved by the application of suitable coat[54].

Therefore, the development of a new tablet dosage form that may offer an easily swallowing with taste masking property is necessary to alleviate the above barriers and to overcome some of the limitations of the previously mentioned buccal, SL and ODTs. Once putting in the mouth, these tablets supposed to hydrate quickly offering an easy slipperiness of the tablet down to the GIT as intact form without the need of water. These tablets called oroslippery tablets (OSTs) and could be implemented to give an immediate release effect.

1.6 Immediate release tablets

Immediate release tablets are those which disintegrate rapidly and get dissolved to release the medicament, The term “release” includes the provision (or presentation) of drug from the formulation to the gastrointestinal tract, to body tissues and/or into systemic circulation. This may be provided by using an appropriate diluents or carrier which does not prolong, to an appreciable extent, the rate of drug release and/or absorption[57,58].

1.6.1 Conventional techniques for tablet preparation

There are traditionally three basic methods (Table 1) for the preparation of compressed tablet: wet granulation, dry granulation including (slugging and roller compaction), and direct compression[39].

❖ Wet granulation:

In this process liquid binder is used to agglomerate the powder mixture, then screening is done to form the granules followed by drying and further screening to give a uniform size granules. The amount of liquid should be properly controlled, as over-wetting may cause a too hard granules while under-wetting will cause them to be friable and too soft. Aqueous systems have the advantage of being safer than solvent-based systems but may not be suitable for medications that are destroyed by hydrolysis[57].

❖ Dry granulation:

By this method, the powder mixture is compacted into large parts that are subsequently broken down and sized into granules. This method is more preferred than wet granulation especially for drugs that destroyed in moisture or high temperature used in wet granulation. It includes slugging and roller compaction. In slugging the powder mixture is compressed or slugged into large flat tablets or pellets (1 inch in diameter), which are then broken up and passed through a screen of suitable mesh for sizing then compressed. While in roller compaction, powder compactors are used to increase the powder density instead of slugging, and this is done by passing the mixture between rollers of 1-6 tons of pressure, after that the compacts are broken up and sized prior to compression[39].

❖ Direct Compression:

Here, tablets are compressed directly from a mixture of the drug and excipients without any previous treatment. This mixture should possess adequate flow properties and cohere under pressure that making pretreatment such as dry or wet granulation unnecessary[57].

Table(1): Steps of various techniques in tablet preparation[59]

Wet Granulation	**Dry granulation**	**Direct Compression**
Blending	Blending	Blending
Wet massing and screening	Slugging/roller Compaction	-
Drying	-	-
Dry screening	Screening	-
Blending (with lubricant)	Blending (with lubricant)	Blending (with lubricant)
Compaction	Compaction	Compaction

1.6.2 Advantages of direct compression

Direct compression is the most preferred technique in tablet manufacturing because of its obvious advantages like:-

1. Faster dissolution: By breaking apart into particles instead of granules that directly come into contact with dissolution medium.

2. Less wear & tear of punches: Due to the fact that direct compression avoids the high pressure involved in the production of tablets by slugging[59].

3. Cost Effectiveness: Because of fewer operation units, less equipments, less chance for contamination of raw materials, lower power consumption, less space, time and effort with easier validation and documentation requirements all leading to reduced cost of tablets production.
4. Stability: Direct compression is more appropriate for moisture and heat sensitive active ingredients due to the elimination of wetting and drying steps[60].

1.6.3 Limitations of direct compression

In spite of the tremendous advantages of direct compression, it possesses certain limitations like:-

1. Segregation: Due to the density differences between the active ingredient and excipients, in addition to the static charges induced during mixing the dry state of the materials which leading to weight variation and content non-uniformity[59].
2. Dusting problem: Resulting in personal and environmental hazards[61].
3. Great dependence upon the flowability and compressibility of diluent[60].
4. Limited dilution potential: It is the maximum proportion of the active ingredient that can be compacted into an acceptable compact by the use of binder or filler. As a result of the limited dilution capacity of diluents or binders, most of the directly compressible materials can house only 30-40 % of the poorly compressible materials to produce a tablet with acceptable size[59,61].
5. Lubricant sensitivity: Plastically deforming diluents or fillers are mostly affected by lubricant which exhibits a low-shear strength and forms a non-polar hydrophobic layer on the surface of powder particles which leading

consequently to weak tablets with slow disintegration and dissolution, an effect that is generally controlled by optimizing the lubricant concentration along with blending time to as little as 2-5 minutes[11,59].

1.7 Excipients used in tablet manufacturing

Excipients are additives used to convert the pharmacologically active compounds into pharmaceutical dosage forms suitable for administration to patients, they should have certain criterias like:-

- ❖ physiological inertness.
- ❖ physical and chemical stability.
- ❖ The agreement with the requirements of the regulatory agency.
- ❖ No interaction with the bioavailability of the drug.
- ❖ Absence of microbial contamination.
- ❖ Commercially available at low cost[8,62].

Generally conventional tablet for oral ingestion contain the following excipients: fillers or diluents, binders or adhesives, glidants, lubricants, and disintegrants. It may also contain another optional component like colorants, flavorings and sweeteners[8,12].

1.7.1 Fillers or diluents

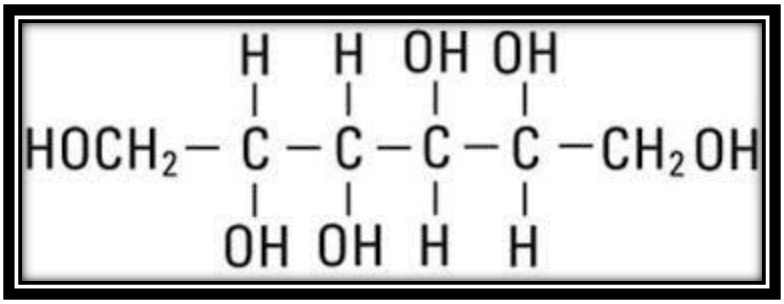
Diluents or fillers are the excipients that employed in all techniques of tablet formulation to increase the bulk of tablets containing a low concentration of therapeutic agent that rendering the manufacturing process more reproducible and reliable[8].

Two types of diluents are present, soluble like lactose, sorbitol, mannitol, and sucrose, and insoluble diluents include both disintegrating

fillers like microcrystalline cellulose (MCC) or avecil® and starch, and non-disintegrating like dibasic calcium phosphate[12,59].

Lactose is a naturally occurring disaccharide with one galactose unit and one dextrose unit. It is a constituent of all forms of mammalian milk, but commercially it is produced from the cow's milk, usually as a by-product in the cheese industry. Lactose can exist in amorphous or crystalline form as two isomeric forms, α-lactose and β-lactose. Crystalline α-lactose occurs in both monohydrate and anhydrous forms, but β-lactose only exists in the anhydrous form. Spray-dried lactose is the most preferred diluent in direct compression, it is a mixture of crystalline α-lactose monohydrate (80%-90%) and (10%-20%) of an amorphous lactose[12,60]. lactose may give highly colored products when mixed with substances containing a primary amine group (Maillard reaction), therefore, its use is contraindicated in such formulations[11].

Sorbitol and mannitol are the commonly used polyols in direct compression, they are white crystalline powders that can be obtained from natural sources but usually manufactured by hydrogenation of the parent sugar molecule. Both of them are freely soluble in water, non-caloric, non-cariogenic and have a negative heat of solution which produces a cooling sensation in the mouth making them diluents of choice in chewable tablets[60]. However, being a non-hygroscopic and compatible with the majority of active ingredients, mannitol (Figure 4) is preferred over sorbitol as a diluent in tablet formulation[63,64].



***Figure(4): Chemical structure of mannitol*[(12)]**

Sucrose and sucrose-based diluents are avoided by some manufacturer because of unnecessarily subjecting the diabetic patient to a large quantity of sugar[(8)].

MCC (avecil) is crystalline powder discovered at 1955 prepared by acid hydrolysis of cellulose and can be used as diluent, binder and disintegrant[(8,65)]. Different grades are available commercially that differ in their physicochemical properties like flow properties, density, particle size distribution and morphology, with the two most commonly used grades avecil PH-101 (powder) and avecil PH-102 (granules)[(12,66)].

Starch is a polysaccharide composed of amylopectin and amylose also used as a diluent, binder and disintegrant[(12)]. It is commercially obtained from different natural sources e.g. wheat, barley, maize, potato, arrowroot, and tapioca, which gives different particle shape, size and ratio of amylose to the amylopectin[(67,68)]. However, its poor flowability and compressibility in addition to the high moisture content leads to the development of directly compressible pregelatinized starch 1500 with excellent flowability and compressibility[(8)].

dibasic calcium phosphate is commonly used water insoluble diluent with excellent flowability and compressibility, available as different

hydrated forms with a range of particle size, but it may interfere with the acidic component in the presence of moisture due to its basic nature[12].

1.7.2 Binders

Binders are mostly polymeric compounds that can be used either in dry or liquid form during wet granulation to form granules or during direct compression to form a cohesive compact[8]. They are generally used in a lower concentration than diluent because of their higher dilution capacity[59]. For example modified natural polymers such as alginates and cellulose derivatives like methylcellulose, hydroxypropyl cellulose and hydroxypropyl methyl cellulose (HPMC) can be used as binder for direct compression in dry form, while their aqueous solution having an adhesive property. In addition, polyvinylpyrrolidone (PVP) is a synthetic polymer which also can be used as a binder in dry or liquid form (aqueous or alcoholic solution)[8,69].

1.7.3 Glidants and lubricants

Glidants are materials planned to enhance the flow of the tablet powder or granules by reducing the interparticulate friction by lodging in the surface irregularities of the powder forming more rounded structures, like colloidal silicon dioxide and talc. While lubricants include materials that intended to reduce the friction or sticking between die wall and tablet surface e.g. magnesium stearate (Mg stearate) and stearic acid[8,12]. This activity is due to the adhesion of the polar metallic portion of the metallic fatty acid salt to the powder surface, leaving the non-polar hydrocarbon portion oriented away from the surface which deforms easily upon shearing (on tablet compression) providing a readily deformable film[11].

1.7.4 Disintegrants

Disintegrants are agents added to enhance moisture penetration and dispersion causing tablet break up into smaller pieces in the GIT thereby enhancing the rate of drug release by increasing its available surface area[70]. Since it is essential to achieve rapid disintegration to obtain an immediate release of the medicament in GIT, the formulator gives a special emphasis in the selection of the proper disintegrant for their dosage form[71].

Traditionally, starch has been used as disintegrating agent for many years in concentration 2-10%[11], however, it has the major drawback of adversely affecting the flowability and compactibility if used in concentration higher than 5% especially in direct compression. Therefore, recently a new disintegrants are discovered and named superdisintegrants which can be used in a lower concentration than conventional disintegrants without adversely affecting fluidity or compactibility[72]. An ideal superdisintegrant should have the following properties:

- low water solubility with adequate hydration capacity.
- A low tendency for gel formation.
- adequate compressibility & flowability.
- Non-toxic and inert[73,74].

1.7.4.1 Mechanism of action of superdisintegrants

Tablets are generally break down to their primary particles by one or more mechanisms including: Capillary action (wicking), swelling, deformation, disintegrating particle/particle repulsive forces, heat of wetting, release of gases and enzymatic action[71,75]. Figure (5) illustrates the most common mechanisms of tablet disintegration

❖ Capillary action (wicking): This is generally the first step in tablet disintegration & occurs when the surrounding aqueous medium penetrates into the tablet replacing the air adsorbed on the particle surface, which weakens the intermolecular bond and breaks the tablet into small particles. This water uptake by tablet depends upon hydrophilicity of the drug/excipient and on tableting conditions. Therefore, maintenance of porous structure and low interfacial tension towards aqueous fluid is essential for disintegration process by the formation a hydrophilic network around the drug particles[(76)].

❖ Swelling: It is the most widely accepted mechanism of action for tablet disintegration. Tablets with high porosity show poor disintegration due to the inadequate swelling force. However, in case of high-density tablets, fluid is unable to penetrate in the tablet and the disintegration is slowed down again[(71)].

❖ Deformation: During the process of tablet compression, the particles get deformed (elastically), and they get back into their normal structure directly after contacting the aqueous media or water. But, with the high compression forces involved in the process of tableting, these particles are believed to be deformed more permanently and are said to be "energy rich" with this energy being released upon exposure to water. This mechanism has been recently studied on starch grains and it shows the ability for compressed starch to swell is greater compared to starch grains before compression[(70,76)].

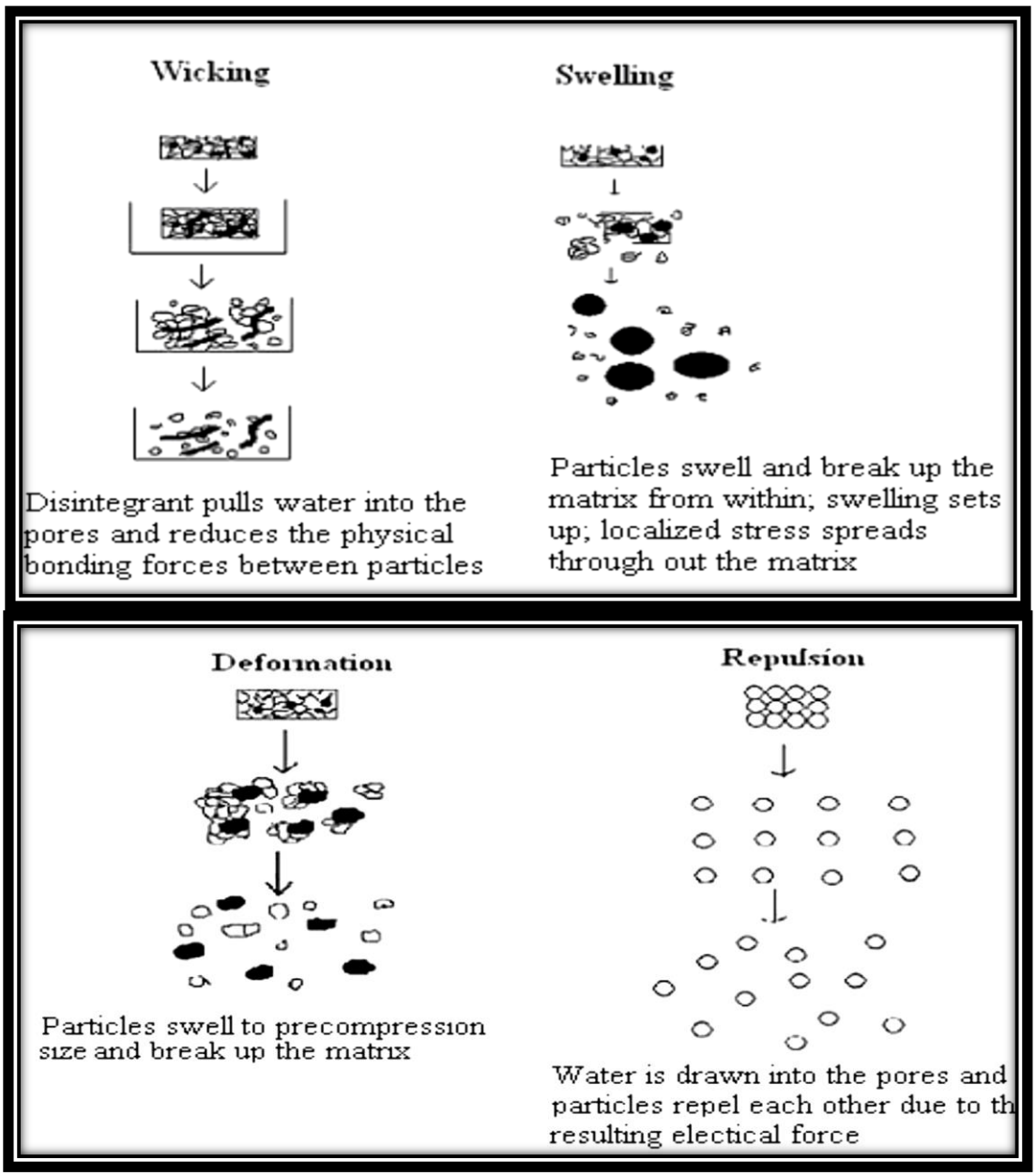
❖ Disintegrating particle/particle repulsive forces: This mechanism is secondary to the wicking and it explains the disintegration of tablets made from a non-swellable disintegrants. It was believed that electric repulsive

forces between particles in the presence of water is responsible for this process[75].

❖ Heat of wetting: This theory is limited to only some types of disintegrants and supposed that a localized stress is generated due to capillary air expansion when disintegrants with exothermic properties get wetted leading to tablet disintegration.

❖ Release of gases: The tablet is disintegrated quickly due to the pressure that is generated by the internal liberation of CO_2 in water as a result to the interaction between tartaric acid or citric acid (acids) with alkali metal carbonates or bicarbonates (bases) in the presence of water[71].

❖ Enzymatic action: In this mechanism the enzymes present in the body act as disintegrants that destroying the binding action of binder and helps in tablet disintegration[75].



Figure(5):Common mechanisms of tablet disintegration [75]

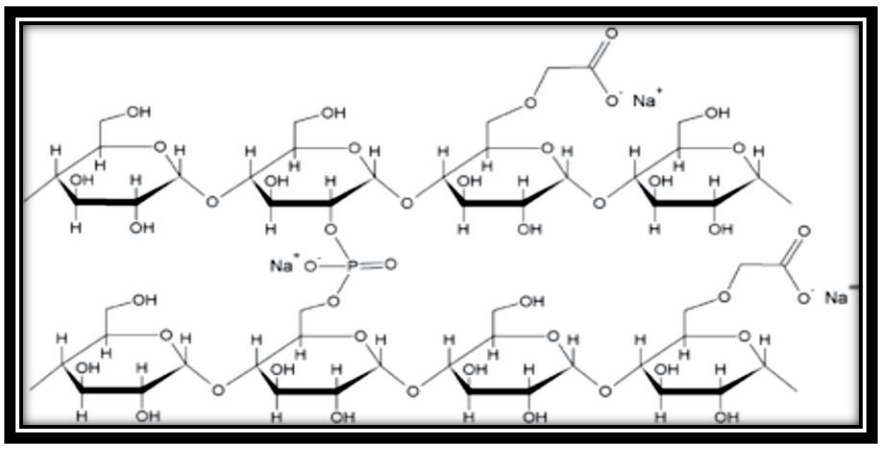
1.7.4.2 Types of superdisintegrants

Generally there are two types of superdisintegrants natural and synthetic. Natural superdisintegrants includes gums and mucilages like alginates, agar, pectin, chitosan, gum karaya, guar gum, gellan gum, isphagula, locust bean gum..etc[77,78]. Synthetic superdisintegrants includes

synthetic derivatives like sodium starch glycolate (SSG), crosscarmellose sodium (CCS), crosspovidone (CP), ion exchange resins like indion 414 kyron 314, low substituted hydroxypropyl cellulose, and cross-linked alginic acid[71].

❖ Modified starch (Sodium Starch Glycolate (SSG), Explotab®, Primogel®):

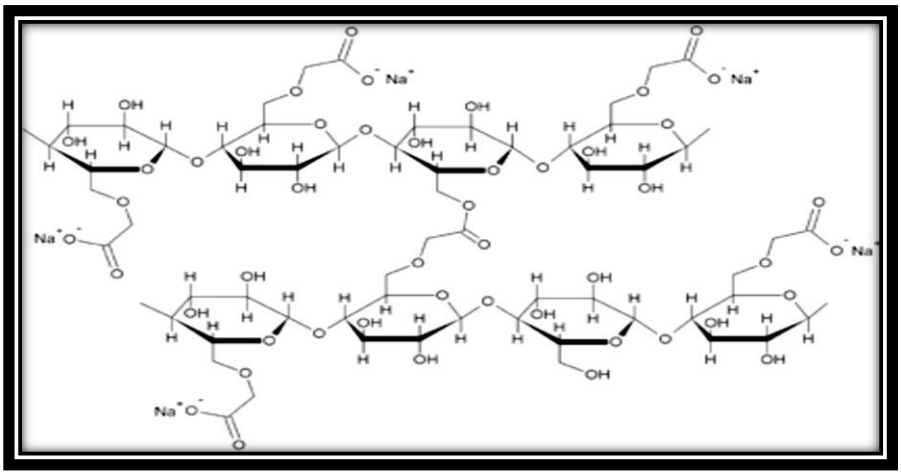
It is the sodium salt of a carboxymethyl ether of starch (Figure 6) that is mainly synthesized by cross-linking of potato starch[79,80]. The effectiveness of these superdisintegrants depends mainly on the degree of cross-linking and substitution. While crosslinking is used to reduce both the viscosity of the dispersion in water and the water soluble fraction of the polymer. The introduction of the large hydrophilic carboxymethyl groups is to disrupt the hydrogen bonding within the polymer structure which allows water penetration inside the molecule and the polymer becomes cold water soluble[71]. Optimum balance between both the degree of substitution and the extent of cross-linking allows rapid water uptake by the polymer without the formation of a viscous gel which might impede the dissolution process[79]. The mechanism of action involves rapid absorption of water leading to a massive increase in volume by 200-300 comparing to the natural starch which swells only to the extent of 10-20 percent of granules, this gives the rapid and uniform disintegration of the SSG[71].



Figure(6): Chemical structure of sodium starch glycolate (SSG)[(79)]

❖ Modified Cellulose (Crosscarmellose sodium (CCS), Ac-Di-Sol®):

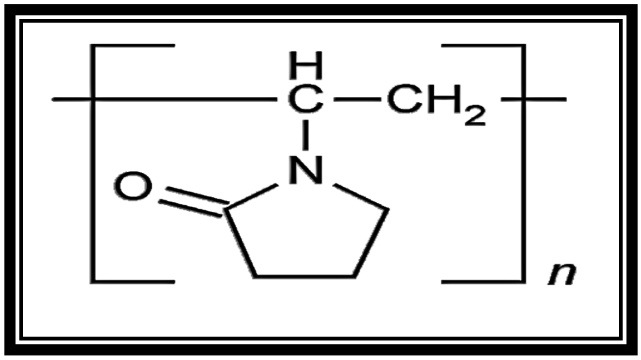
It is a cross-linked polymer of carboxymethylcellulose (Figure 7). It differs from SSG in its backbone, degree of substitution and in the mechanism of cross-linking. As it consists of cellulosic backbone with higher degree of substitution than SSG, at which some of the carboxymethyl groups themselves are used to cross-link the cellulose chains in the form of carboxyl ester links rather than phosphate ester links as in SSG[(79)]. It acts by wicking mechanism due to its fibrous nature, in addition to its high swelling capacity and minimal gelling tendency which gives a rapid disintegration process[(71)].



Figure(7): Chemical structure of crosscarmellose sodium (CCS)[(79)]

❖ Cross-linked polyvinyl Pyrrolidone (Crosspovidone (CP), Polyplasdone®):

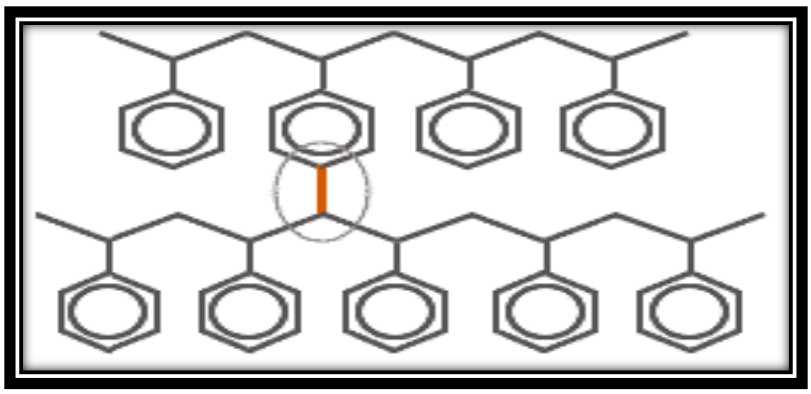
Crosspovidone (Figure 8) particles are found to be granular and highly porous under scanning electron microscope, which makes it highly compressible and facilitates wicking of liquid into the tablet and particles to generate rapid disintegration, It can be also used as solubility enhancer and available in two particle sizes in the form of Polyplasdone XL and Polyplasdone XL-10[71]. CP acts by both swelling and wicking, although, it has a limited swelling capacity which results from the deformation recovery upon wetting[81,82], with no gelling tendency even at high concentration unlike SSG and CCS[79].



Figure(8): Chemical structure of crosspovidone (CP)[80]

❖ Ion Exchange Resins (Indion® 414):

It is a weak acid cation exchange resin with COO^- as a functional group and K^+ as an exchangeable cation, that is fixed on cross-linked polystyrene as a backbone by using divinylbenzene as cross-linker (Figure 9). It is high purity pharmaceutical grade with a high water uptake capacity which can be used as a disintegrant, it also can be used in taste masking by adsorbing the bitter taste drug on its surface[83].



Figure(9): Chemical structure of cross-linked polystyrene [83]

1.8 Tablet coating

Tablet coating is a process of applying palatable paint on the surface of a pharmaceutical dosage form to attain specific benefits[84].

1.8.1 Historical perspective

Generally, modern and sophisticated methods of tablet coating sharing the same humble origin in the early 19th century, which was done by dusting or gilding methods. However, the development of sugar coating by the French in the mid-19th century had called for replacing the older methods of dusting and gilding by dipping and pan coating methods. The process of dipping was initially done by the placement of the freshly prepared pill onto long pins that dipped, several times, into a hot dipping solution. however, the difficulties in piercing a tablet with a needle called for the development of an alternative method. For this reason, J.B. Russell invented a new apparatus which was later adopted by Parke, Davis & Co. In this apparatus, the pins were replaced with a suction tube which covered one-half of the tablet. This allowing tablets to be dipped in the dipping solution and allowed to cool. Once cool, another set of tubes with a vacuum was applied to the

opposite side of the tablet while the first set was removed, and the same procedure was repeated.

Within time and where the turn of the 19th century approached, sugar coating in rotating pans was becoming the coating standard in large pharmaceutical fields[85]. In 1953, a dramatic changes was made when Abbott laboratories marketed the first film coated tablet, which consequently leads to the development of a series perforated pans, in addition to the air suspension coater which was invented by Dr. Dale Wurster, a professor in Wisconsin university, which leads to large progress in the tablet coating technology[86].

1.8.2 Mandatory for tablet coating

It is obvious that tablet coating adds additional expense to the production of pharmaceutical dosage form, but it's necessity generally arise from one or more of the following:-

1. To mask unpleasant color, odor or taste of the active ingredient.
2. To provide physical and chemical protection of the medicament.
3. To improve tablet appearance and facilitating its identification.
4. To modify the release of the active ingredient by the application of enteric coating polymers which is acid resistant or polymers that controlling the release of the drug.
5. To avoid chemical incompatibilities by the application of another drug or additive or to give sequential release of the drug[86,87].

1.9 Types of tablet coating

Generally there are two types of tablet coating; sugar coating and film coating

1.9.1 Sugar coating

It is one of the oldest techniques in pharmaceutical practice that still exist today which was originally developed for taste masking and presenting an attractive appearance for the tablets. It comprises mainly five stages:- sealing, subcoating, grossing (smoothing), coloring, polishing (glossing)[(84)].

❖ Sealing: It is performed by the application of an organic polymeric solution on the tablet surface to protect the tablet core from moisture penetration, e.g. shellac, zein, cellulose acetate phthalate[(88)].

❖ Subcoating: It is the major step in sugar coating to provide a coated tablet with rounded edges and build up the tablet weight. This is done by the application of 3 to 5 subcoats of sucrose based water syrup that also contains gelatin, acacia or PVP to improve coating structural integrity. To facilitate this build up, they sprinkled with dusting powder of sucrose mixed with starch and sometime acacia, talc or kaolin between the syrup subcoats[(39)].

❖ Grossing (smoothing): It is done to cover the surface imperfections and complete rounding of the coated tablet by the application of 5 to 10 additional coating of thick syrup with or without starch or calcium carbonate[(84)].

❖ Coloring: It is done by the application of appropriate dye or pigment that is dissolved or dispersed in a coating syrup[(88)].

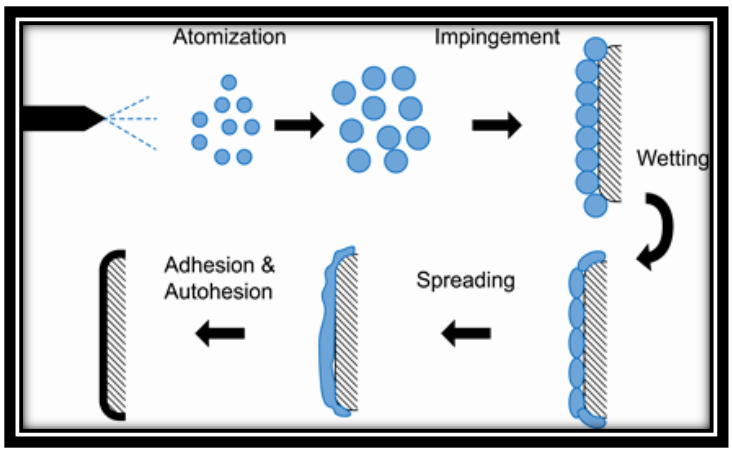
❖ Polishing (glossing): It is the final step and done by adding the coated tablet to a clean standard coating pan or canvas-lined coating pan and

carefully applying a beeswax or carnauba wax either as a dry powder or as a warm solution in a suitable volatile solvents[86].

1.9.2 Film coating

Film coating is a complex process which involves the application of a thin film (20-200 µm) of a polymer-based coating onto a suitable core (tablet, capsule, granule, bead and drug powder). It is applied either by manual lading or spray atomization that is the most common technique[88]. In case of spraying process, the sprayed droplets of the coating material are able to wet the surface of the substrate being coated followed by spreading and coalescence to form a thin film. Coalescence is enhanced by solvent evaporation which causes the polymer spheres to come together as a result of the cohesive forces between them[89]. Figure (10) shows the stages of film coating process.

Generally, the process of coalescence requires heating to a temperature in excess of the glass transition temperature (T_g) of the polymer (T_g can be defined as the temperature below which the polymer is brittle and above is flexible), in addition, solvent loss is governed by the amount of space between the polymer molecules (usually termed the free volume). As solvent loss progresses, the T_g of the polymer increases and the free volume decreases. Ultimately, the free volume becomes so small that further solvent loss becomes almost impossible. However, it is apparent that blocking or sticking of the coated products becomes a problem at temperatures in excess of 20 ºC above the T_g of the polymer, thus, an optimum processing condition for polymeric coating occurs over only a narrow range of temperatures[88].



Figure(10): Stages of film coating process [88]

1.10 Types of Film coating

Depending on the functionality of the film forming polymer, there are generally two types of film coating:-

1.10.1 Functional film coating

In this type the film coating has the ability to modify the release of the active ingredient to give either extended or delayed release:-

❖ Extended-release which also called sustained or controlled release is the dosage form that designed to release the drug at predetermined rate maintaining a constant drug concentration for a long period of time to minimize the side effect and dosage frequency.

❖ Delayed release dosage form is the one that releases the drug in a time other than directly after administration, and it includes the enteric coated product which has been applied to protect the active ingredient from degradation in the acidic pH of the stomach, that designed to decrease the gastric irritation or to target the drug to the small intestine[88,89].

1.10.2 Non-functional film coating

In this type, coating is done for any reason other than modification of the release characteristic of the active ingredient such as improving the product appearance, enhancing its stability or achieving a taste masking effect[88].

1.11 *Coating equipments*

Coating is generally applied by using one of the following equipments:-

❖ Standard coating pan: It is the oldest type and used mostly for sugar coating but it has several limitations represented by poor agitation of the tablet bed, poor heat transfer with a relatively long processing time which adds more cost to the coating process[90]. It includes three types: Pellegrini pan, immersion sword and immersion tube systems[86].

❖ Perforated coating pan: This type is suitable for both sugar and film coating with a high capacity for large batch size in a short processing time & high potential for atomization, but it is not suitable for a very small tablet or spheres[86]. It includes four types: Accella-Cota, Hi-Coater system, Driacoater and, Glatt coater.

❖ Fluidized bed (air suspension) coating system: It is also called Wurster column coating which can be used for both sugar and film coating. In this type the coating solution are sprayed along with a fluidizing air stream in the bottom of a long vertical column where the tablet are circulated as they are coated, with the evaporated solvent being removed from the top of this chamber[91]. This type is suitable to very small tablets or spheres that are easily fluidized and having adequate integrity to withstand the impact of

attrition with the chamber wall. Its limitations are the smaller batch size (comparing to perforated pan system), limitation of size and weight of the tablet in addition to its high cost[90].

❖ Specialized coating: It includes different techniques like:-

➢ Electrostatic coating: It is a dry coating process and it is done by applying an electrical charge to a conductive substrate and then applying the coating material which contains ionic species of the opposite charge to give a uniform coating of the substrate. This type is limited because of the non-conductive nature of the pharmaceutical ingredients, in addition, the repulsion between similar charge coating material limit the increase in coating thickness to a certain extent[84,86].

➢ Magnetically assisted impaction coating: In this type of dry coating an excited magnetic particle used for temporarily holding the coating material (guest particle) in order to deliver it to the surface of the substrate (host particle)[84].

➢ Dip coating: In this type coating liquid is applied to the core tablet by alternate dipping and drying of the tablet to get the desired coating[86].

➢ Vacuum film coating: It is a new procedure with specially designed sealed baffled pans that is hot water jacketed at which tablet are placed. Air is displaced by nitrogen and then the coating liquid is applied using a high-pressure airless spray system and the evaporated solvent is removed by a special vacuum system. This system has low energy requirement and high coating efficiency with suitability for organic solvent with a minimum environmental or safety hazards[86].

➢ Compression coating: It requires a specialized tablet machine and used to separate incompatible ingredients, providing a delayed or enteric properties

to the product and can be used when the tablet core cannot tolerate aqueous or organic solvents[86,91].

1.12 Materials used in film coating

Generally an ideal film coating formula consisting mainly from the film forming polymer, solvent (aqueous or organic) and plasticizer in addition to other miscellaneous components which are mixed together and applied to the core tablet[86].

1.12.1 Film forming polymer

Materials generally used to coat pharmaceutical dosage forms primarily made from acrylic and cellulosic polymers, and their use are governed by their aqueous solubility. Water soluble polymers including HPMC, hydroxypropyl cellulose, sodium carboxymethyl cellulose, PVP, polyethylene glycol (PEG) are often used for rapid disintegrating film coated tablet. On the other hand, water insoluble or swellable polymers (through which the drug are slowly diffuse) are generally used to give sustained release effect like ethyl cellulose and polymethacrylate polymers. Another type of polymers gives an enteric or delayed effect like cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate and several methacrylic acid copolymers. These polymers containing an acidic or acidic ester functional groups, which are unionized (insoluble) in the low pH of the stomach, while they are ionized (soluble) in the high intestinal pH[89].

Film forming polymer is the major ingredient in film coating formulations, consequently, it has the greatest impact on the final properties

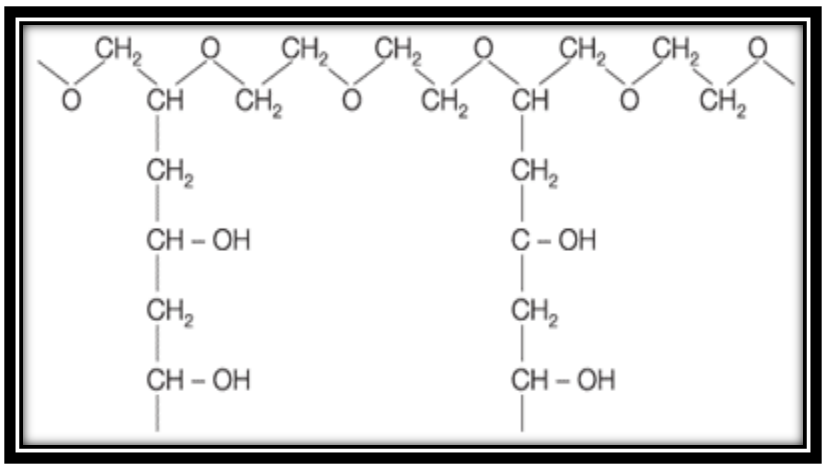
of the coated product. Therefore, the selection of a suitable film forming polymer is an essential task in order to ensure a good quality of the coating[88]. One of the newly discovered film former with unique properties is Kollicoat IR.

Kollicoat IR (Figure 11) is a neutral grafted polymer consisting of 75% polyvinyl alcohol (PVA) - 25% PEG with a molecular mass of ~ 45,000 Da and T_g of 45 C°. It was introduced to pharmaceutical research as an excipient and a film coating polymer by BASF Chemical Co. (Ludwigshafen, Germany) for producing an immediate release dosage form. Its backbone consisting of PEG (1000 or 3000) as internal plasticizer while the film forming polymer PVA forming its branches. It possesses a high pigment binding capacity, easy printing, with no tackiness as observed in PVA and PEG physical mixture, and with much lower viscosity and longer elongation at break comparing to the films of cellulose derivatives. Till now two dosage forms coated with kollicoat IR have been registered, 1000 mg metformin and Ibuprofen coated tablets indicating its new applications[92,93].

There are three types of Kollicoat IR differing mainly in compositions: Kollicoat IR, Kollicoat IR White and Kollicoat Protect[92]. These types and their major differences are listed below in table (2).

Table(2): Major differences between different types of kollicoat IR[92,93]

Criteria	Kollicoat IR	Kollicoat IR White	Kollicoat Protect
Composition	-Pure grafted polymer of 75% PVA, 25% PEG, 0.3% silicon dioxide	-Ready to use powder consisting of 45-74% KollicoatIR, 5-10% copovidon, 10-20%titanium dioxide, 10-20% Kaolin, 1-5% sodium lauryl sulfate	-Consisting of 55-65%Kollicoat IR, 35-45% PVA, 0.1-0.3% silicon dioxide
Solubility and dispersibility	-Readily soluble in water up to 50%.	-Due to its pigment content it disperses rather than dissolve in water to give a suspension.	-Readily soluble in water up to 30%.
Applications	-Immediate release film former for tablet and capsules. -Binder in wet granulation. -Film-forming agent in sprays and transdermal systems. -Pore forming agent in sustained release tablets and pellets -Stabilizer in suspensions. -Hydrophilic polymer for solid dispersion.	-Readily mixed film forming agent to produce white tablets to which other colors or pigments can be added.	-Protective film against oxidation and hydrolysis of the active ingredient with an excellent taste masking effect.



Figure(11): Chemical structure of kollicoat IR [92]

1.12.2 Solvent

Solvents are applied to dissolve or disperse the polymers and other additives in order to be delivered to the substrate surface. They are either aqueous or organic like ethanol, methanol, isopropanolol, chloroform or methylene chloride[86]. The primary criteria for their selection including cost, solvency, volatility, toxicity and environmental hazards. Therefore, unless the drug is unstable in the aqueous system, water is the preferred solvent to be applied in film coating process[89].

1.12.3 Plasticizer

Most polymers used in film coating are amorphous in nature, having T_g at which a temperature below it cause a cessation of molecular motion of the polymer. Due to the fact that T_g of most polymers is higher than any temperature condition experienced in the typical coating process, a further modification is performed by the addition of plasticizers[88]. Therefore, plasticizers act by weakening the intermolecular attraction between polymer chains, reduce T_g and tensile strength and increasing the

flexibility of the film[89]. There are two types of plasticizers internal and external plasticizers. The internal plasticizer is added to the basic polymer chain by certain chemical modification like PEG in kollicoat IR[86,93]. While external plasticizer is added as an external additive to the film coating formula like castor oil, PEG 200 and 400, surfactant like polysorbate (tween) and sorbitan esters (span)[86]. Therefore, to be effective, the external plasticizer must partition from the solvent into the polymer phase in order to diffuse between polymer's chain and disrupting the intermolecular interaction, for this reason, a sufficient time must be allowed prior coating initiation to provide an even distribution of the plasticizer within the film formula[89].

1.12.4 Miscellaneous components

❖ Colorants: Water insoluble pigments like an aluminum lake of water soluble dye and inorganic material like iron oxide are the most frequently used colorant nowadays which avoid color migration that is seen in the older water soluble dye.

❖ Opacifiers: Like titanium dioxide, talc, and aluminum silicate that are used to provide more pastel color, increasing film coverage, and to reduce the amount of the much expensive colorant[86].

❖ Flavorings and sweeteners: To mask the undesired odor or taste[86].

❖ Antioxidants and antimicrobials: To enhance the stability of the coat towards oxidation and microbial contamination consequently[86].

❖ Surfactants: To homogenize the coating formula, improving the wettability of the substrate and facilitating the spreading of the polymeric material on its surface.

❖ Antiadherents: Like talc which used to reduce stickiness and agglomeration of the coated substrate[89].

❖ Stabilizer and flavor retaining agent: like xanthan gum[94,95].

Xanthan gum is a natural anionic extracellular heteropolysaccharide, this important biopolymer is produced by the gram-negative bacteria *Xanthomonas campestris*[96]. Commercially, it is produced by a fermentation process using mostly glucose as a carbohydrate source[94]. It is a creamy colored powder with molecular weight ranges from $2x10^6$ to $20x10^6$ Da depending on the fermentation process[96]. Xanthan molecular structure (Figure 12) consisting from repeating pentasaccharide units, of two glucose units as a backbone that is connected to a trisaccharide side chain consisting from two mannose and one glucuronic acid with pyruvic acid at its terminal. The trisaccharide branches appear to be closely aligned with the polymer backbone giving a stiff chain which may exists as single, double, or triple helix[94,96]. Xanthan gum is one of the most commonly used hydrocolloids because of its versatile features like:

1. Having a viscous and slippery mouth feel upon hydration[97,98].
2. Non-toxic, non-sensitizing, compatible with various ingredients and does not cause any skin and eye irritation, therefore, approved by the united states FDA to be used without any quantity limitations[96,99]
3. Having high viscosity at rest even at very low concentrations[95], this viscosity is greatly reduced on heating up to 40 °C, after that it will gradually increase until 60 °C reached where it starts to decline, which may be attributed to the conformational changes in its helical structure due to temperature raising[96].

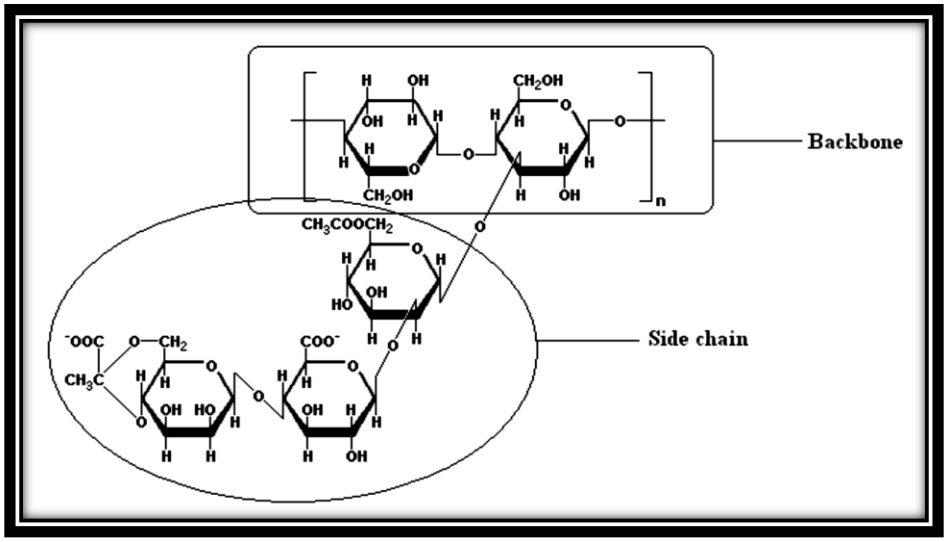
4. Having non-Newtonian, thixotropic, pseudoplastic behavior i.e. reversible shear thinning, with a yield stress that must be overcome to initiate the flow[96,100].

5. Soluble in both cold and hot water with rapid hydration rate that is improved by increasing the number of trisaccharides side chains as they holds the backbone apart from each other thus preventing hydrogen bond formation between them[101].

6. Having a good stability against thermal, enzymatic and pH (1-13) variations which may be attributed to its ordered helical conformation[102].

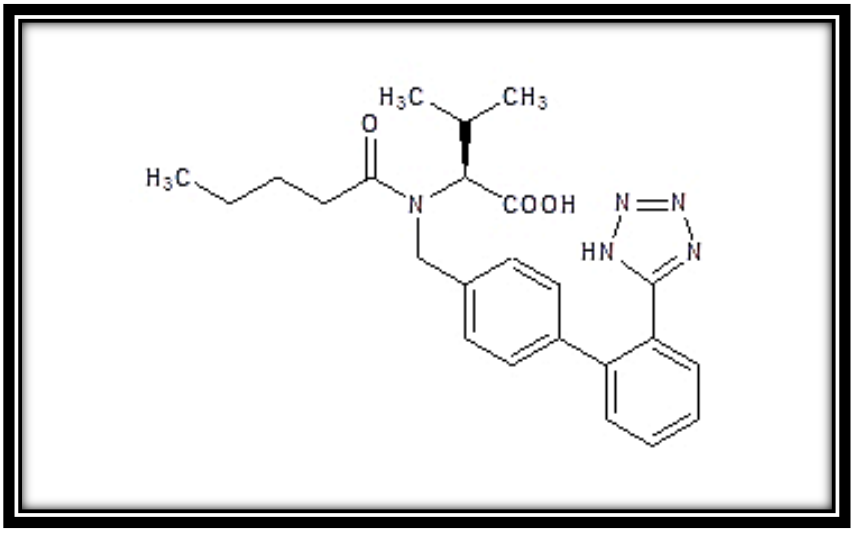
7. Have a synergistic viscosity when added to solutions of guar gum or locust been gum as these gums linked to the helices of xanthan gum giving more rigid gel like structure[103].

Because of its unique properties xanthan gum had versatile applications as thickening, suspending, stabilizing, gelling, emulsifying and flavor retaining agent for pharmaceutical and food processing purposes[94.95]. In addition, it is also used in the preparation of modified release, bioadhesive and floating drug delivery systems[104].



Figure(12): Chemical structure of xanthan gum[98]

1.13 Valsartan



Figure(13): Chemical structure of valsartan[105]

Valsartan (Figure 13) is an antihypertensive drug with a chemical name of N-[p-(o-1H-Tetrazol–5–ylphenyl)benzyl]-N-valeryl-L-valine and molecular weight equal to 435.5[106]. It contains two weakly acidic groups with a pKa 3.9 and 4.7[107]. It is a white to practically white fine powder, with slightly bitter or metallic taste having a melting point from 116°C to 117°C. It is soluble in ethanol and methanol, slightly soluble in water, partition coefficient (n-octanol/aq. phosphate buffer) equals to 0.033[105,108]. Valsartan is marketed under the trade name Diovan®[106], and available in a three dosage forms, film coated tablet (40,80,160,320 mg), capsules (40,80,160 mg), and recently as an oral solution (3mg/ml), mostly recommended for doses ≤ 80 mg[109,110].

1.13.1 Pharmacokinetics

Valsartan has a rapid absorption after oral administration, regardless food intake, with a peak plasma concentration after 2-4 hours[111]. It has high protein binding 94 to 97% mainly to albumin[106]with a bioavailability about 25%. Valsartan's half-life is 6-9 hours and its antihypertensive effect lasts for 24 hours. Less than 10% of its orally administered dose undergoes biotransformation in the liver with no active metabolites. It is eliminated mostly as unchanged drug primarily via the bile (86%) and to a lesser extent via the kidneys (13%)[111].

1.13.2 Indications and mechanism of action

Valsartan is an antihypertensive drug belongs to the group of angiotensin receptor blockers (ARB), it acts by competitively inhibiting the binding of angiotensin II (Ang II) to AT_1 recepter that presents in many tissues like adrenal gland and vascular small muscle, thus efficiently inhibits the AT_1-mediated vasopressor and the aldosterone-secreting effect of Ang II which eventually leading to reduced vascular resistance and blood pressure[107,112]. Therefore, valsartan is mainly used in the management of hypertension, heart failure and to reduce cardiovascular mortality in patients with left ventricular dysfunction after myocardial infarction[113].

Recently, the researchers show that valsartan can also act as a selective modulator to the gamma peroxisome proliferator-activated receptor which is a central regulator to the metabolism of insulin and glucose. Therefore, this dual mode of action give valsartan the protective benefits towards the vascular and renal damage that caused by diabetic and cardiovascular disorders[114].

In addition a new study find that ARB including valsartan is effective protector against stroke due to hyperstimulation of AT_2 by Ang II that increases 3 to 5 folds after the blockage of AT_1 receptor by ARB (valsartan)[115].

1.13.3 Administrations and adverse effects

In hypertension, valsartan is administered in an initial dose of 80 mg once daily. This may be increased, on need, to 160 mg once daily, the maximum dose is 320 mg once daily. In patients with myocardial infarction, valsartan may be started as early as 12 hours after the infarction in clinically stable patients, with an initial dose of 20 mg twice daily, this dose may be doubled at intervals over the next few weeks up to 160 mg twice daily if tolerated. In heart failure, valsartan is administered in an initial dose of 40 mg twice daily. The dose should be increased, as tolerated, to 160 mg twice daily.

Valsartan's side effects have been reported to be usually mild and transient including dizziness, headache, and dose-related orthostatic hypotension. Impaired renal function and, rarely, rash, urticaria, pruritus, angioedema, and raised liver enzymes may occur. Hyperkalaemia, myalgia, and arthralgia have been reported. It is less likely to cause a dry cough comparing with angiotensin converting enzyme inhibitors[113].

1.14 Recent technologies to overcome swallowing difficulties

In addition to the various technologies that implemented recently to overcome the problem of swallowing difficulties like rapid disintegrating films, buccal patches, chewing gums and chewable tablets[116], several new technologies were developed in the past few years like oral jellies, easily swallowed films and lubricating sprays.

❖ It was reported that easily handling and swallowing Jelly-like preparations are found to be useful as an oral dosage form for elderly people. These preparation was formulated using different materials like sodium caseinate, glycerogelatin and dried gelatin gel powder. But the heating procedure that is required in their formulation rendering them not suitable for thermolabile drugs. Recently, silk fibroin is used in the medical field in addition to its use as a biomaterial and as a food additive[117]. Silk fibroin is a specific silk protein-based material that is produced from a number of arthropods mostly from the silkworm *Bombyx mori*[118]. It was used for the development of easily swallowing silk fibroin based gel of salbutamol[119] and drotaverin HCl[120]. Although, it carries the disadvantage of physical, chemical and microbial instability due to the presence of water[121], in addition to its comparatively high cost[122].

❖ Easily swallowed film formulation was developed that consisting from a dry film that swells immediately upon contact with a small amount of saliva and converts into easily swallowed jelly. It consists of a drug-containing layer that placed in the middle of two gelating layers which restrain the elution of the active ingredient in the mouth to give an efficient taste masking. It is clearly obvious that this dosage form has a limited drug

loading capacity which is due to its small volume (15 mm diameter x 0.2 mm thickness)[122].

❖ The lubricating spray (Pill Glide®) manufactured by FLAVORx company, is a water-based lubricating spray which creates a frictionless barrier between pills and the tongue/throat. It is effective in the prevention the "stuck in the throat" feeling that are experienced by many people, and it is also useful in preventing the bad tasting/smelling tablets from contacting the taste buds[123]. It is available in 5 flavors like Grape, Orange, Peach, Strawberry, and Bubblegum[124] and is applied by spraying the mouth (2-3 times) directly before swallowing the pill with water[125].

Aim of study

The aim of this study is to prepare an easily swallowed oroslippery tablet (OST) of valsartan with suitable taste masking and immediate release effect in the GIT, these tablets quickly hydrate and turn slippery upon contact with saliva (due to the presence of a special coat) leading to an easy swallowing of the intact tablet without the need of water. The prepared tablets are to be optimized by studying the effect of different variables in order to provide new tablets that may be used as an alternative to other tablets which were designed to overcome swallowing difficulties.

Chapter Two

Experimental Work

2. Experimental work

2.1 Materials

The materials used in this study are listed below in table (3).

Table(3): Materials used in the study

No.	Materials	Company
1.	Corn starch	Sigma-Aldrich co., Germany
2.	Crosscarmellose sodium (CCS)	Samara drug industry, Iraq
3.	Crosspovidon (CP)	Aladdin chemistry, China
4.	Diovan®-160mg	Novartis pharmaceutical co., Switzerland
5.	Hydrochloric acid (HCl)	Biosolve, Germany
6.	Hydroxypropylmethyl cellulose (HPMC 50 cps)	Provizer pharma, India
7.	Indion 414	Gift from ion exchange resin co., India
8.	Kollicoat IR (kol.)	Sigma-Aldrich co., Germany
9.	Magnesium stearate	Scharlab S.L., Spain
10.	Mannitol	Provizer pharma, India
11.	Microcrystalline cellulose (Avecil) PH 101	Caleva process solutions Ltd, UK
12.	Peppermint oil	BDH chemicals Ltd Poole, England

Table(3): Continued

13.	Polyvinylpyrrolidone (PVP)	Samara drug industry, Iraq
14.	Potassium dihydrogen orthophosphate	Gainland chemical company, UK
15.	Red iron oxide	Laboratory chemical, India
16.	Sodium bicarbonate	Samara drug industry, Iraq
17.	Sodium hydroxide	Sinopharm chemical reagent co. Ltd, China
18.	Sodium starch glycolate (SSG)	Aladdin chemistry, China
19.	Spray dried lactose (SDL)	Samara drug industry, Iraq
20.	Talc	Himedia, India
21.	Titanium dioxide	Himedia, India
22.	Valsartan	Provizer pharma, India
23.	Xanthan gum (xan.)	Himedia, India

2.2 Instruments

The instruments used in this study are listed below in table (4).

Table(4): Instruments used in the study

No.	Instruments	Manufacturer
1.	Digital vernier caliper	Copley, UK
2.	Disintegration apparatus	Copley, U.K.
3.	Electronic balance	Kern, Germany
4.	Friabilator	Vanguard, USA
5.	FTIR spectrophotometer	Shimadzu 8300, Japan
6.	Hardness tester	Guoming, India
7.	Hot air oven	Nuve EN 400, Germany
8.	Hot plate magnetic stirrer	Dragon lab., China
9.	Melting point apparatus	Stuart, England
10.	pH meter	Inolab, Germany
11.	Single punch tablet machine	Riva, Germany
12.	USP dissolution tester type II (paddle)	Vanguard, USA
13.	UV-Visible spectrophotometer	Shimadzu, Japan

2.3 Methods

2.3.1 Characterization of valsartan

2.3.1.1 Determination of valsartan melting point

According to the USP; melting point or melting range is the temperature(s) at which the solid coalesces and is completely melted. In our study it was measured by placing the capillary tube inside an electrical melting point apparatus with a gradual increasing in its temperature, until a point at which the powder passes completely into liquid phase was reached, this temperature was recorded and considered as the melting point[(126)].

2.3.1.2 Determination of valsartan λ_{max}

Stock solutions of valsartan (0.5 mg/ml) in phosphate buffer pH 6.8 and (0.05 mg/ml) in HCl pH 1.2 were prepared separately, which was suitably diluted in order to be scanned by UV-Visible spectrophotometer from 200-400 nm for the determination of valsartan's wavelength of maximum absorbance (λ_{max}).

2.3.1.3 Construction of valsartan calibration curve

Calibration curve of valsartan was constructed by preparation of appropriate serial dilutions from the prepared stock solutions of both phosphate buffer pH 6.8 and HCl pH 1.2, where they further analyzed at the previously determined λ_{max} using UV-visible spectrophotometer, and the recorded absorbance for each sample was plotted versus the concentration in order to obtain valsartan calibration curve.

2.3.1.4 Determination of valsartan pH-solubility profile

The solubility of valsartan was determined using saturation shake flask method. This was done by adding 200 mg of valsartan to 20 ml of HCl pH 1.2 and phosphate buffer pH 6.8 respectively and mixing for 48 hours at 25 ºC by magnetic stirrer at 100 rpm, three independent experiments were carried out for each solution. After that, each solution was filtered and three samples of filtrate for each experiment was analyzed separately under UV-visible spectrophotometer at the previously determined λ_{max}, then the average concentration was taken[127,128].

2.3.2 Preparation of the oroslippery tablets

2.3.2.1 Preparation of core tablets

The core tablets of valsartan and the blank (drug-free) were prepared by using the ingredients shown in table (5). All formulas were prepared by direct compression method except for C19 which was formulated by wet granulation. In the direct compression method, a pre-weighed amounts of all ingredients were passed through sieve number 25 and then mixed in a geometric order (except Mg stearate) for 10 minutes, which continued for another 5 minutes after the addition of Mg stearate[129]. While, in wet granulation, the pre-weighed amount of all ingredients except the lubricant were thoroughly blended in a dry mortar and granulated with sufficient quantity of water as a granulating fluid, then the wet mass was pressed via a sieve number 8 to obtain wet granules. These wet granules were dried at 60°C for 1 hour in order to obtain discrete granules, the dried granules were further passed through sieve number 18 and mixed with the

lubricant[130]. The lubricated blend in both methods was directly compressed using 11mm circular concave punch in a single punch tablet machine.

2.3.2.2 Preparation of the aqueous coating dispersion

The aqueous coating dispersion prepared in four steps:

❖ Step 1: Preparation of the pigment suspension

The red iron oxide (pigment), titanium dioxide (opacifier) and talc (anti-adherent) were suspended in distilled water at room temperature with continuous stirring using magnetic stirrer at 400 rpm for about 10 minutes until we get a homogeneous, lump-free dispersion.

❖ Step 2: Preparation of the polymer solution

Kollicoat IR (kol.) was added gradually with continuous stirring to the aqueous solution containing mannitol as a sweetening and flavor retaining agent[131] using magnetic stirrer at 100 rpm, the stirring was continued for 15 minutes at room temperature until a clear solution was obtained.

❖ Step 3: Preparation of the xanthan gum mixture

The slipperiness inducing agent, xanthan gum[97,98] (xan.), was added to distilled water that was previously heated to 40°C and mixed using magnetic stirrer at 600 rpm for about 5minutes.

❖ Step 4: Preparation of the coating dispersion

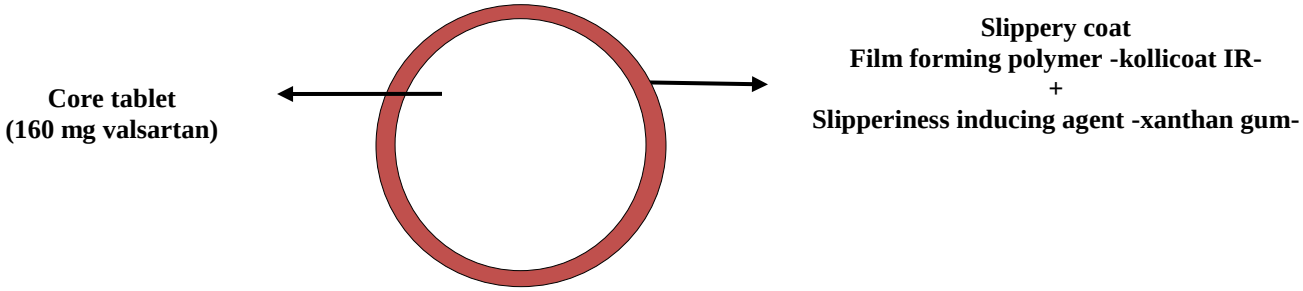
This was done by the addition of the homogenized pigment dispersion (step1) (after passing it through a sieve number 50 in order to remove any agglomerated residue) to the polymer solution (step 2) and mixing together in magnetic stirrer at 400 rpm for about 5 minutes at room temperature, this was followed by its addition to the xan. dispersion (step 3) gradually, followed by adding peppermint oil with continuous stirring at 400

rpm for another 5 minutes at room temperature. Peppermint oil here act as flavoring and cooling agent[132]; which further increases patient compliance, and also enhances the swallowing process throughout the induction of salivation[131] and cold perception which stimulates the trigeminal nerve which further improving the swallowing reflex[36]. All components of the coating dispersion are shown in table (6).

2.3.2.3 Coating of core tablets

The prepared OSTs (Figure 14- A and B) were obtained by dipping the prepared core tablets in the prepared coating dispersion with the help of suitable forceps, followed by drying for about 5 minutes at temperature around 60°C using a hot air dryer. Tables (7) and (8) illustrates the compositions of the prepared valsartan and blank OSTs respectively.

Figure(14): A- Sample of the prepared valsartan OSTs



Figure(14):B- Graphical diagram of the prepared valsartan OST

Table(5): Composition of the core tablets (mg)

Ingredients	C1	C2	C3	C4	C5	C6	C7	C8	C9	C10	C11
Valsartan	160	160	160	160	160	160	160	160	160	160	160
HPMC 50cps	8	16	24	24	24	24	24	24	24	24	24
Corn starch	8	8	8	16	24						
CP						8	16	24			
SSG									8	16	24
Indion 414											
CCS											
Mannitol	220	212	204	196	188	204	196	188	204	196	188
Mg stearate	4	4	4	4	4	4	4	4	4	4	4
Total weight	400	400	400	400	400	400	400	400	400	400	400

Table(5): Continued

Ingredients	C12	C13	C14	C15	C16	C17	C18	C19*	C20	C21	C22
Valsartan	160	160	160	160	160	160	160	160	160	160	
HPMC 50cps	24	24	24	24	24	24	24	24			24
Indion 414	8	16	24								
CCS				8	16	24	24	24	24	24	24
Mannitol	204	196	188	204	196	188		188	204	204	
SDL							188				
PVP									8		
Avecil										8	348
Mg stearate	4	4	4	4	4	4	4	4	4	4	4
Total weight	400	400	400	400	400	400	400	400	400	400	400

C19 was prepared by wet granulation

Table (6): Composition of coating dispersion (% w/w)

Ingredients	T1	T2	T3	T4	T5	T6
Kollicoat IR	15%	10%	20%	15%	15%	15%
Mannitol	2.5%	2.5%	2.5%	2.5%	2.5%	2.5%
Red iron oxide	1%	1%	1%	1%	1%	1%
Titanium dioxide	2%	2%	2%	2%	2%	2%
Talc	2%	2%	2%	2%	2%	2%
Xanthan gum	0.3%	0.3%	0.3%	0%	0.1%	0.5%
Peppermint oil	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%
Distilled water	76.7%	81.7%	71.7%	77%	76.9%	76.5%

Table(7): Compositions of the prepared valsartan OSTs

Prepared valsartan OSTs	Compositions
F1-F21	C1-C21(T1)
F22	C17(T2)
F23	C17(T3)
F24	C21(T2)
F25	C21(T3)
F26	C17(T4)
F27	C17(T5)
F28	C17(T6)
F29	C21(T4)
F30	C21(T5)
F31	C21(T6)
F32	$C17(T1)^{2*}$
F33	$C17(T1)^{3*}$
F34	$C21(T1)^{2*}$
F35	$C21(T1)^{3*}$

***$(T1)^2$ and $(T1)^3$: Representing double coating and triple coating respectively**

C: Representing the formula of the core tablet

T: Representing the formula of the coating dispersion

F: Representing the formula of the prepared valsartan OSTs

Table(8): Compositions of the prepared blank OSTs

Prepared blank OSTs	Compositions
B1	**C22(T1)**
B2	**C22(T2)**
B3	**C22(T3)**
B4	**C22(T4)**
B5	**C22(T5)**
B6	**C22(T6)**
B7	**$C22(T1)^2$**
B8	**$C22(T1)^3$**

2.3.3 Pre-compression evaluation of the core powder mixture

Flowability of the powder mixture is of critical importance in the production of tablet dosage forms, and is commonly evaluated by measuring angle of repose, Carr's index (compressibility index) and Hausner ratio[126].

2.3.3.1 Angle of repose

It is the maximum possible angle between the surface of the pile of powders or granules and the horizontal plane[133]. The static angle of repose was measured by the fixed base method using a circular dish with sharp edges. The powder poured into the center of the dish from the funnel, that can be raised vertically without vibration to maintain approximately (2-4 cm) from the top of the powder pile, until a maximum cone height is obtained, then the angle of repose (θ) was calculated from the equation below[8,126]. Table (9) illustrated the angles of repose along with their corresponding flow properties.

$$\tan(\theta) = \text{Height}/\text{Radius}$$

Table(9): Flow properties and corresponding angles of repose according to the USP[126]

Flow property	Angle of repose (degrees)
Excellent	25-30
Good	31-35
Fair- aid not needed	36-40
Passable-may hang up	41-45
Poor-must agitate or vibrate	46-55
Very poor	56-65
Very, very poor	>66

2.3.3.2 Compressibility index and Hausner ratio

These were calculated by measuring the unsettled apparent bulk volume of 8 gm sample contained in 10 mL measuring cylinder, followed by measuring the powder's final tapped volume after tapping the material until no further reduction in the volume occur[126], as they will be used further for calculation of bulk density and tapped density respectively. The compressibility index (Carr's index) and Hausner ratio and the corresponding flow properties were shown in table (10) and calculated as follows[134,135]:

$$Compressibility\ index = \left[\frac{\text{tapped density} - \text{bulk density}}{\text{tapped density}}\right] * 100$$

$$Hausner\ tatio = \left[\frac{\text{tapped density}}{\text{bulk density}}\right]$$

Table (10): Flowability and its corresponding values of compressibility index and Hausner ratio according to the USP[126]

Compressibility index	Flow character	Hausner ratio
<10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very, very poor	>1.60

2.3.4 Post-compression evaluation of the prepared core and coated oroslippery tablets

2.3.4.1 Thickness

The thickness of the prepared core and coated OSTs was measured using vernier caliper[136], and the result for each was the average of three individual readings ± SD.

2.3.4.2 Hardness

Tablet hardness is the force required to break a tablet in a diametric compression test, normally tablets require a certain value of hardness to withstand the mechanical shock[137]. This test was applied for the prepared core and coated OSTs using an electrical hardness tester, and the result was expressed as an average value of three individual readings ± SD.

2.3.4.3 Friability

Friability test was performed to assess the effect of shocks and friction during handling which may cause tablets to cap, chip or break[138]. This test was done by placing a pre-weighed, clean 20 cores or coated OSTs in the friabilator, which were allowed to fall freely from the height of 6 inch at a speed of 25 rpm for 4 minutes. Tablets were de-dusted and re-weighed and weight loss was recorded. The acceptable percentage weight loss or % friability should be lower than 1% and calculated as follow[126,139]:

$$\%\ Friability = \left[\frac{initial\ weight - final\ weight}{initial\ weight}\right] * 100$$

2.3.4.4 Weight variation

Weight variation test for both core and prepared OSTs was achieved by individually weighing 20 tablets and comparing each individual weight to the average. Tablets pass the test if no more than 2 tablets were outside 5% of the average, and no tablet differs by more than 10% of the average weight, as shown in table (11)[126,140] .

Table (11): Weight variation according to the USP[126]

Average weight of tablets (mg)	Maximum % difference allowed
130 or less	10
130 - 324	7.5
More than 324	5

2.3.4.5 In-vitro disintegration test

According to the USP, disintegration is the state at which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on a screen or attached to the lower surface of a disk (if used), is a soft mass with no palpable firm core. The disintegration apparatus consisting of a one-liter beaker with a basket rack assembly containing six tubes open in one end and with a 10-mesh screen in the other end[126]. The disintegration test was performed for the prepared OSTs and also for the marketed tablet (Diovan® -160 mg) at 37 ± 0.5°C in HCl pH 1.2. One tablet was placed in each tube and the time for complete disintegration of the six OSTs was recorded.

2.3.4.6 In-vitro release study

In-vitro dissolution of the prepared OSTs and the marketed conventional tablet (Diovan®-160 mg) was performed using USP apparatus type II (paddle) at 37 ± 0.5°C in 1000 ml, phosphate buffer pH 6.8 at 50rpm[141,142]. In addition the release profile of the optimum OSTs formulas F32,F34 and the marketed Diovan® was also performed in HCl pH 1.2 as dissolution media under the same conditions. Five milliliters samples were periodically withdrawn at (5,10,15,20,30,45,60,90,120) minutes intervals and each sample was replaced with an equal volume of fresh dissolution medium. Then, the withdrawn samples were filtered and suitably diluted to be analyzed spectrophotometrically at 250 nm and 203 nm for phosphate buffer pH 6.8 and HCl pH 1.2 respectively. Each experiment was done in triplicate and the result was expressed as a mean ± SD. The time required for

80% release ($T_{80\%}$) and percent drug released in 30 minutes ($\%D_{30min}$) were used for comparison.

2.3.4.7 In-vivo evaluation of slipperiness and taste masking effect

The in-vivo slipperiness evaluation was performed to the prepared blank (drug-free) OSTs formulas B1-B8 on five healthy human volunteers from whom informed consent was first obtained, and the time (in seconds) required for the blank tablets to become slippery and swallowed without water was recorded and expressed as an average value ± SD.

In order to assure that the prepared OSTs remained intact with adequate taste masking during their residence in the oral cavity, the taste masking effect was performed by using the rolling method[(132)] on the selected OSTs formulas F17,F22,F23,F26-F28,F32,F33 on five healthy human volunteers whom got detailed briefing on the purpose of this test, after that they told to roll the OSTs gently in their oral cavity without chewing or biting, and at the first sensation of a slight bitterness they were told to spit the OSTs along with the saliva and to rinse their mouth immediately. The time required to feel bitterness was recorded and considered as an indicator for taste masking property for the prepared OSTs. The results were also expressed as average values ± SDs. Therefore, a lower slipperiness values along with higher taste masking results were considered to be the best results.

2.3.5 Variables affecting the formulation of the prepared oroslippery tablets

Two types of variables were studied:

❖ Variables related to the core tablet: Including the effect of disintegrant and binder type and concentration, diluent type and method of core tablet preparation on the disintegration and dissolution of the prepared OSTs.

❖ Variables related to the coat: Including the effect of kol. and xan. concentration in addition to the coating level on the disintegration and dissolution of the prepared OSTs in addition to their influence on the slipperiness and taste masking effect.

2.3.5.1 Effect of HPMC concentration in the core

The prepared OSTs formulas F1-F3 were used to study the effect of different concentrations (2%,4%,6%) of the binder (HPMC) in the core on the disintegration and drug release in the presence of corn starch as disintegrating agent.

2.3.5.2 Effect of corn starch concentration in the core

Formulas F3-F5 were prepared to determine the effect of different concentrations of corn starch (2%,4%,6%) in the core tablet on the disintegration and the release of the drug from the prepared OSTs.

2.3.5.3 Effect of superdisntegrant type and concentration in the core

The prepared OSTs formulas F6-F17 were formulated to demonstrate the effect of different superdisintegrants (CP, SSG, indion 414, CCS) and their concentrations (2%,4%,6%) on the disintegration time and release.

2.3.5.4 Effect of diluent type in the core

Mannitol and spray dried lactose (SDL) are used in the core tablets of F17 and F18 respectively to show the effect of diluent type on the disintegration and drug dissolution of the prepared valsartan OSTs.

2.3.5.5 Effect of method of core tablet preparation

The core tablet of the prepared OST formula F19 was prepared by wet granulation method, to be compared with F17, in which the core tablet was prepared by direct compression method, in order to show the effect of core tablet preparation method on the disintegration and dissolution of valsartan OSTs.

2.3.5.6 Effect of binder type in the core

The formulas F17,F20,F21 were used to demonstrate the effect of different types of binders (HPMC, PVP, and avecil) respectively in their corresponding core tablets, on the disintegration and dissolution of the valsartan OSTs.

2.3.5.7 Effect of kollicoat IR concentration in the coat

The film forming polymer kol. was used in three different concentrations (10%,15%,20%) in the coating dispersion. Formulas F17 and F21-F25 were prepared in order to illustrate this effect on the disintegration and dissolution of the prepared OSTs. In addition, formulas F17,F22 and F23 were used to study the effect of different kol. concentrations on the taste masking effect of valsartan OSTs, while blank (drug-free) OSTs formulas B1-B3 were used to study the impact of kol. concentration on the slipperiness of the prepared OSTs.

2.3.5.8 Effect of xanthan gum concentration in the coat

The slipperiness inducing agent xan. was used in different concentrations (0%,0.1%,0.3%,0.5%) in the coating dispersion. Formulas F17,F21, and F26-F31 were prepared to demonstrate the effect of xanthan gum and its concentration on the disintegration and dissolution of valsartan OSTs. Valsartan OSTs formulas F17,F26-F28 were used to study the effect of xan. presence and concentration on the in-vivo taste masking property of the prepared OSTs, while the blank OSTs formulas B4-B6 were prepared to show the effect of xan. on the slipperiness of the prepared tablets.

2.3.5.9 Effect of coating level

The prepared core tablets were coated by dipping once (single layer coating), twice (double layer coating) and three times (triple layer coating), as they were suitably dried between each consecutive dipping process. The prepared OSTs formulas F17,F21,F32-F35 were studied to demonstrate the effect of coating level on the disintegration and dissolution

of valsartan OSTs. On the other hand, formulas F17,F32, and F33 were used to study the effect of these different coating levels on the taste masking effect of the prepared valsartan OSTs, in addition, the in-vivo slipperiness of the prepared OSTs were studied using the blank OSTs formulas B1,B7,B8.

2.3.5.10 Effect of rotational speed of the dissolution apparatus on the dissolution of the optimum OST formulas

To demonstrate the effect of GIT peristalsis and contractions on the dissolution of the prepared valsartan OSTs, the dissolution of the optimum formulas F32,F34 was carried out using three paddle rotational speeds (25,50,100 rpm), and the changes in drug release were observed.

2.3.6 Comparison of the optimum OSTs formulas with their core tablets

In order to see the impact of the oroslippery coat on the disintegration and drug release of the prepared OSTs, the in-vitro disintegration and dissolution for the optimum OSTs formulas F32,F34 and their corresponding core tablets C17,C21 were studied.

2.3.7 Comparison of the optimum OSTs formulas with the conventional marketed tablet (Diovan®)

Optimum formulas F32,F34 were compared with the marketed Diovan® with respect to their disintegration time and release profile using both HCl pH 1.2 and phosphate buffer pH 6.8 as dissolution media. The similarity between the release profiles for the optimum formulas and the marketed conventional tablet was determined using both similarity factor (f_2)

and difference factor (f_1) which were calculated using the equations below. The release profiles were considered to be similar when they have (f_2) values more than 50, and (f_1) values less than 15[(143)].

$$f_1 = \left\{ \frac{[\sum_{t=1}^{n} |R_t - T_t|]}{[\sum_{t=1}^{n} R_t]} \right\} * 100$$

$$f_2 = 50 * log \left\{ \left[1 + \frac{1}{n} \sum_{t-1}^{n} (R_t - T_t)^2 \right]^{-0.5} * 100 \right\}$$

Where,

n= number of time points.

R= % drug released of the reference at time t.

T= % drug release of the test at time t.

2.3.8 Content uniformity

Content uniformity was applied to the optimum OSTs formulas F32,F34 according to the USP specifications by randomly selecting 30 OSTs from each formula, ten of these OSTs were assayed individually and only one tablet should be outside the range 85-115% but not outside the range of 75-125%. If these requirements not achieved, the remaining 20 OSTs should be tested and none of them could be outside the range 85-115%[(8)]. Drug content measured by grinding the OST in a mortar, and accurately weighed powder equivalent to 20 mg valsartan was dissolved in 100 ml phosphate buffer pH 6.8, the resultant solution was filtered and the filtrate was collected and suitably diluted with phosphate buffer pH 6.8 and assayed for valsartan at 250 nm[(130)].

2.3.9 Drug excipients compatibility

Physicochemical compatibility between valsartan and different excipients were tested using Fourier transform infrared spectroscopy (FTIR). The pure drug powder (valsartan) and mannitol powder, as well as the optimum core tablets formulas C17,C21 and their corresponding OSTs formulas F32,F34 (which were previously grinded into a fine powder), were analyzed in FTIR from 4000-400 cm^{-1} by the pressed disk technique. The disc was prepared by mixing 0.5-1mg of the drug sample with approximately 100 mg of dry powdered potassium bromide, the mixture was pressed with special dies under a pressure of 10,000-15,000 psi to form a transparent disc[144].

2.3.10 Stability study

Stability of the selected OSTs formulas F32,F34 were tested in three temperatures (40,50,60°C) for 3 months[145]. Samples were withdrawn every 14 days and analyzed using UV- spectrophotometer at 250 nm.

2.3.11 Statistical analysis

The results were expressed as average values ± SDs in the form of error bars, and were analyzed using analysis of variance (ANOVA) single factor to compare the samples means and to determine the statistical significance, at which ($p<0.05$) was considered to be significant.

Chapter Three

Results and Discussions

3. Results and discussions

3.1 Characterization of valsartan

3.1.1 Determination of valsartan melting point

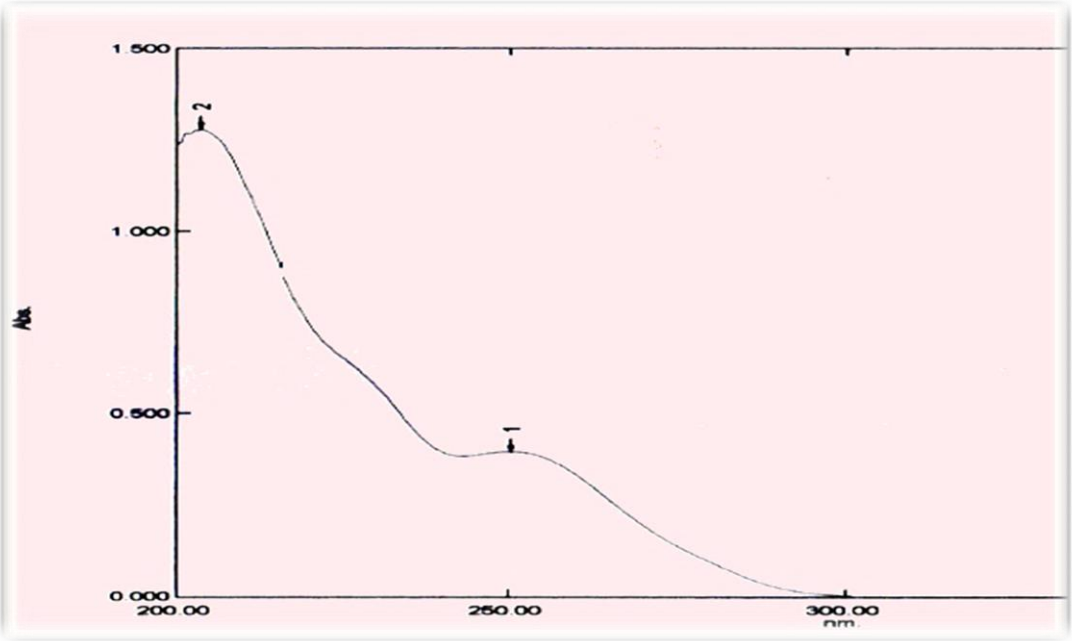
The measured melting point for valsartan was found to be 116°C, that is in consistent with the reported range 116-117°C[106,146], indicating the purity of the drug powder.

3.1.2 Determination of valsartan λ_{max}

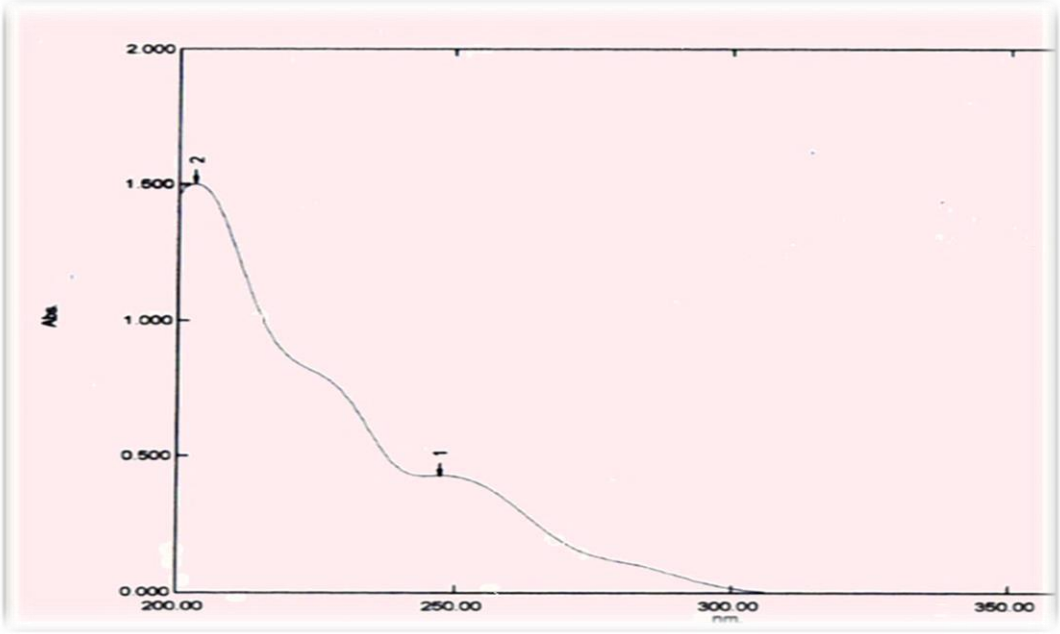
The spectrum showed that valsartan had a λ_{max} equal to 250 nm and 203 nm in both phosphate buffer pH 6.8 and HCl pH 1.2[106] as shown in figures (15 and 16).

3.1.3 Construction of valsartan calibration curve

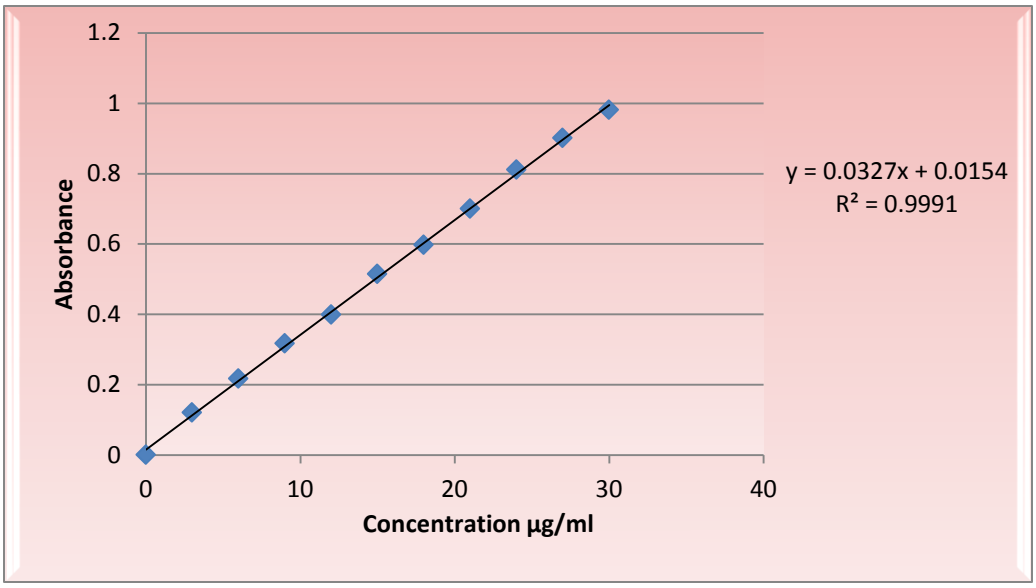
Calibration curve of valsartan in phosphate buffer pH 6.8 (at 250 nm) and in HCl pH 1.2 (at 203 nm) are shown in figures (17 and 18) respectively. Straight lines were obtained by plotting the absorbance versus the concentration with high regression coefficient, indicating that the calibration curves obey beer's law within the concentration range used.



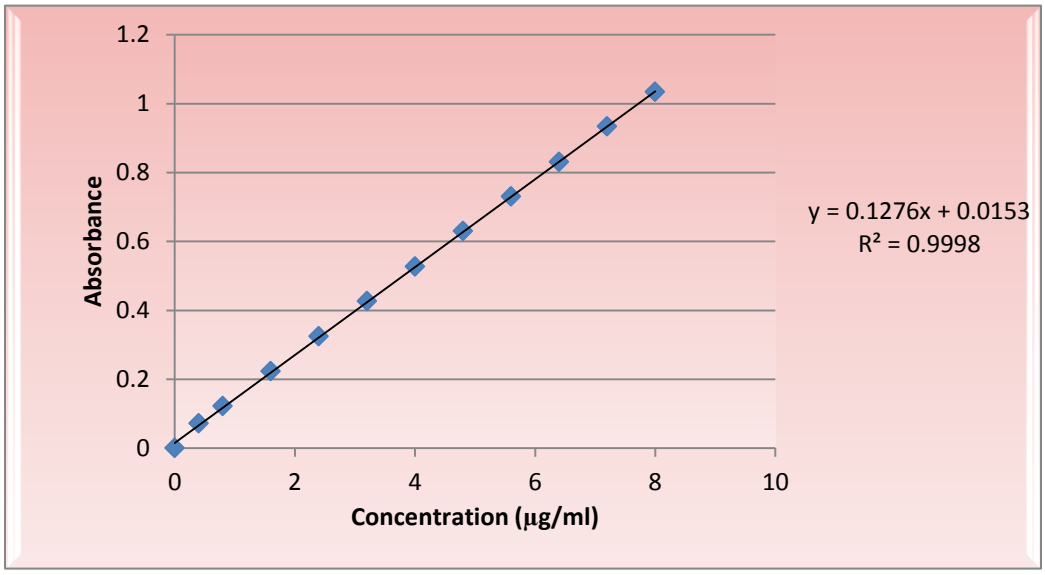
Figure(15): UV-Spectrum of valsartan in phosphate buffer pH 6.8



Figure(16): UV-Spectrum of valsartan in HCl pH 1.2



Figure(17): Calibration curve of valsartan in phosphate buffer pH 6.8 (λ_{max}= 250nm)



Figure(18): Calibration curve of valsartan in HCl pH 1.2 (λ_{max} =203 nm)

3.1.4 Determination of valsartan pH-solubility profile

The results of valsartan saturated solubilities in two pH medias at room temperature and their expressions according to the USP[126] are shown in table (12).

Table(12): Saturated solubilities of valsartan at different pH medias

pH	Solubility (mg/ml)	Expression
1.2 (HCl pH 1.2)	0.079±0.06	Practically insoluble
6.8 (phosphate buffer)	41.83±0.86	Soluble

These solubility values were in accordance with the weekly acidic nature of valsartan, as it will be in the unionized form in an acidic medium, but upon increasing the pH the ionized species predominated, which explains the sharp increase in the solubility at the alkaline pH[147,148].

3.2 Pre-compression evaluation of the core powder mixture

The measured values of angle of repose, Carr's index and Hausner ratio with their corresponding type of flow for the prepared core powder mixture for each formula are illustrated in table (13). These results indicated that all core powder mixtures have acceptable flow properties.

Table(13): Pre-compression parameters for the core tablet mixture

Formulas	Angle of repose (Degree)	Carr's index	Hausner ratio	Type of flow
C1	37.81±1.05	17.45±1.6	1.23±0.04	Fair
C2	36.45±0.53	18.67±2.86	1.21±0.05	Fair
C3	37.75±3.08	19.95±1.07	1.2±0.04	Fair
C4	43.21±1.34	22.56±2.7	1.27±0.13	Passable
C5	44.68±1.77	24.39±3.65	1.31±0.65	Passable
C6	31.96±0.66	14.34±2.05	1.17±0.35	Good
C7	32.53±0.57	15.97±1.04	1.16±0.5	Good
C8	32.88±0.29	13.86±3.8	1.15±0.05	Good
C9	34.76±2.06	14.43±2.73	1.18±0.15	Good
C10	31.43±0.78	12.63±1.5	1.13±0.05	Good
C11	29.14±1.87	9.14±2.03	1.1±0.03	Excellent
C12	32.17±1.68	13.95±2.45	1.16±0.04	Good
C13	32.47±0.53	12.66±1.18	1.16±0.05	Good
C14	31.13±0.78	11.94±1.23	1.13±0.44	Good
C15	32.12±1.94	12.32±1.6	1.15±0.6	Good
C16	33.67±2.30	13.99±2.85	1.17±0.05	Good
C17	28.17±1.55	9.45±1.54	1.11±0.53	Excellent
C18	32.13±2.99	12.74±3.43	1.13±0.53	Good
C19	27.18±1.04	8.44±2.21	1.08±0.7	Excellent
C20	27.94±2.8	9.12±3.2	1.1±0.03	Excellent

Table(13): Continued

Formulas	Angle of repose (Degree)	Carr's index	Hausner ratio	Type of flow
C21	26.41±1.9	7.12±0.83	1.07±0.16	Excellent
C22	31.5±0.06	14.75±1.05	1.14±0.06	Good

3.3 Post-compression evaluation of the prepared core and coated oroslippery tablets

- *Physical properties of the prepared core tablet formulas*

The prepared core tablet formulas were evaluated for hardness, friability, weight variation, thickness and the results are shown in table (14).

The results of the core tablet hardness in C1-C3 containing (2-6%) HPMC respectively showed a slight increase in tablet hardness due to the binding effect of HPMC[(149)] that increases upon increasing its concentration. In addition non-significant differences were observed among other core tablets hardness with slight increase in C22 (blank), which might be attributed to the high binding effect of avecil that was used as a diluent in this formula, since it is a ductile material that shows plastic deformation by dislocation of particles forming a hard compacts[(150)].

Results of the friability and weight variation agreed with the requirement of USP indicating that the core tablet formulas were suitably prepared with low friability (<1%) and with an accepted average weight deviation (<5%) in each formula. A non-significant lower friability value was observed in C22 which might be due to the presence of avecil.

Results of thickness, on the other hand, indicated that there were no significant differences between the prepared core tablet formulas C1-C22.

Table(14): Physical Properties of the core tablet formulas

Formulas	Hardness (Kg/cm^2)	Friability (%)	Weight variation (mg)	Thickness (mm)
C1	4.61± 0.04	0.78±0.02	399.7±0.32	5.42±0.06
C2	4.82±0.16	0.73±0.09	398.9±0.06	5.41±0.46
C3	5.21±0.33	0.71±0.04	399.9±0.02	5.43±0.07
C4	5.1±0.43	0.79±0.05	400±0.08	5.41±0.14
C5	4.93±0.07	0.81±0.04	400.1±0.22	5.42±0.16
C6	5.23±0.56	0.75±0.02	499.5±0.06	5.42±0.24
C7	5.11±0.44	0.66±0.08	389.2±0.43	5.44±0.11
C8	5.21±0.04	0.68±0.09	399.6±0.39	5.43±0.07
C9	5.13±0.26	0.72±0.03	400±0.06	5.41±0.05
C10	5.57±0.44	0.67±0.05	399.6±0.45	5.43±0.23
C11	5.18±0.02	0.74±0.09	399.5±0.17	5.42±0.32
C12	5.17±0.65	0.75±0.07	399.9±0.18	5.43±0.37
C13	5.21±0.19	0.79±0.08	398.5±0.09	5.44±0.04
C14	5.67±0.04	0.68±0.03	400±0.55	5.41±0.45
C15	5.37±0.08	0.77±0.06	399.8±0.54	5.41±0.14
C16	5.15±0.56	0.75±0.06	398.7±0.05	5.4±0.63
C17	5.24±0.16	0.74±0.06	399.7±0.09	5.43±0.03

Table(14): Continued

Formulas	Hardness (Kg/cm^2)	Friability (%)	Weight variation (mg)	Thickness (mm)
C18	5.43±0.22	0.79±0.06	399.8±0.37	5.43±0.67
C19	5.96±0.08	0.63±0.02	399.7±0.05	5.42±0.08
C20	5.63±0.58	0.71±0.04	400±0.56	5.43±0.36
C21	5.55±0.04	0.72±0.06	398.7±0.55	5.41±0.68
C22	6.54±0.16	0.54±0.03	399.7±0.45	5.42±0.04

- *Physical properties of the prepared OSTs*

Tests of hardness, friability, weight variation and thickness performed for the prepared valsartan and blank (drug-free) OSTs and the results are shown in table (15).

Results of the coated tablet hardness showed no significant differences, with the blank OSTs formulas B1-B8 containing avecil having the highest values that might be attributed to the higher hardness of their corresponding core tablets. It is also important to note that there were no significant differences in the hardness before and after coating for each formula, indicating that coating had no significant influence on the core tablet hardness.

Friability results were all within the acceptable range with no significant differences. A slight decrease were observed in formulas F32-F35 and B7,B8 which had multilayer coating, due to increasing coat thickness. In addition, there was a significant difference in the friability

between each OST and its corresponding core tablet due to the presence of the protective outer layer of the coat.

Formulas F1-F21 showed no significant differences in the coated tablet thickness with an acceptable average weight deviation for each formula, indicating the reproducibility of the coating process. In addition, comparing to F17,F21 and B1 (coated with a single layer of 15% kol.+ 0.3% xanthan), there was a significant reduction in weight and thickness of formulas F22,F24 and B2 due to the presence of lower kol. concentration (10%) which resulted in lower viscosity of the coating dispersion, while a significant increase was observed upon increasing kol. concentration to 20% in formulas F23,F25 and B3. On the other hand, formulas F26,F27,F29,F30,B4 and B5 showed a significant reduction in weight and thickness comparing to F17,F21 and B1respectively, due to the presence of no or low concentration of xan. in these formulations. On the contrary, increasing xan. concentration to 0.5% in formulas F28,F31 and B6 led to significant increase in the weight and thickness of the prepared formulas. These results might be due to increasing the viscosity of the coating dispersion which increases the hydrodynamic drag of the liquid during the tablet withdrawal (at the same withdrawal speed) during the dipping process, leading to a thicker film layer[151,152,153]. Finally, a significant increment were observed in weight and thickness of formulas F32-F35,B7 and B8 which can be explained by increasing coating level in these formulas.

Table(15): Physical properties of the prepared OSTS

Formulas	Hardness (Kg/cm^2)	Friability (%)	Weight variation (mg)	Thickness (mm)
F1	4.89±0.23	0.22±0.02	437.3±0.51	5.63±0.28
F2	5.12±0.95	0.15±0.02	437.5±0.68	5.62±0.59
F3	5.43±0.77	0.2±0.03	435.3±0.46	5.63±0.52
F4	5.14±0.95	0.13±0.01	437.4±0.58	5.61±0.89
F5	4.95±0.42	0.19±0.01	435.1±0.96	5.62±0.68
F6	5.43±0.67	0.26±0.02	436.2±0.73	5.62±0.93
F7	5.12±0.4	0.15±0.06	437.12±0.47	5.63±0.81
F8	5.34±0.75	0.1±0.05	436.3±0.78	5.62±0.92
F9	5.23±0.67	0.2±0.05	435.3±0.28	5.63±0.37
F10	5.85±0.5	0.17±0.01	436.1±0.74	5.61±0.44
F11	5.23±0.24	0.26±0.03	436.7±0.64	5.62±0.68
F12	5.35±0.81	0.22±0.05	437.2±0.63	5.63±0.96
F13	5.36±0.89	0.14±0.06	436.3±0.73	5.6±0.97
F14	5.74±0.46	0.1±0.04	435.7±0.6	5.63±0.45
F15	5.58±0.97	0.27±0.02	434.9±0.7	5.63±0.84
F16	5.42±0.67	0.19±0.08	436.5±0.23	5.62±0.54
F17	5.61±0.56	0.29±0.06	436.9±0.89	5.61±0.62
F18	5.93±0.99	0.19±0.09	435.9±0.59	5.62±0.46
F19	5.99±0.58	0.17±0.04	437.3±0.78	5.62±0.76
F20	5.98±0.58	0.11±0.02	435.2±0.4	5.63±0.44

Table(15):Continued

Formulas	Hardness (Kg/cm^2)	Friability (%)	Weight variation (mg)	Thickness (mm)
F21	5.9±0.63	0.17±0.03	436±0.68	5.62±0.83
F22	5.52±0.74	0.28±0.09	430.2±0.47	5.56±0.82
F23	5.73±0.85	0.11±0.02	445.6±0.96	5.69±0.36
F24	5.77±0.68	0.14±0.05	429.7±0.48	5.57±0.94
F25	5.92±0.9	0.21±0.08	446.4±0.66	5.70±0.58
F26	5.59±0.59	0.29±0.06	428.4±0.84	5.55±0.68
F27	5.52±0.76	0.25±0.03	430.5±0.58	5.59±0.86
F28	5.66±0.78	0.21±0.02	443.3±0.78	5.68±0.56
F29	5.83±0.57	0.31±0.09	429.2±0.38	5.53±0.4
F30	5.88±0.78	0.25±0.02	431.6±0.8	5.59±0.67
F31	5.98±0.6	0.1±0.04	443.3±0.78	5.67±0.74
F32	5.69±0.58	0.09±0.02	454.2±0.48	5.71±0.55
F33	5.73±0.62	0.07±0.04	478.4±0.74	5.73±0.63
F34	5.99±0.97	0.09±0.03	455.12±0.94	5.7±0.76
F35	6.05±0.6	0.06±0.05	477.3±0.77	5.72±0.86
B1	6.57±0.37	0.21±0.03	436.3±0.25	5.63±0.49
B2	6.55±0.79	0.26±0.08	431.1±0.68	5.58±0.94
B3	6.57±0.5	0.2±0.05	445.2±0.85	5.69±0.67

Table(15):Continued

Formulas	Hardness (Kg/cm^2)	Friability (%)	Weight variation (mg)	Thickness (mm)
B4	6.51±0.66	0.31±0.08	429.2±0.88	5.54±0.79
B5	6.53±0.73	0.29±0.02	431.4±0.9	5.59±0.54
B6	6.58±0.89	0.11±0.03	442.2±0.46	5.67±0.22
B7	6.61±0.57	0.09±0.01	454.3±0.36	5.69±0.67
B8	6.63±0.66	0.08±0.01	477.4±0.44	5.71±0.56

3.4 Variables affecting the formulation of the prepared oroslippery tablets

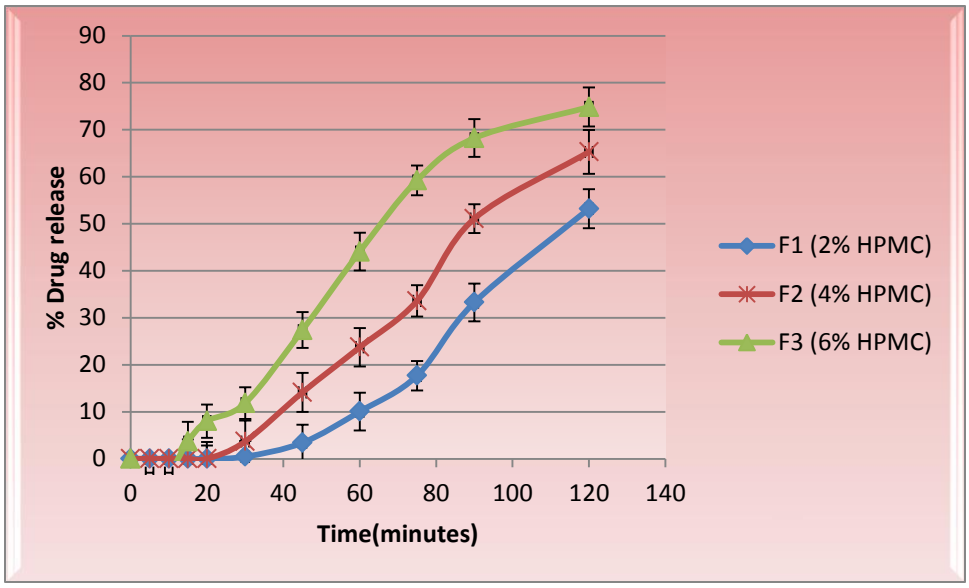
3.4.1 Effect of HPMC concentration in the core

The results of formulas F1-F3 (which were formulated to see the effect of HPMC concentration on disintegration and release of the prepared OSTs) are summarized in table (16) and figure (19). It was obvious that valsartan OSTs formulas F1-F3 required more than the time specified in the British pharmacopeia for complete disintegration (> 30 minutes)[(154)], and more than 120 minutes for 80% release. There was a significant increase in $\%D_{30min}$ ($p<0.05$) in formulas F1-F3 containing (2%,4% and 6% HPMC), which indicated that increasing HPMC concentration caused a reduction in disintegration time and enhancing valsartan release, this might be due to the fact that these concentration of HPMC are less than its percolation threshold (percolation threshold is the critical concentration necessary to form a continuous coherent layer and dominating the properties of the entire

system)[155], therefore, besides to its role as a binder HPMC in this case acted as disintegrating agent rather than release retarding agent, as the swelled HPMC particles could not effectively bind the adjacent particles to form a continuous gel layer due to the insufficient particles available, hence, the pressure from the swelled polymer particles was released in the disintegration process leading to a faster dissolution rate due to the higher available surface area for drug release[156,157].

Table(16): Effect of HPMC concentration on the disintegration and release of valsartan from the prepared OSTs formulas

Formulas	**HPMC 50 cps (%)**	**DT (minutes)**	**$T_{80\%}$ (minutes)**	**$\%D_{30min}$ (%)**
F1	2	More than 30	More than 120	0.45±0.02
F2	4	More than 30	More than 120	3.66±0.06
F3	6	More than 30	More than 120	11.83±0.35



Figure(19): Effect of HPMC concentration on the release of valsartan from the prepared OSTs in phosphate buffer pH 6.8, 37 ± 0.5 ºC

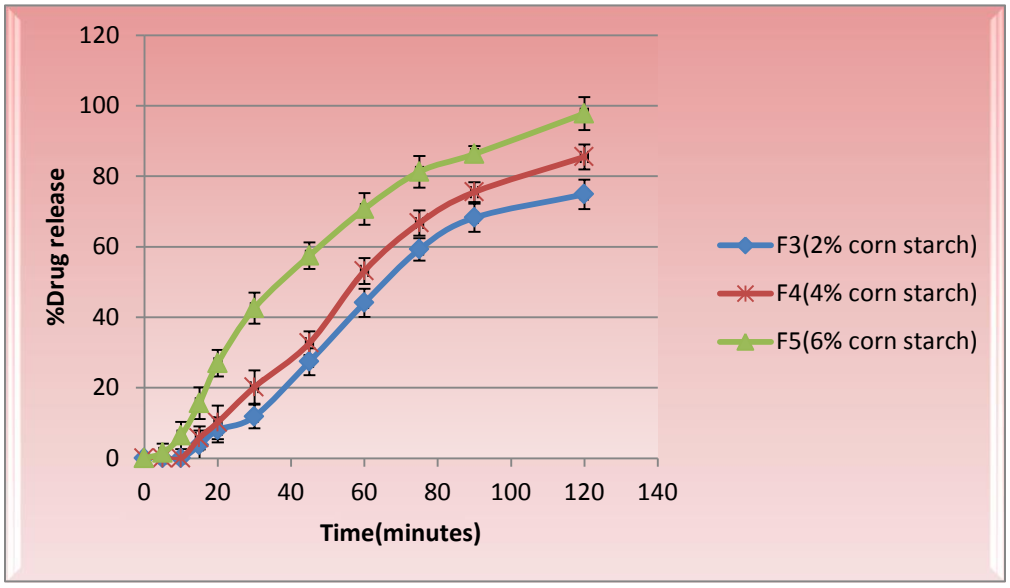
3.4.2 Effect of corn starch concentration in the core

Formulas F3-F5 were designed to see the effect of increasing corn starch concentration on the disintegration and release of valsartan from the prepared OSTs, and their results are summarized in table (17) and figure (20). The result showed that although increasing corn starch concentration from (2%-6%) in F3-F5 led to a significant reduction $T_{80\%}$, with a significant increment in the $\%D_{30\ min}$, but all the three formulas required more than 30 minutes for complete disintegration, indicating that these concentrations were not enough to generate the swelling force required for complete disintegration in less than 30 minutes[(158)],for that reason a higher concentration of corn starch is required that may adversely affecting the

flowability and compactibility of our prepared tablets[72], which calls for the use of the superdisintegrants in the next formulas.

Table(17): Effect of corn starch concentration on the disintegration and release of valsartan from the prepared OSTs

Formulas	Corn starch concentration (%)	DT (minutes)	$T_{80\%}$ (minutes)	$\%D_{30min}$ (%)
F3	2	More than 30	More than 120	11.83±0.35
F4	4	More than 30	100±0.33	20.16±1.72
F5	6	More than 30	72±0.76	42.59±1.38



Figure(20): Effect of corn starch concentration on the release of valsartan from the prepared OSTs in phosphate buffer pH 6.8, 37 ± 0.5 ºC

3.4.3 Effect of superdisntegrant type and concentration in the core

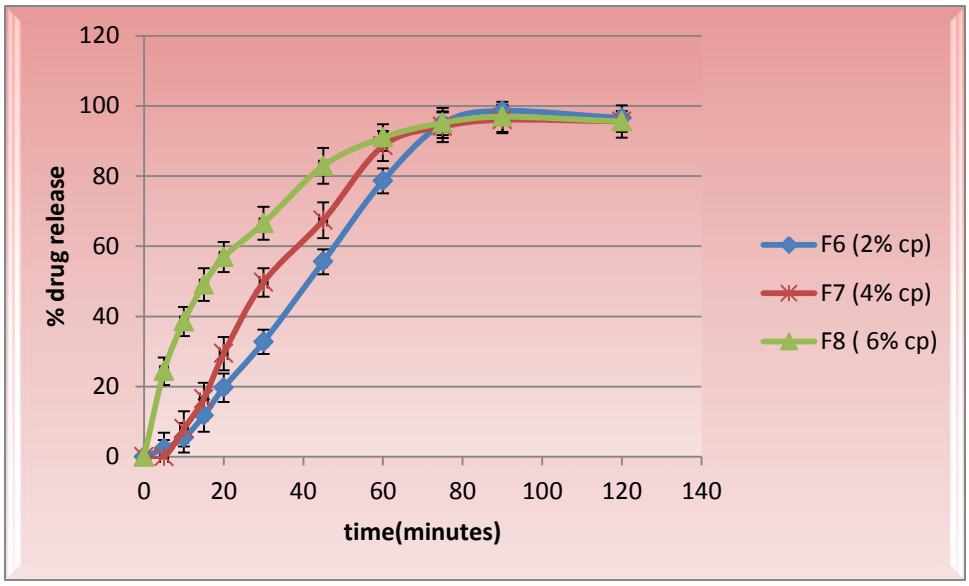
Results of the formulas F6-F17 (that were prepared to see the effect of different superdisintegrants (CP,SSG,indion and CCS) and their concentrations (2%,4% and 6%) on the disintegration and release of the drug from the prepared OSTs) are illustrated in table (18) and figures (21-24). The results showed that all formulas prepared using different concentrations of SSG and indion 414 (except F14 containing 6% indion), in addition to F6 (2% CP) and F15 (2% CCS) took more than 30 minutes for complete disintegration, but increasing the concentration of CP and CCS to 4% and 6% as in F7,F8 and F16,F17 respectively, led to a significant reduction in the disintegration time. Furthermore, increasing the concentration of each superdisintegrant gave a significant decrease in $T_{80\%}$, accompanied with a significant increase in the $\%D_{30min}$. Additionally, superdisintegrants are arranged in the following order CCS> CP>indion>SSG with respect to DT, $T_{80\%}$ reduction, and $\%D_{30min}$ increment, with CCS in concentration 6% (F17) gave faster disintegration and release.

The faster disintegration and release accompanied with the CCS may be due to the fact that it possesses the greatest extent of swelling in addition to its wicking effect which is mostly because of its fibrous nature that acts as a hydrophilic channel facilitating water uptake by the tablet[159,160,161]. On the other hand, CP not swells significantly but act by wicking or capillary action which quickly wicks the water into the tablet that generate the necessary hydrostatic pressure to provide rapid disintegration and release of the drug[162]. Finally, the faster disintegration and release of

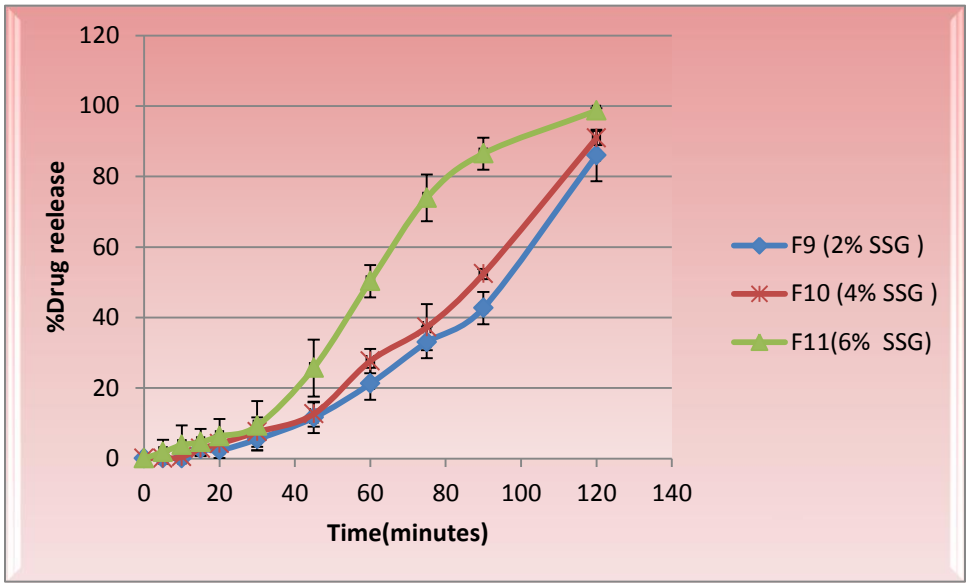
OSTs prepared using indion 414 in comparison to that prepared using SSG may be due to the greater degree of swelling of indion 414 in addition to the tendency of SSG to form a viscous gel with increasing its concentration which retards water penetration leading to slower disintegration and release[163].

Table(18): Effect of superdisintegrant type and concentration on the disintegration and release of valsartan from the prepared OSTs

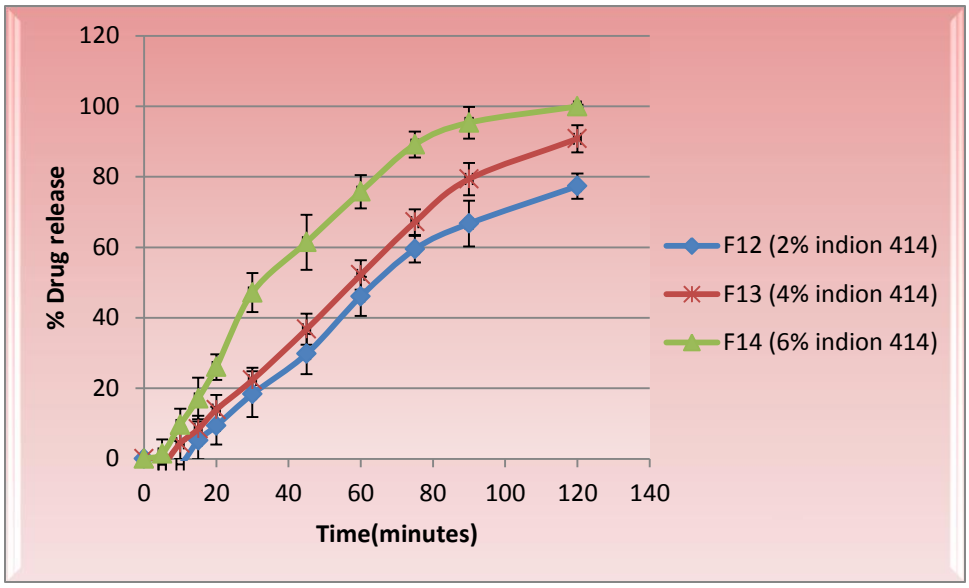
Formulas	Type	Concentration (%)	DT (minutes)	$T_{80\%}$ (minutes)	$\%D_{30min}$ (%)
F6	CP	2	More than 30	62±1.57	32.74±0.46
F7	CP	4	29.10±1.67	54±0.86	49.49±1.04
F8	CP	6	14.12±0.7	42±0.34	66.89±1.7
F9	SSG	2	More than 30	120±1.78	5.46±0.05
F10	SSG	4	More than 30	112±0.03	7.5±0.15
F11	SSG	6	More than 30	80±0.06	9.2±0.96
F12	Indion 414	2	More than 30	116±1.57	18.33±1.52
0F13	Indion 414	4	More than 30	91±1.98	22.34±1.46
F14	Indion 414	6	28.23±1.8	64±0.67	47.14±0.56
F15	CCS	2	More than 30	58±1.08	41.3±0.45
F16	CCS	4	12.27±0.78	44±0.95	72.2±1.01
F17	CCS	6	3.30±0.02	6±0.34	95.17±1.85



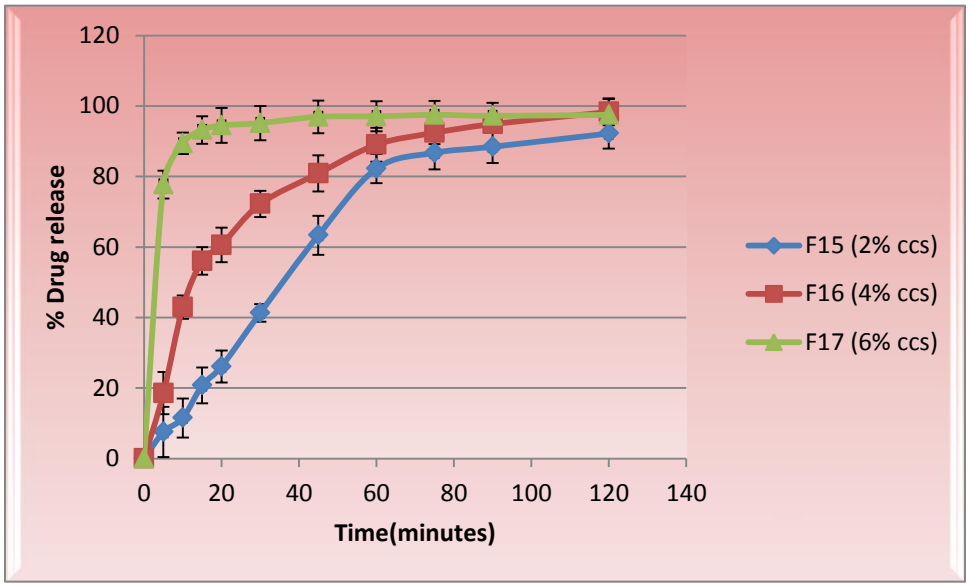
Figure(21): Effect of CP concentration on the release of valsartan from the prepared OSTs in phosphate buffer pH 6.8, 37 ± 0.5 ºC



Figure(22): Effect of SSG concentration on the release of valsartan from the prepared OSTs in phosphate buffer pH 6.8, 37 ± 0.5 ºC



Figure(23): Effect of indion 414 concentration on the release of valsartan from the prepared OSTs in phosphate buffer pH 6.8, 37 ± 0.5 ºC



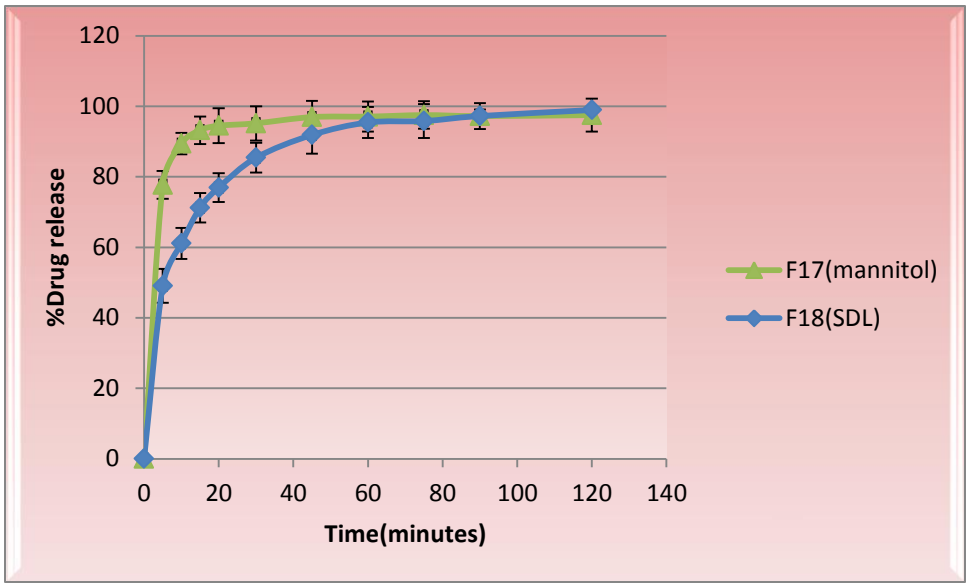
Figure(24): Effect of CCS concentration on the release of valsartan from the prepared OSTs in phosphate buffer pH 6.8, 37 ± 0.5 ºC

3.4.4 Effect of diluent type in the core

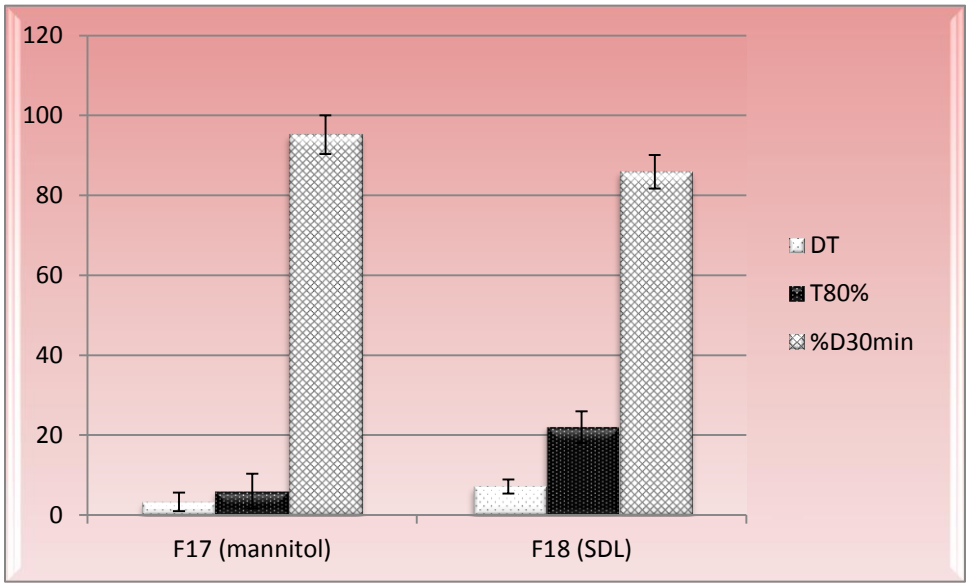
Results in table (19) and figures (25 and 26) clearly demonstrated the effect of diluent type on the disintegration and release of valsartan OSTs in formulas F17 and F18. The results showed that using SDL as a diluent instead of mannitol significantly increased the OSTs disintegration time (DT) and $T_{80\%}$ with a significant reduction in $\%D_{30min}$. This might be due to the amorphous part of SDL which gave less solid planes where the swelling force can be exerted in addition to its higher solubility which formed a sticky layer on the tablet surface leading to hindrance of further water uptake[161,164].

Table(19): Effect of diluent type on the disintegration and release of valsartan from the prepared OSTs

Formulas	**Diluent**	**DT (minutes)**	**$T_{80\%}$ (minutes)**	**$\%D_{30min}$ (%)**
F17	Mannitol	3.30±0.32	6±0.04	95.17±1.85
F18	SDL	7.14±1.78	22±1.98	85.88±1.18



Figure(25): Effect of diluent type on the release of valsartan from the prepared OSTs in phosphate buffer pH 6.8, 37 ± 0.5 ºC



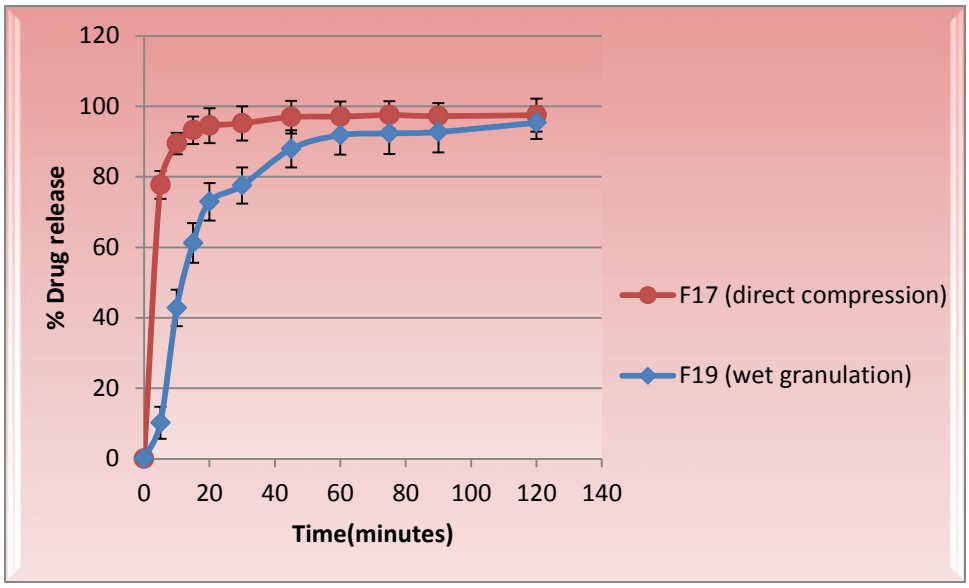
Figure(26): Effect of diluent type on the DT and release of valsartan from the prepared OSTs, 37 ± 0.5 ºC

3.4.5 Effect of method of core tablet preparation

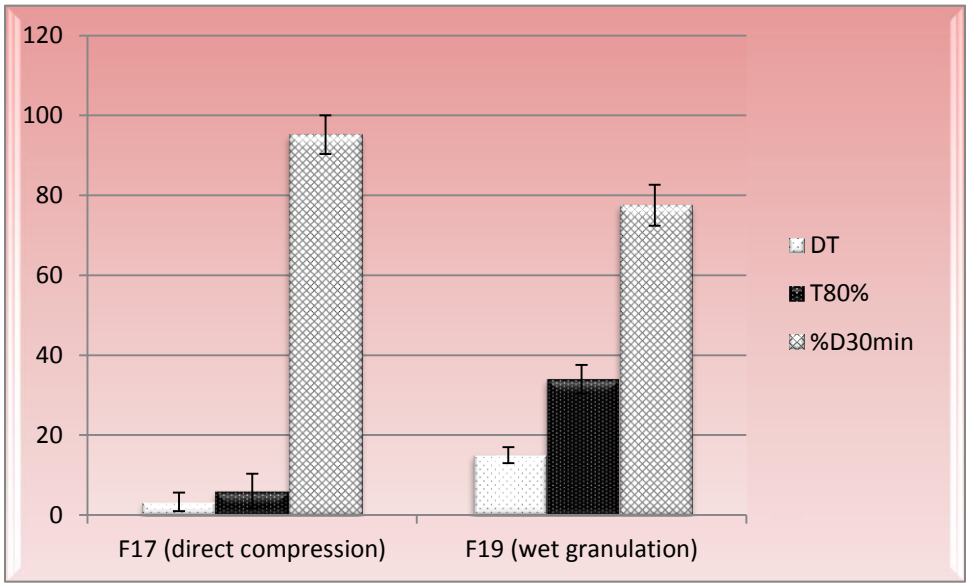
The core tablets in formulas F17 and F19 were prepared to estimate the effect of core tablet preparation method on the DT and release of valsartan OSTs and the results are shown in table (20) and figures (27 and 28). There was a significant increase in the DT and $T_{80\%}$, in addition to the significant reduction in $\%D_{30min}$ in F19 (prepared by wet granulation) comparing to F17 (prepared by direct compression). This result can be explained by the fact that in direct compression the OSTs are disintegrated into the primary drug particles rather than granules (as in case of wet granulation) which gave faster disintegration and release from the prepared OSTs[165,166].

Table(20): Effect of the preparation methods on the disintegration and release of valsartan from the prepared OSTs

Formulas	**Methods of preparation**	**DT (minutes)**	**$T_{80\%}$ (minutes)**	**$\%D_{30min}$ (%)**
F17	Direct compression	3.30±0.02	6±0.34	95.17±1.85
F19	Wet granulation	15±1.01	34±1.55	77.53±0.14



Figure(27): Effect of the preparation method on the release of valsartan from the prepared OSTs in phosphate buffer pH 6.8, 37 ± 0.5 ºC



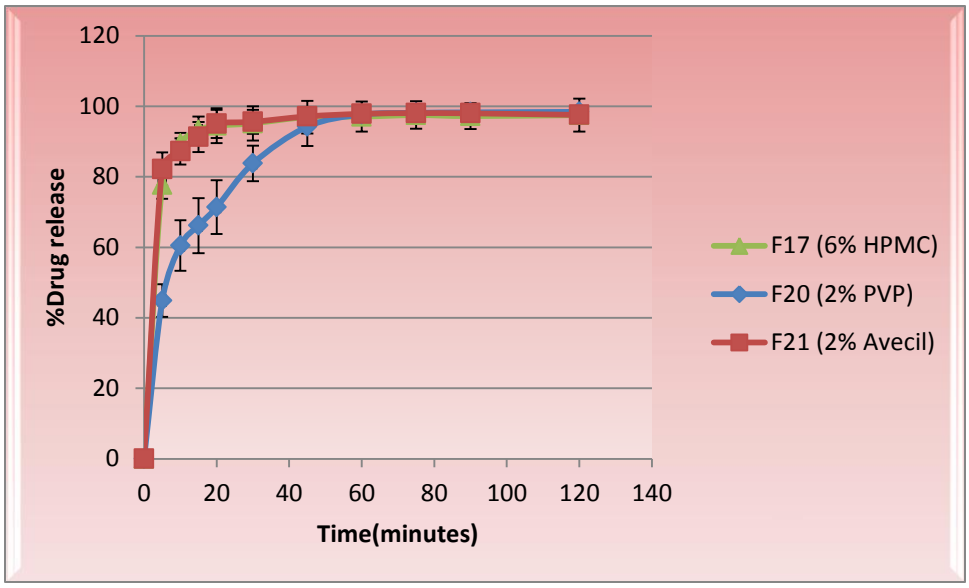
Figure(28): Effect of the preparation method on the DT and release of valsartan from the prepared OSTs, 37 ± 0.5 ºC

3.4.6 Effect of binder type in the core

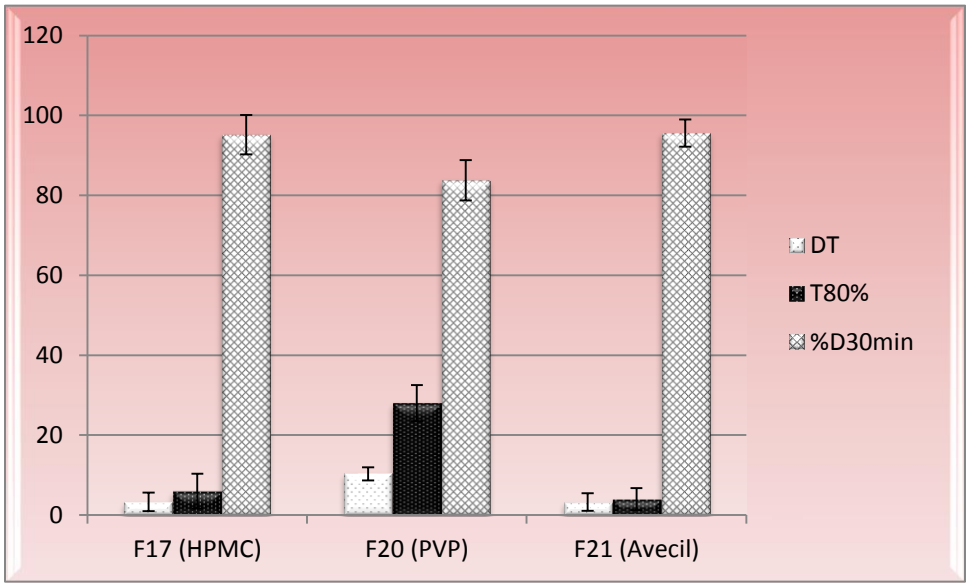
Results of formulas F17,F20 and F21 (which were prepared using different binders in their core tablets namely HPMC, PVP and avecil respectively) are shown in table (21) and figures (29 and 30). The result demonstrated that a significant difference in DT and release rate was observed between F17 and F20, while a non-significant difference was observed between F17 and F21. These results may be due to the fact that although both PVP and avecil have a binding effect, avecil (unlike PVP) possess also an excellent disintegrating property due to its wicking action which breaks hydrogen bonding between the neighboring bundles[76]. Therefore, both F17 and F21 were selected for further evaluations.

Table(21): Effect of binder type on the disintegration and release of valsartan OSTs

Formulas	Binder type	DT (minutes)	$T_{80\%}$ (minutes)	$\%D_{30min}$ (%)
F17	HPMC 50cps	3.30±0.02	6±0.04	95.17±1.85
F20	PVP	10.32±0.66	28±0.55	83.78±1.06
F21	Avecil	3.25±0.03	5±0.06	95.58±1.39



Figure(29): Effect of binder type on the release of valsartan from the prepared OSTs in phosphate buffer pH 6.8, 37 ± 0.5 ºC



Figure(30): Effect of binder type on the DT and release of valsartan from the prepared OSTs, 37 ± 0.5 ºC

3.4.7 Effect of kollicoat IR concentration in the coat

In order to see the effect of kol. concentration on the DT and release of valsartan OSTs, formulas F17,F22,F23 and F21,F24,F25 (containing HPMC and avecil respectively) were designed, and the results are presented in table (22), figure (31-A and B) and figure (32). The results showed that the DT and $T_{80\%}$ decreased significantly with a significant increase in $\%D_{30min}$ upon raising kol. concentration from 10% in formulas F22 and F24 to 15% in formulas F17 and F21. while a non-significant reduction in DT and $T_{80\%}$ accompanied with a non-significant increase in $\%D_{30min}$ was observed upon increasing kol. concentration to 20% in F23 and F25. These results indicating that increasing kol. concentration led to increasing coating permeability, that is mainly due to increasing rate and extent of water uptake due to the hydrophilic nature of the polymer, and partially due to increasing the rate and extent of dry mass loss from the polymeric film resulting from PVA/PEG leaching on contacting the aqueous media[167], leading consequently to a faster disintegration and release.

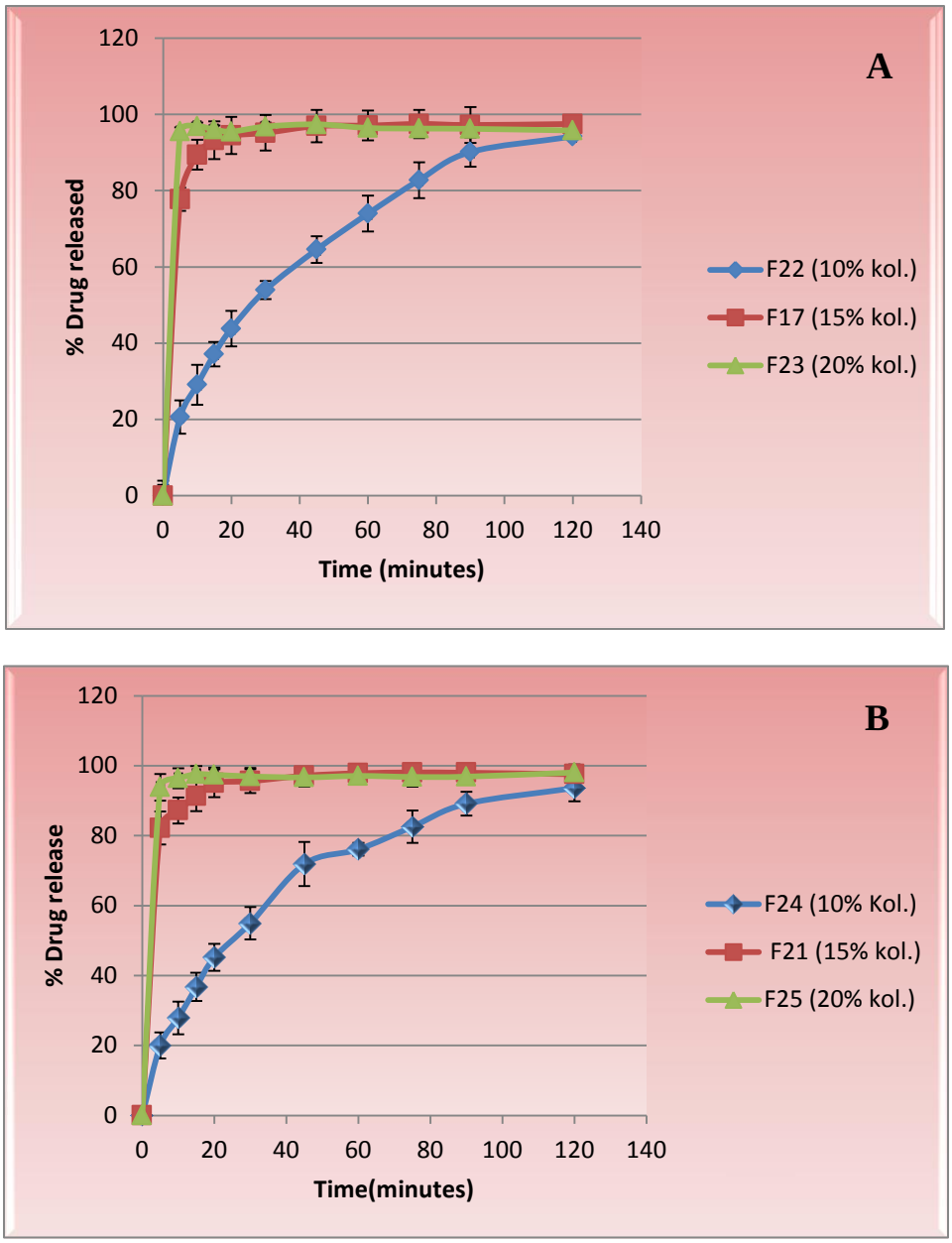
Tables (23 and 24), figures (33 and 34) showed the effect of kol. concentration on the in-vivo slipperiness and taste masking effect. The results indicated that increasing kol. concentration caused a non-significant increase in the degree of slipperiness. In addition, a significant increase in the taste masking effect was observed by increasing the polymer concentration from 10 to 15%, followed by a significant reduction in the taste masking efficiency upon further increase to 20%. These observations might be attributed to increasing the viscosity of the coating formula upon increasing the polymer concentration, which consequently leading to a greater increase in the coating thickness which enhanced the slipperiness and

also cause more efficient taste masking by increasing polymer concentration from 10 to 15%. On the other hand, the significant reduction in the taste masking upon using higher concentration 20% of the polymer can be explained by the higher permeability of the coating layer which gave faster DT and release[167].

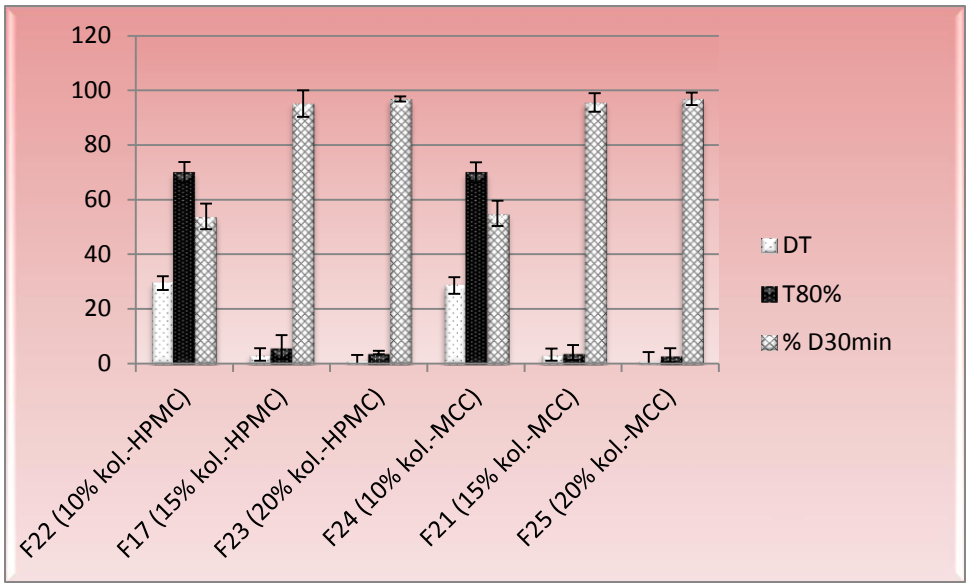
Therefore, formulas F17,F21 containing 15% kol. in their coat were selected in our study for further optimization since it had the most suitable DT and release profile (not too fast to cause destruction of the slippery coat and not too slow to hinder the release of our drug), with efficient slipperiness and taste masking properties.

Table(22): Effect of kollicoat IR concentration on the DT and release of valsartan from the prepared OSTs

Formulas	**Kol. concentration (%w/w)**	**DT (minutes)**	**$T_{80\%}$ (minutes)**	**$\%D_{30min}$ (%)**
F22	10%	29.45±1.54	70±1.77	53.86±1.7
F17	15%	3.30±0.02	6±0.04	95.17±0.85
F23	20%	1.22±0.04	4±0.02	96.86±0.91
F24	10%	28.55±1.05	70±1.67	54.95±1.6
F21	15%	3.25±0.03	5±0.06	95.58±0.39
F25	20%	1.10±0.03	3±0.04	96.9±1.37



Figure(31): Effect of kollicoat IR concentration on the release of valsartan from the prepared OSTs in phosphate buffer pH 6.8; A- OSTs containing HPMC as a binder, B- OSTs containing avecil as a binder, 37 ± 0.5 ºC



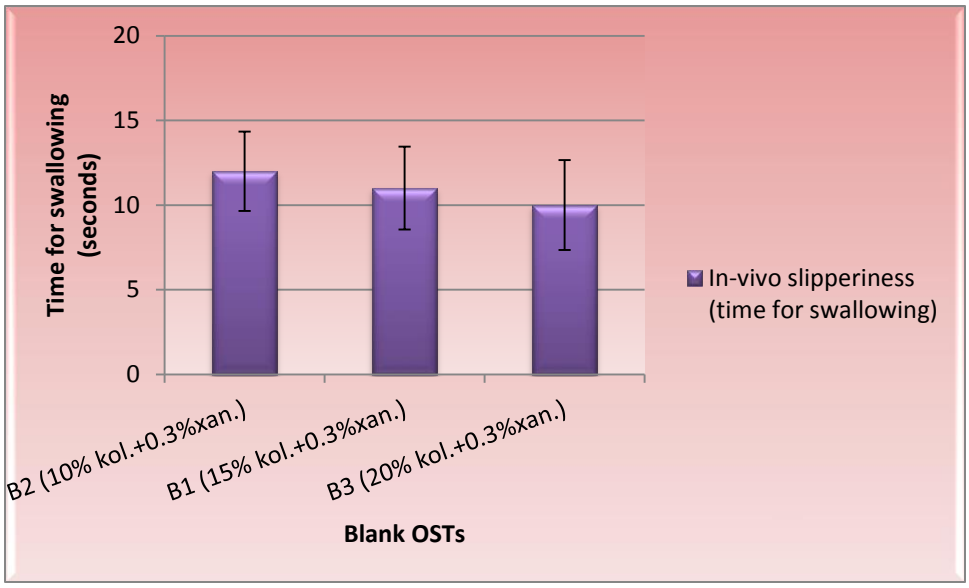
Figure(32): Effect of kollicoat IR concentration on the DT and release of valsartan from the prepared OSTs, 37 ± 0.5 ºC

Table(23): Effect of kollicoat IR concentration on the in-vivo slipperiness of the blank OSTs

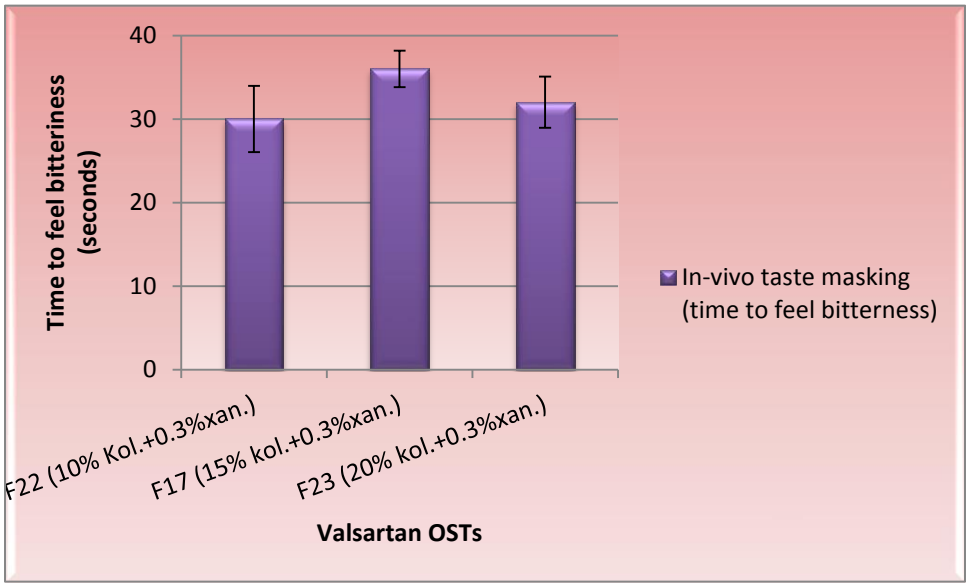
Formulas	Kol. concentration (%w/w)	In-vivo slipperiness (time required for swallowing) (seconds)
B2	10%	12±1.04
B1	15%	11±2.15
B3	20%	10±1.06

Table(24): Effect of kollicoat IR concentration on the in-vivo taste masking effect of valsartan OSTs

Formulas	Kol. concentration (%w/w)	In-vivo taste masking (time required to feel bitterness) (seconds)
F22	10%	30±3.97
F17	15%	36±2.18
F23	20%	32±3.06



Figure(33): Effect of kollicoat IR concentration on the in-vivo slipperiness of the blank OSTs



Figure(34): Effect of kollicoat IR concentration on the in-vivo taste masking effect of the prepared valsartan OSTs

3.4.8 Effect of xanthan gum concentration in the coat

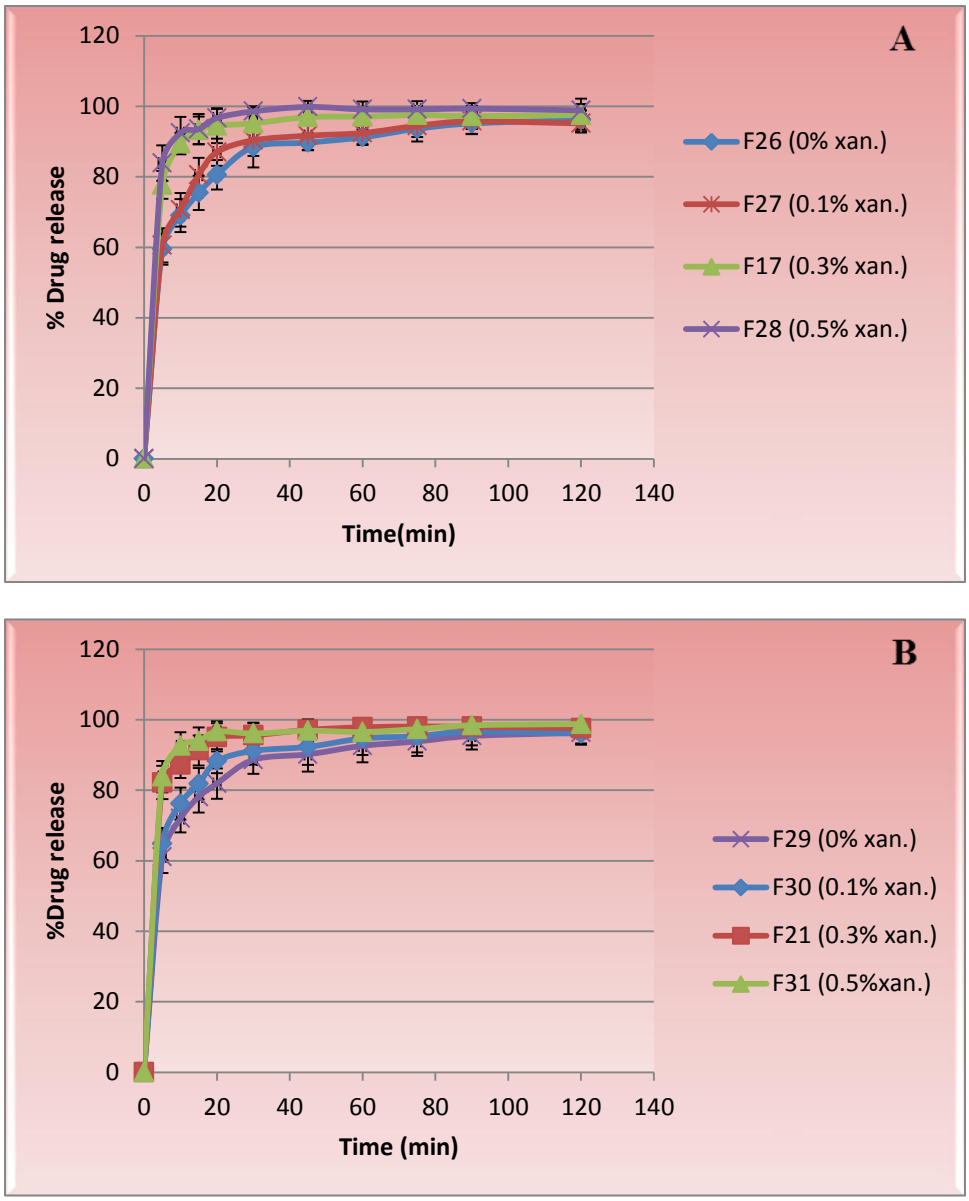
Table (25), and figure (35- A and B) with figure (36) summarize the effect of xan. concentration on DT and release of valsartan OSTs. The results showed that increasing xan. concentration caused a significant enhancement in the disintegration and drug release that is not affected by the type of the binder used, these observations might result from the hydrophilic nature of the xan. due to the presence of hydroxyl groups which allow high water absorption through hydrogen bonding formation[168,169,170].

The results in table (26) and figure (37) demonstrated that there was a significant improvement in the in-vivo slipperiness upon increasing xan. concentration which signifying the importance of xan. as slipperiness inducing agent to facilitate the swallowing process. In addition, the results of the in-vivo taste masking properties of the prepared OSTs (table 27 and figure 38) showed a significant enhancement by increasing the concentration of xan. These results can be explained on the basis that a slight increment in the xan. concentration leading to a high increase in the viscosity of the coating dispersion due to the high intermolecular interaction between the polymer's chain which gives a more effective increase in the macromolecular dimension[48], leading to increase thickness of the coating layer that accompanied by increasing the slipperiness which further facilitates the swallowing process and improves its taste masking property.

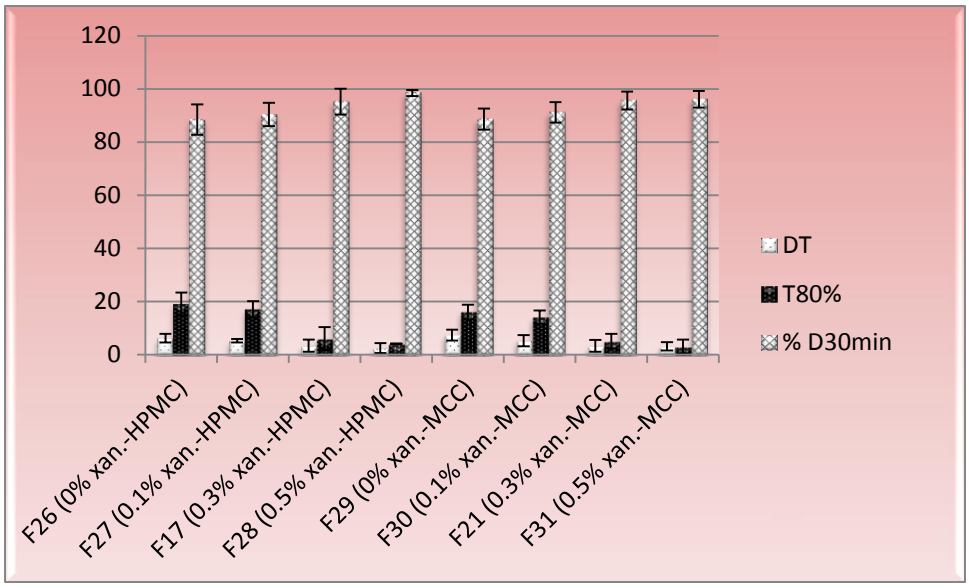
From the previous results, formulas F17,F21 coated with (0.3% xan.+ 15% kol.) were selected for further evaluation since they possessed the most suitable DT, release profile, slipperiness and taste masking properties.

Table(25): Effect of xanthan gum concentration on the DT and release of valsartan from the prepared OSTs

Formulas	Xan. concentration (%w/w)	DT (minutes)	$T_{80\%}$ (minutes)	$\%D_{30min}$ (%)
F26	0%	6.15±0.67	19±0.33	88.45±1.77
F27	0.1%	5.21±0.66	17±0.12	90.34±0.41
F17	0.3%	3.30±0.32	6±0.04	95.17±1.85
F28	0.5%	2.45±0.87	4±0.02	97.11±1.16
F29	0%	7.31±0.07	16±0.78	88.63±0.95
F30	0.1%	5.17±0.11	14±0.54	90.16±0.9
F21	0.3%	3.25±0.23	5±0.16	95.58±1.39
F31	0.5%	3.10±0.56	3±0.04	96.08±1.1



Figure(35): Effect of xanthan gum concentration on the release of valsartan from the prepared OSTs in phosphate buffer pH 6.8; A- OSTs containing HPMC as a binder, B- OSTs containing avecil as a binder, 37 ± 0.5 ºC



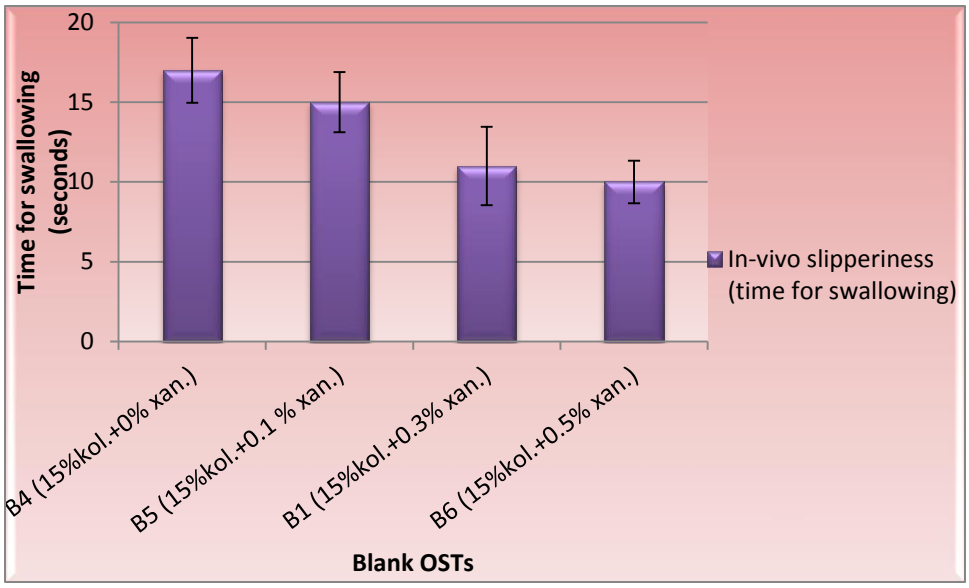
Figure(36): Effect of xanthan gum concentration on the DT and release of valsartan from the prepared OSTs, 37 ± 0.5 ºC

Table(26): Effect of xanthan gum concentration on the in-vivo slipperiness of the blank OSTs

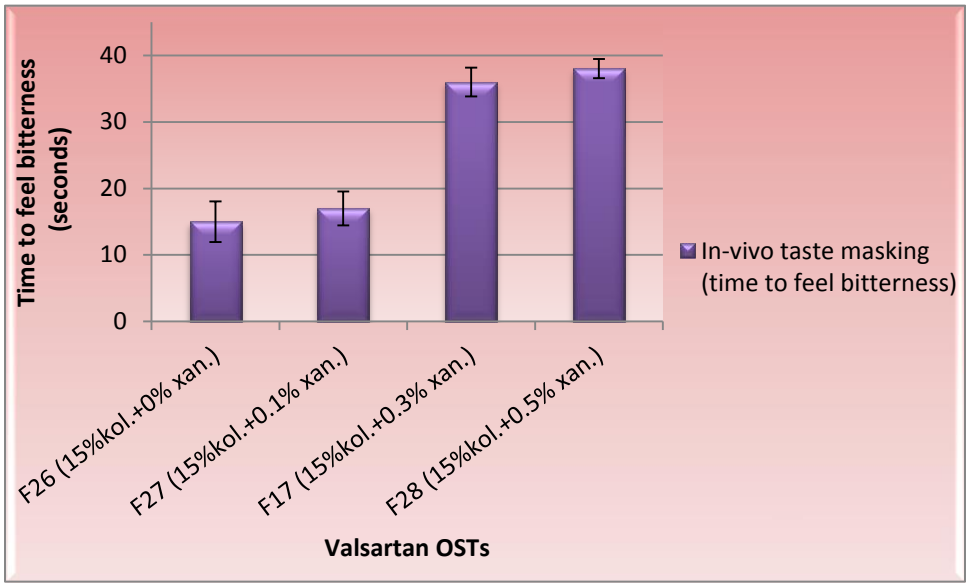
Formulas	Xan. concentration (%w/w)	In-vivo slipperiness (time required for swallowing) (seconds)
B4	0%	17±2.03
B5	0.1%	15±1.88
B1	0.3%	11±2.45
B6	0.5%	10±1.34

Table(27): Effect of xanthan gum concentration on the in-vivo taste masking properties of the prepared valsartan OSTs

Formulas	Xan. concentration (%w/w)	In-vivo taste masking (time required to feel bitterness) (seconds)
F26	0%	15±2.04
F27	0.1%	17±2.56
F17	0.3%	36±2.18
F28	0.5%	38±1.44



Figure(37): Effect of xanthan gum concentration on the in-vivo slipperiness of the blank OSTs



Figure(38): Effect of xanthan gum concentration on the in-vivo taste masking properties of the prepared valsartan OSTs

3.4.9 Effect of coating level

Results in table (28), figure (39-A and B) and figure (40) illustrated the effect of coating level on the disintegration and release of valsartan OSTs prepared either using HPMC as binder in F17,F32,F33 or using avecil in F21,F34,F35. These results showed a significant increase in DT with a non-significant changes in both $T_{80\%}$ and $\%D_{30min}$ after double coating F32 and F34 in comparison to F17 and F21 respectively, although a high significant increase in DT and $T_{80\%}$ accompanied with a significant reduction in the $\%D_{30min}$ of valsartan OSTs upon triple coating F33,F35. This significant delay in the OSTs disintegration and release on triple coating might be due to increase in the coat thickness leading to increase the diffusion pathway through which the solvent must pass giving slower disintegration and release, an effect which might be partly counterbalanced by the increase in film permeability that occurred by increasing the hydrophilic polymer amount in case of double coating[167] giving a small difference in tablet disintegration and release.

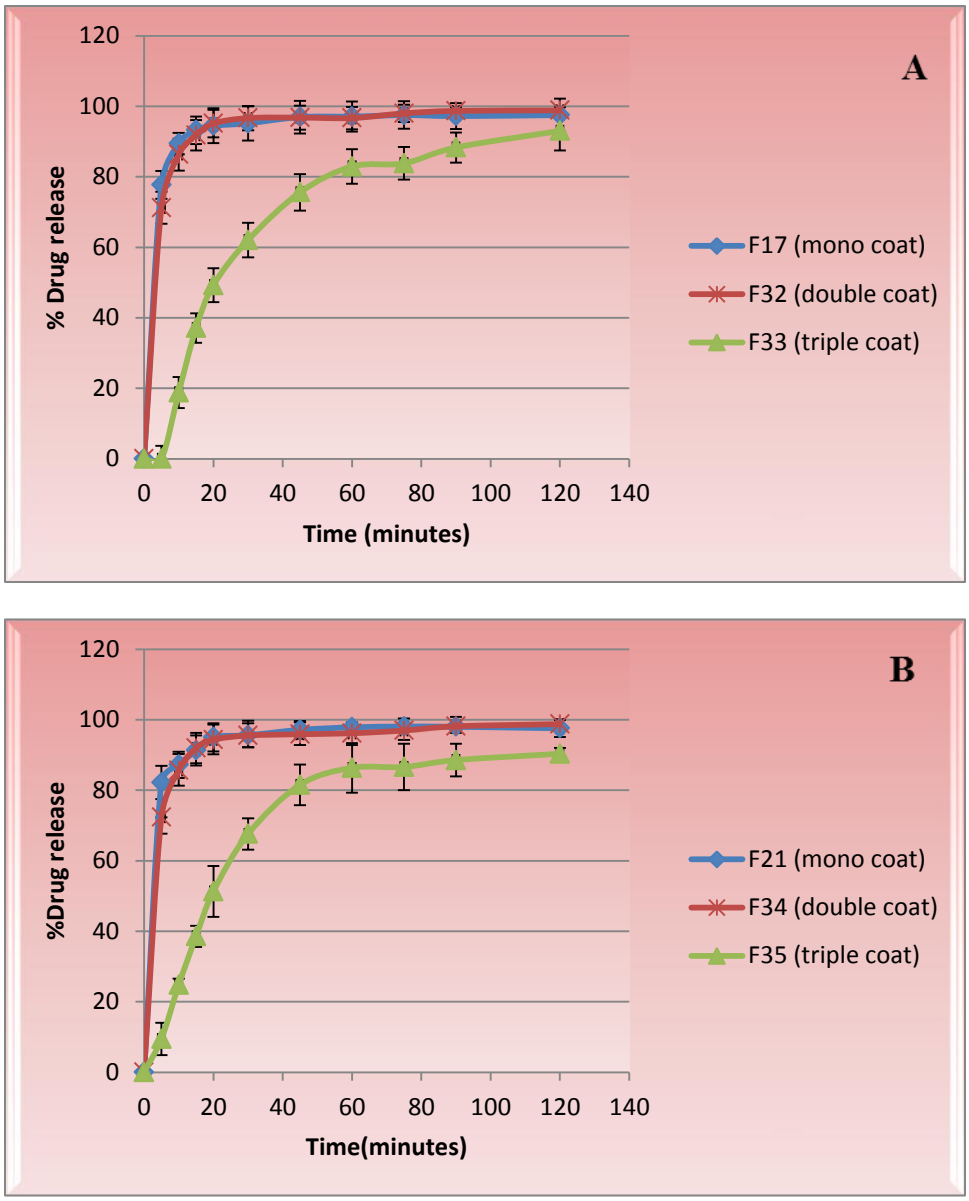
The effect of coating level on the in-vivo slipperiness and taste masking property are summarized in tables (29 and 30), figures (41 and 42). The results showed a slight significant improvement in the in-vivo slipperiness by double coating B7 accompanied with a non-significant improvement upon triple coating B8, while a significant improvement in taste masking effect was observed upon application of double and triple coat F32,F33 respectively. These results might be attributed to the increase in film thickness by each additional application of the coat. Formulas F21,F34,F35 containing avecil as a binder showed similar in-vivo taste

masking results upon double and triple coating in addition to other physical properties.

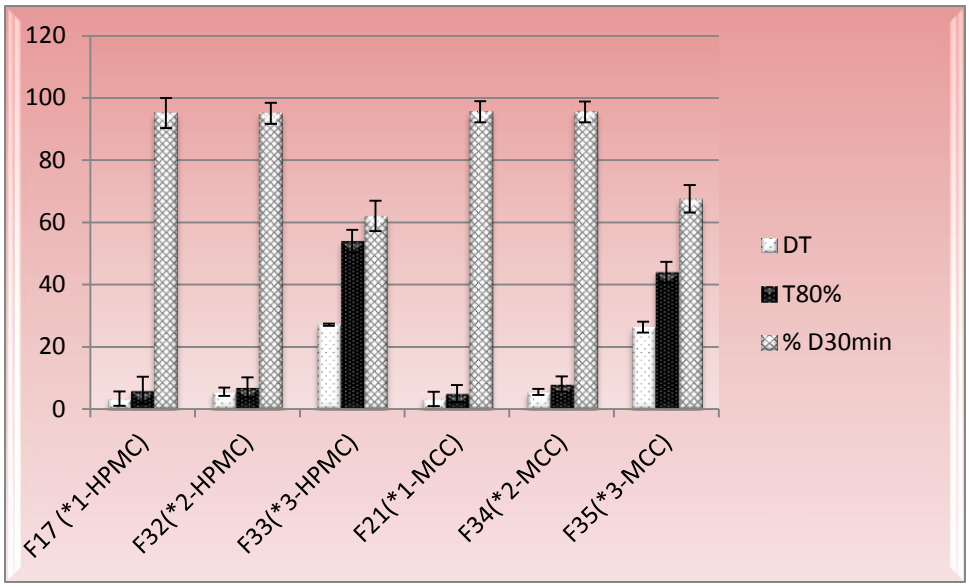
Therefore, formulas F32,F34 double coated with (0.3% xan.+ 15% kol.) were the optimum OSTs formulas that significantly prolonging the DT of the OSTs without significantly affecting the release profile, in addition, these formulas providing adequate slipperiness and taste masking property.

Table(28): Effect of coating level on the DT and release of valsartan from the prepared OSTs

Formulas	**Coating level**	**DT (minutes)**	**$T_{80\%}$ (minutes)**	**$\%D_{30min}$ (%)**
F17	Mono coat	3.30±0.32	6±0.34	95.17±1.85
F32	Double coat	5.57±0.36	7±0.21	95.05±1.42
F33	Triple coat	27.13±0.34	54±1.65	62.04±0.89
F21	Mono coat	3.25±0.23	5±0.76	95.58±1.39
F34	Double coat	5.55±0.98	6.5±0.46	95.52±0.36
F35	Triple coat	26.33±1.73	44±0.44	67.58±0.41



Figure(39): Effect of coating level on the release of valsartan from the prepared OSTs in phosphate buffer pH 6.8; A- OSTs containing HPMC as a binder, B- OSTs containing avecil as a binder, 37 ± 0.5 ºC



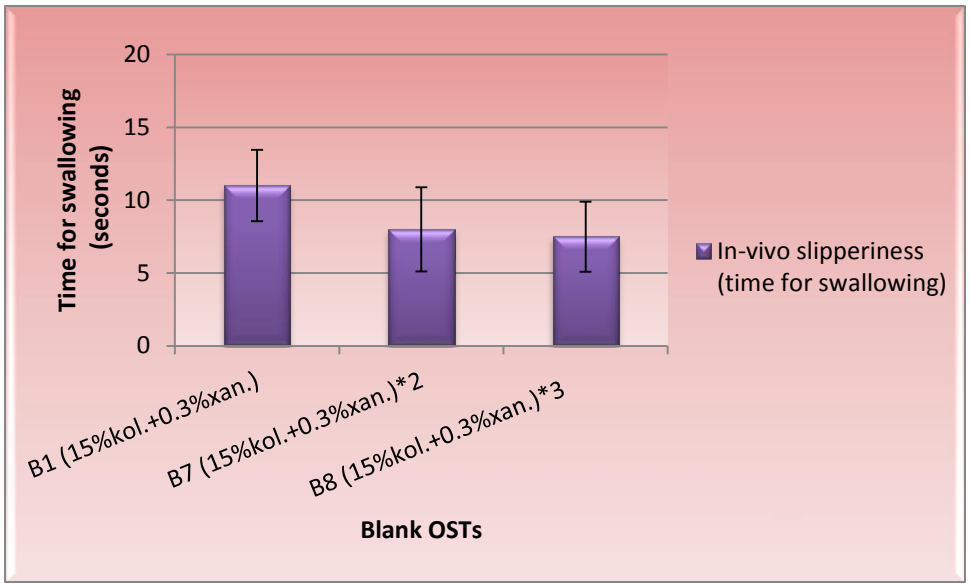
Figure(40): Effect of coating level on the DT and release of valsartan OSTs, 37 ± 0.5 ºC

Table(29): Effect of coating level on the in-vivo slipperiness of the blank OSTs

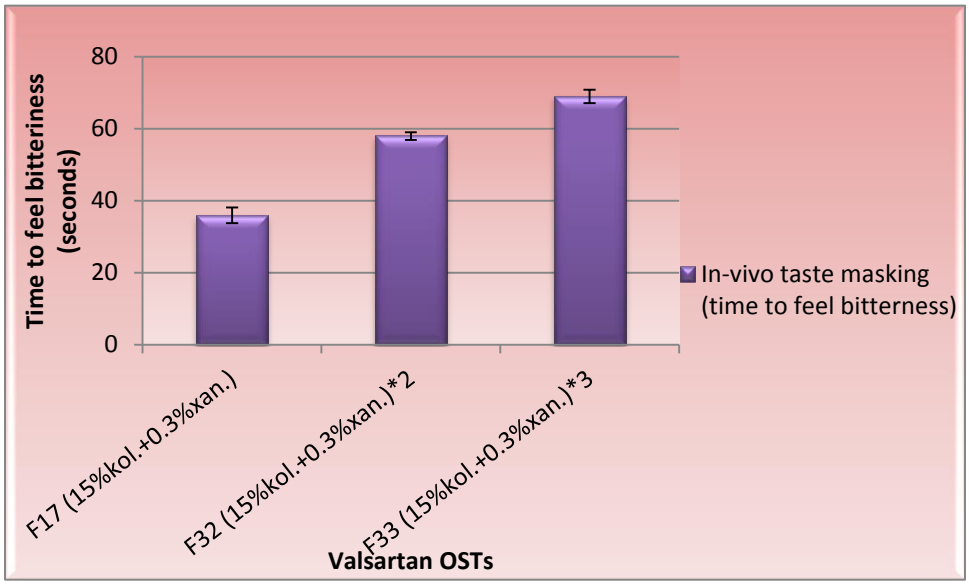
Formulas	Coating level	In-vivo slipperiness (time required for swallowing) (seconds)
B1	Mono coat	11±2.45
B7	Double coat	8±2.88
B8	Triple coat	7.5±2.41

Table(30): Effect of coating level on the in-vivo taste masking properties of the prepared valsartan OSTs

Formulas	Coating level	In-vivo taste masking (time required to feel bitterness) (seconds)
F17	Mono coat	36±2.18
F32	Double coat	58±1.06
F33	Triple coat	69±1.85



Figure(41): Effect of coating level on the in-vivo slipperiness of the blank OSTs



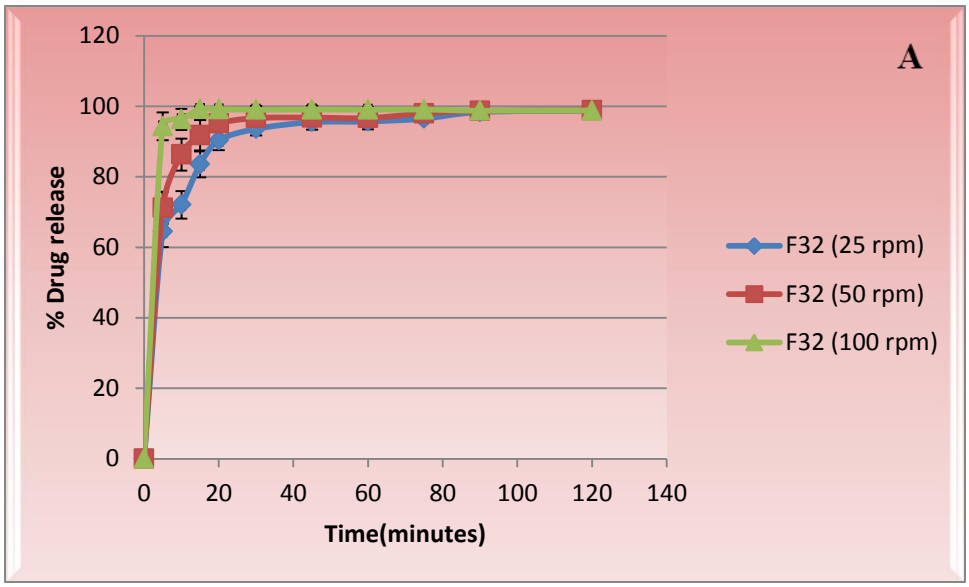
Figure(42): Effect of coating level on the in-vivo taste masking properties of the prepared valsartan OSTs

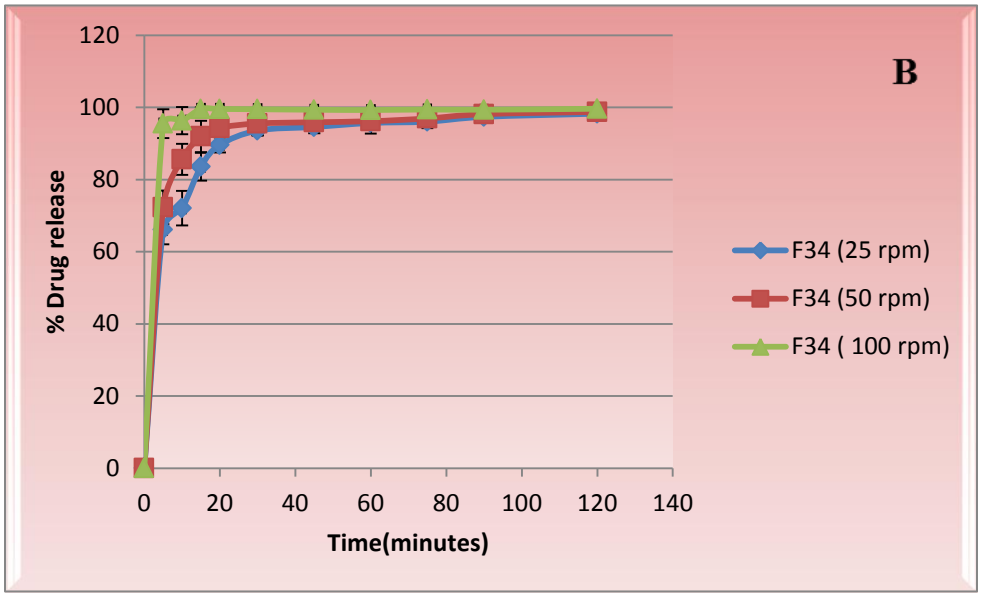
3.4.10 Effect of rotational speed of the dissolution apparatus on the dissolution of the optimum OST formulas

The results in table (31), figure (43-A and B) and figure (44) demonstrate the effect of rotational speed on the two optimum OSTs formulas F32 and F34. A significant enhancement in drug release was observed by increasing rpm from (25 to 100), due to increased rate and extent of water diffusion along with increasing dry mass loss of the oroslippery coat leading to faster breakdown and release of the drug. Similar results were reported with the film-coated immediate release valsartan tablet [143].

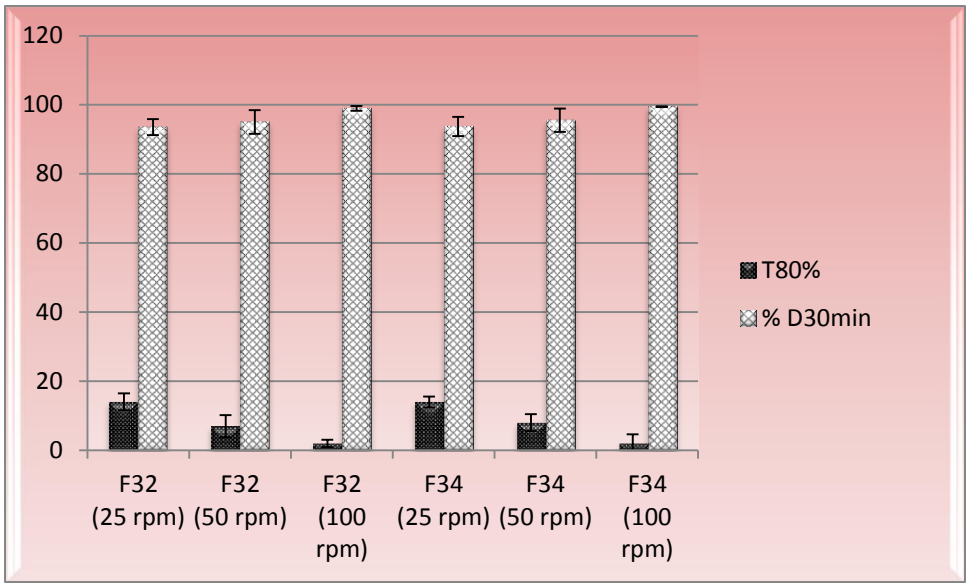
Table(31): Effect of rotational speed on the release of valsartan from the prepared OSTs

Formulas	**rpm**	**$T_{80\%}$ (minutes)**	**$\%D_{30min}$ (%)**
F32	25	14±1.45	93.57±2.34
F32	50	7±0.21	96.05±1.42
F32	100	2±0.01	99.0±0.706
F34	25	14±0.56	93.45±2.78
F34	50	8±0.46	96.52±1.36
F34	100	2±0.05	99.47±0.12





Figure(43): Effect of rotational speed on the release of valsartan from the prepared OSTs in phosphate buffer pH 6.8; A- OSTs containing HPMC as a binder, B- OSTs containing avecil as a binder, 37 ± 0.5 ºC



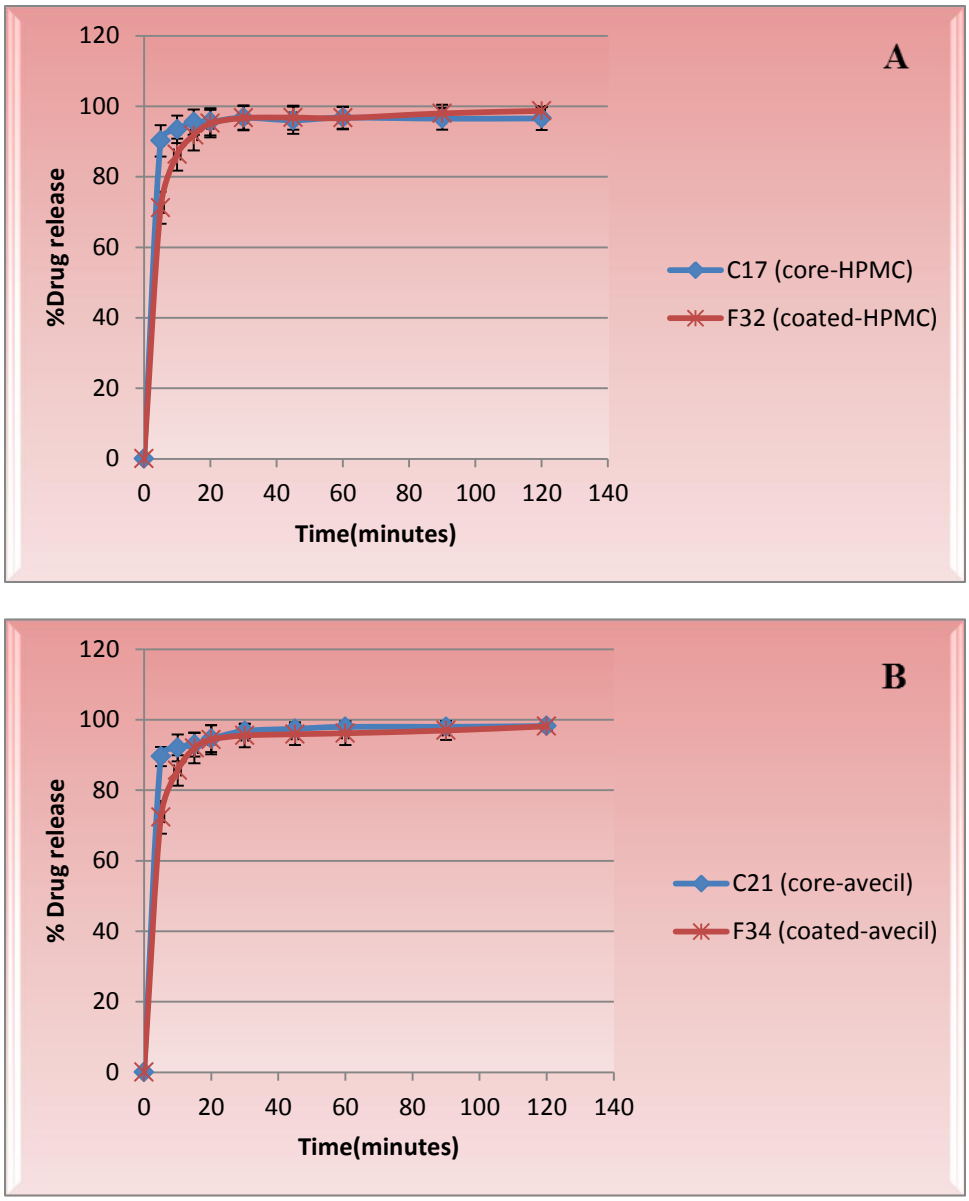
Figure(44): Effect of rotational speed on the $T_{80\%}$ and D_{30min} of valsartan from the prepared OSTs, 37 ± 0.5 ºC

3.5 Comparison of the optimum OSTs formulas with their core tablets

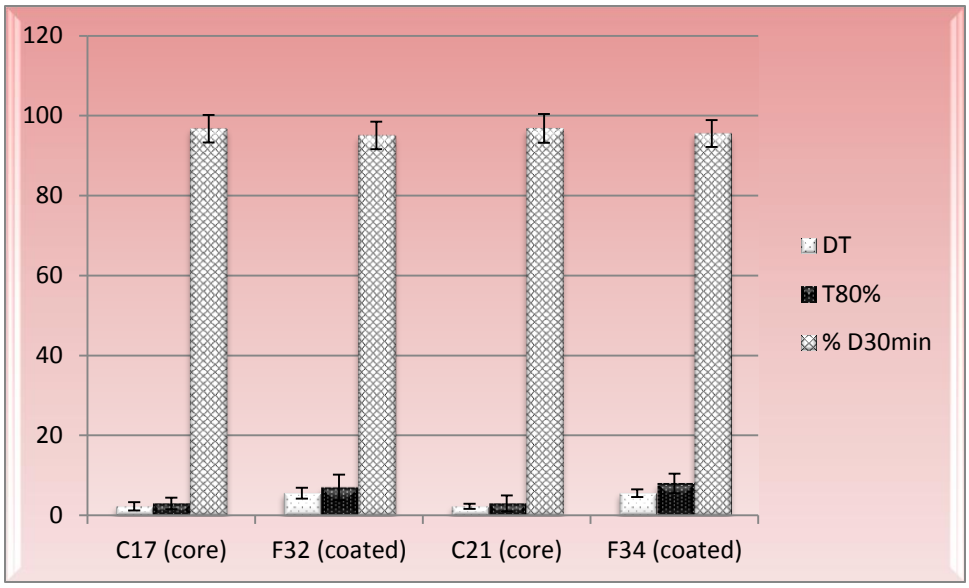
Results for the core and coated OSTs disintegration time and release are shown in table (32), figure (45-A and B) and figure (46). The results showed that application of oroslippery coat in F32 and F34 significantly increased both DT and $T_{80\%}$ but had a non-significant influence on $\%D_{30min}$.

Table(32): Disintegration time (DT) and release of valsartan from the optimum OST formulas (before and after coating)

Formulas	**DT (minutes)**	**$T_{80\%}$ (minutes)**	**$\%D_{30min}$ (%)**
C17(core)	2.25±0.06	3±0.04	96.76±1.44
F32(coated)	5.57±0.36	7±0.01	95.05±0.42
C21(core)	2.27±0.03	3±0.01	96.79±2.6
F34(coated)	5.55±0.98	8±0.06	95.52±1.36



Figure(45): Release profile of valsartan from the optimum OSTs formulas (before and after coating) in phosphate buffer pH 6.8; A- Tablets containing HPMC as a binder, B- Tablets containing avecil as a binder, 37 ± 0.5 ºC



Figure(46): Disintegration time (DT) and release of valsartan from the prepared core and coated tablets, 37 ± 0.5 ºC

3.6 Comparison of the optimum OSTs formulas with the conventional marketed tablet (Diovan®)

A comparison between the two optimum formulas (F32,F34) with the conventional marketed tablet Diovan® in DT and release profile in phosphate buffer pH 6.8 and HCl pH 1.2 is summarized in table (33) and figures (47,48). The result showed that although significant differences were observed between the optimum formulas and Diovan® in DT and $T_{80\%}$ (in phosphate buffer pH 6.8) but there was no significant difference in the release profile represented by $T_{80\%}$ (in HCl pH 1.2) and $\%D_{30min}$ in both media. The difference and similarity factors (f1 and f2) were calculated for the two optimum formulas in comparison to Diovan® tablet and are represented in table (34). The difference factors (f_1) was found to be less than 15, while the similarity factors (f_2) was more than 50 in both medias for the two optimum formulas F32,F34, indicating that the selected OST

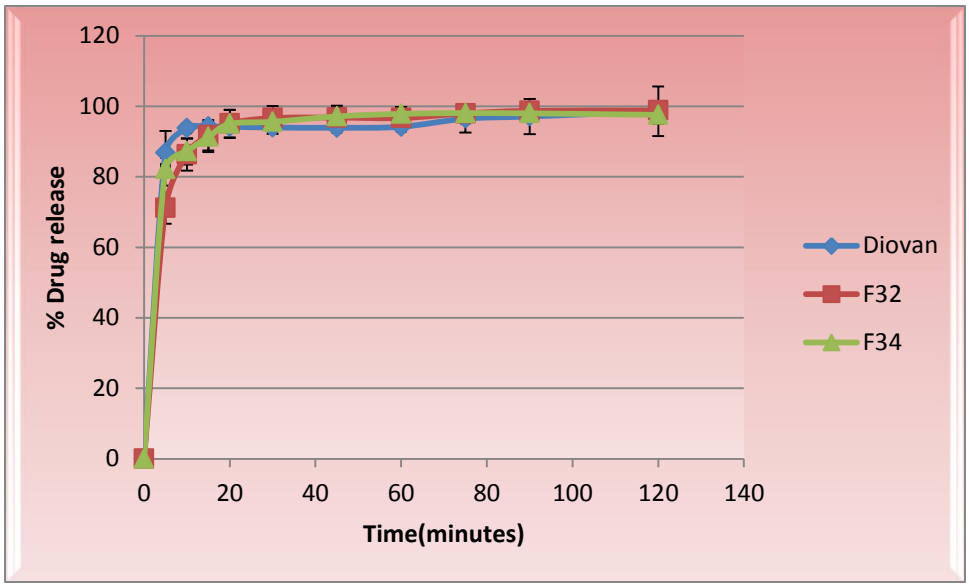
formulas have immediate release profile similar to the marketed tablet Diovan®.

Table(33): Disintegration time (DT) and release of the optimum OST formulas and marketed Diovan® tablet

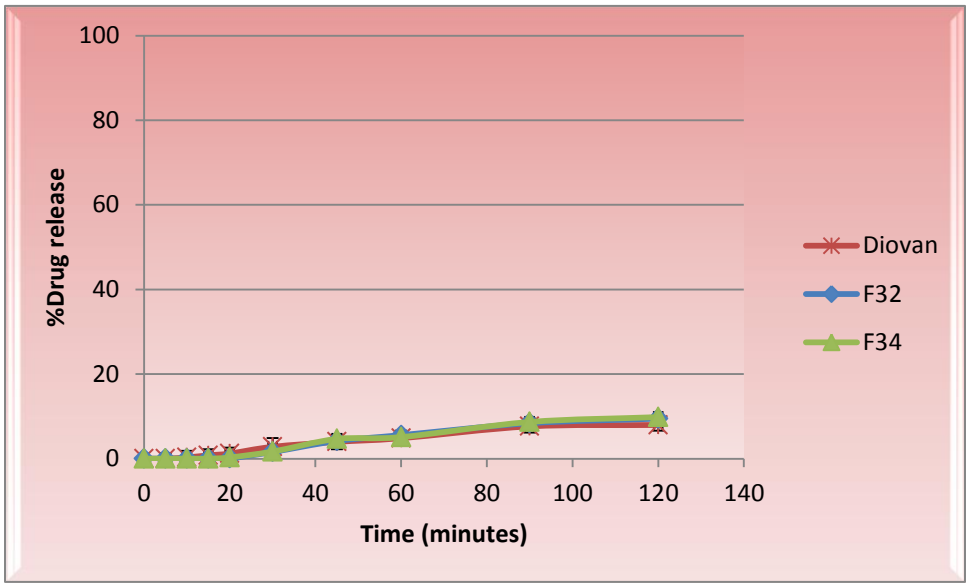
Formulas	DT (minutes) (HCl pH 1.2)	$T_{80\%}$ (minutes) (phosphate buffer pH 6.8)	$\%D_{30min}$ (%) (phosphate buffer pH 6.8)	$T_{80\%}$ (minutes) (HCl pH 1.2)	$\%D_{30min}$ (%) (HCl pH 1.2)
F32	5.57±0.36	7±0.01	95.05±1.42	>120	1.58±0.02
F34	5.55±0.08	8±0.46	95.52±1.36	>120	1.68±0.06
Diovan®	2.10±0.06	4±0.03	93.97±0.31	>120	2.09±0.07

Table(34): Differences and similarity factors (f1 and f2) for the optimum OST formulas in phosphate buffer pH 6.8 and HCl pH 1.2

Formulas	f1 (HCl pH 1.2)	f1 (phosphate buffer pH 6.8)	f2 (HCl pH 1.2)	f2 (phosphate buffer pH 6.8)
F32	1.09	1.39	99.88	68.4
F34	4.02	0.35	98.58	91.98



Figure(47): Release profile of valsartan from the optimum OST formulas and marketed Diovan® tablet in phosphate buffer pH 6.8, 37 ± 0.5 ºC



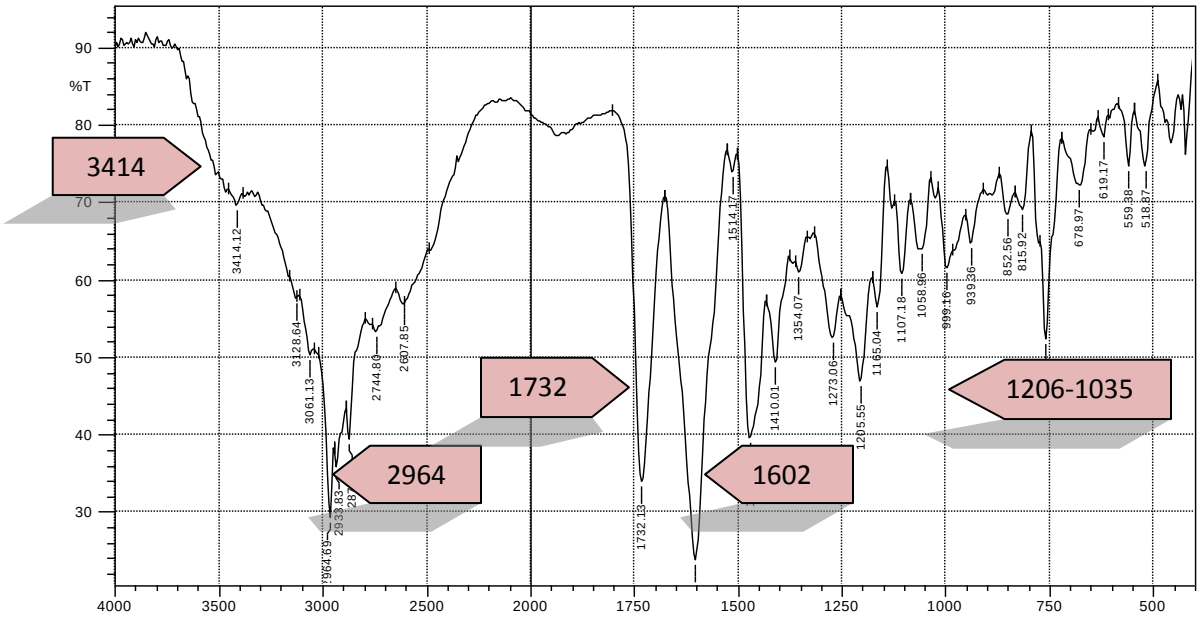
Figure(48): Release profile of the valsartan from the optimum OST formulas and marketed Diovan® tablet in HCl pH 1.2, 37 ± 0.5 ºC

3.7 Content uniformity

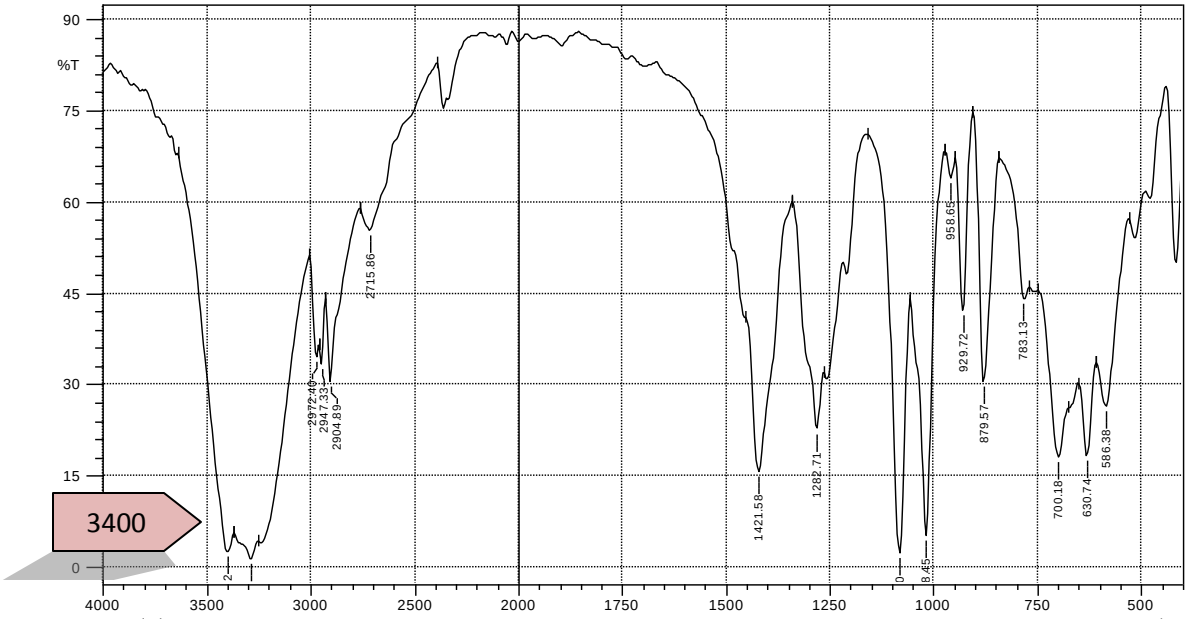
Content uniformity of the selected OST formulas F32 and F34 were complied with the USP requirement in that no tablet of the ten OSTs tested individually from each formula was laid outside the range 85-115%, indicating the uniform distribution of valsartan in the prepared OSTs.

3.8 Drug excipients compatibility

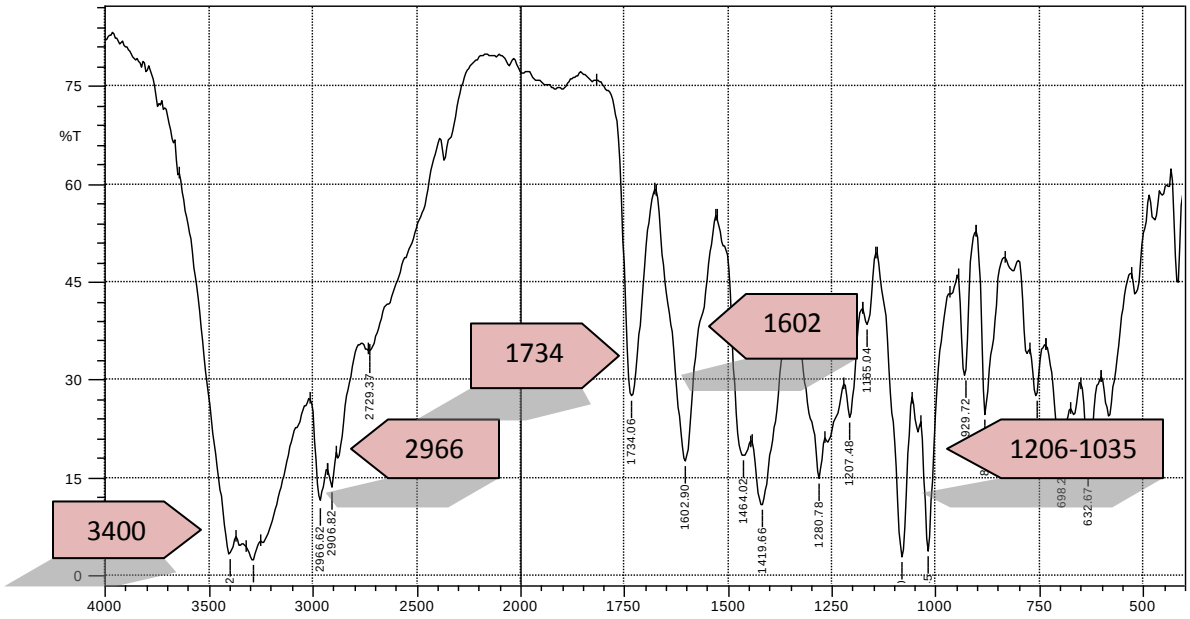
The FTIR spectra of the pure valsartan and mannitol powder are shown in figures (49) and (50) respectively. Valsartan spectrum showed a charachteristic peak at 3414 cm^{-1} indicated the presence of N-H and O-H stretching, while the peak at 2964 cm^{-1} resulted from aliphatic C-H stretching. The characteristic peak at 1732 cm^{-1} representing the carboxylic acid C=O stretching, whereas the C=N stretching caused the peak at 1602 cm^{-1}. Finally, the presence of the bands in the region 1206-1035 cm^{-1} were due to the C-N stretching in tetrazole ring (CN4)[171,172,173]. The broader and higher intensity in the peak at the region of 3400 cm^{-1} of the grinded cores C17,C21 and coated OSTs for the two optimum formulas F32,F34, as shown in figures (51-54), might be due to O-H stretching of the diluent (mannitol). Other peaks showed no significant shifting in the FTIR spectrum indicating that no interactions were occurred between the drug and other components of the prepared OSTs.



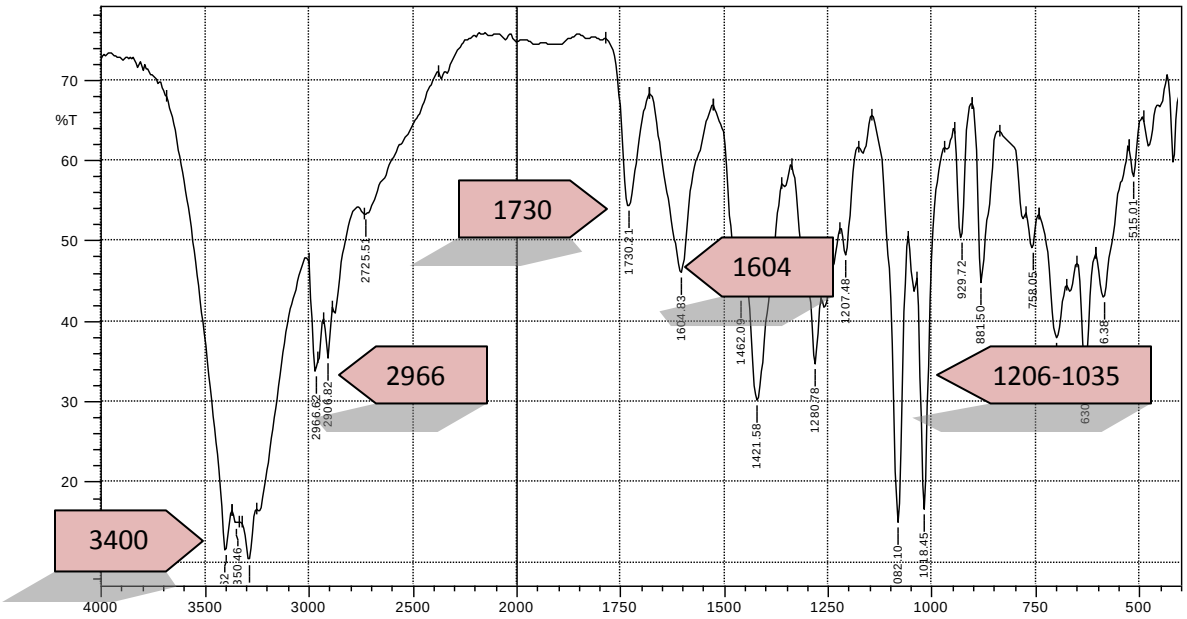
Figure(49): FTIR spectrum of pure valsartan powder



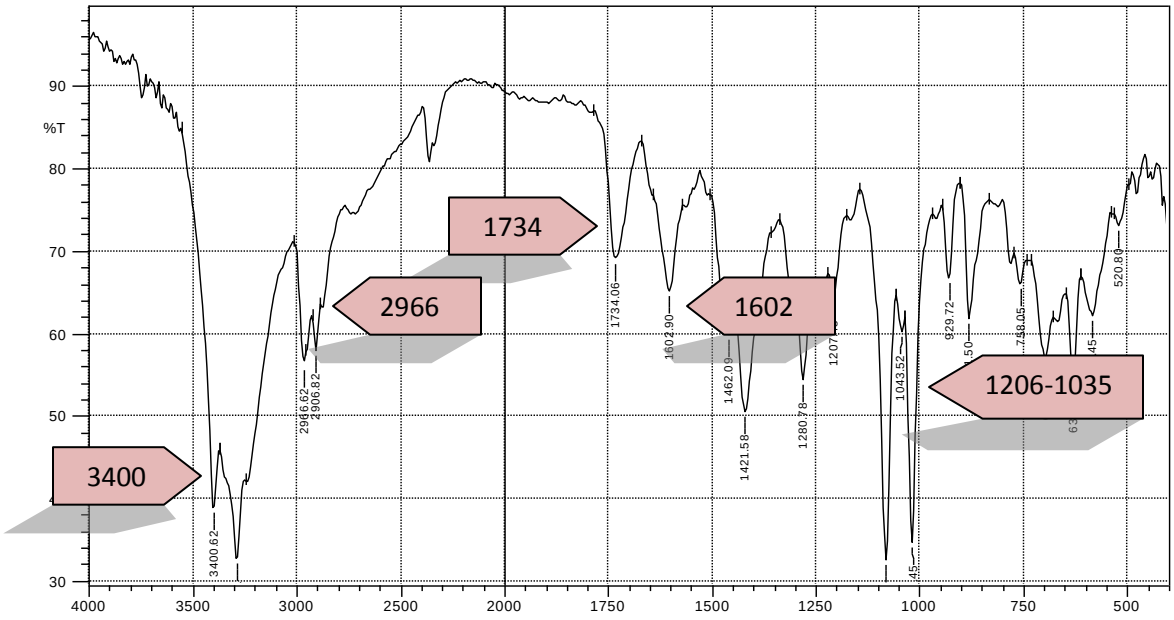
Figure(50): FTIR spectrum of mannitol powder



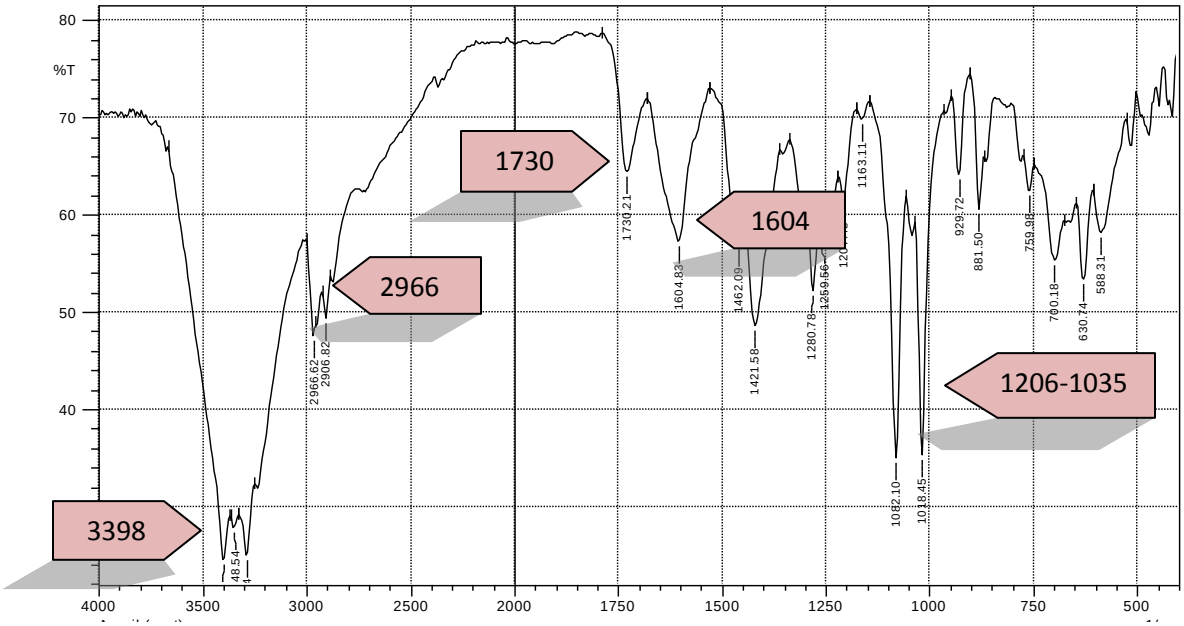
Figure(51): FTIR spectrum of C17 (core for the optimum formula F32)



Figure(52): FTIR spectrum of C21 (core for the optimum formula F34)



Figure(53): FTIR spectrum of the optimum formula (F32)



Figure(54): FTIR spectrum of the optimum formula (F34)

3.9 Stability study

In order to determine the effect of temperature on the prepared valsartan OSTs, the stability of the selected formulas F32,F34 were studied in three different temperatures (40,50 and 60°C) for three months. A straight line was obtained by plotting the logarithm of percent valsartan remaining versus time in weeks (Figures 55 and 56) indicating that the degradation profile follows a first-order kinetics. The degradation rate constant (K) were obtained from each line slope, and results for both formulas are shown in tables (35 and 36).

First order equation ……$\log C_t = log\, C_0 - \frac{K\, t}{2.303}$

Arrhenius equation …… $logk = \log A - \frac{Ea}{2.303\, KT}$

Therefore, Arrhenius plots for both formulas (Figures 57 and 58) were constructed to predict the degradation rate constant at 25 °C (K_{25}), that can be used later for the determination of the expiration date or the time required for the drug to lose 10% of its potency ($t_{10\%}$) using the following equation:

$$t_{10\%} = \frac{0.105}{K_{25}}$$

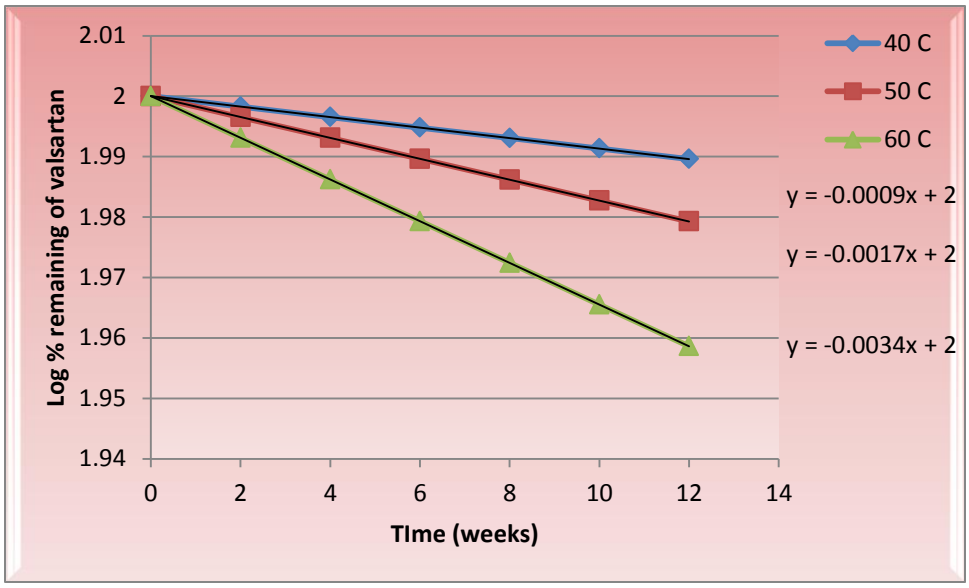
The calculated values of K_{25} were found to be (6.65×10^{-4} and 6.86×10^{-4} $week^{-1}$) which giving $t_{10\%}$ equals to (3.28 and 3.18 years) for F32 and F34 respectively.

Table(35): Degradation rate constant (K) of the optimum valsartan OST (F32) at three different temperatures

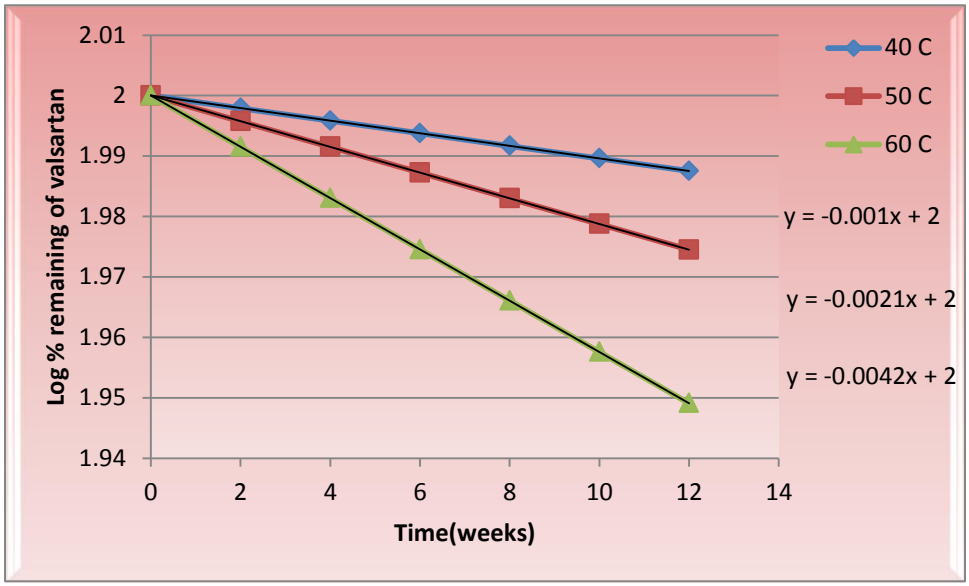
Temperature (°C)	***K (week $^{-1}$)***
40	2.073×10^{-3}
50	3.915×10^{-3}
60	7.83×10^{-3}

Table(36): Degradation rate constant (K) of the optimum valsartan OST (F34) at three different temperatures

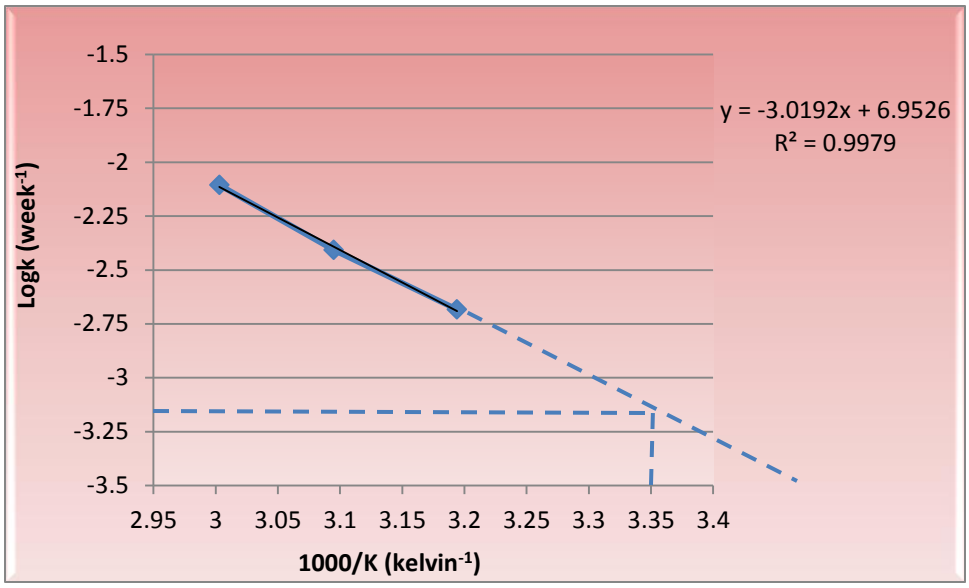
Temperature (°C)	***K (week $^{-1}$)***
40	2.303×10^{-3}
50	4.836×10^{-3}
60	9.673×10^{-3}



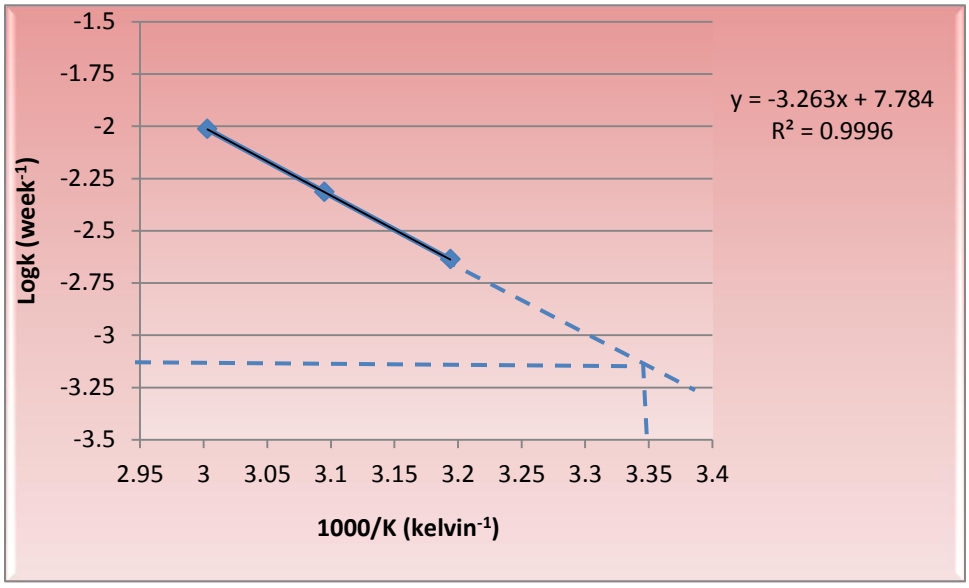
Figure(55): Accelerated degradation of optimum valsartan OSTs (F32) at different temperatures



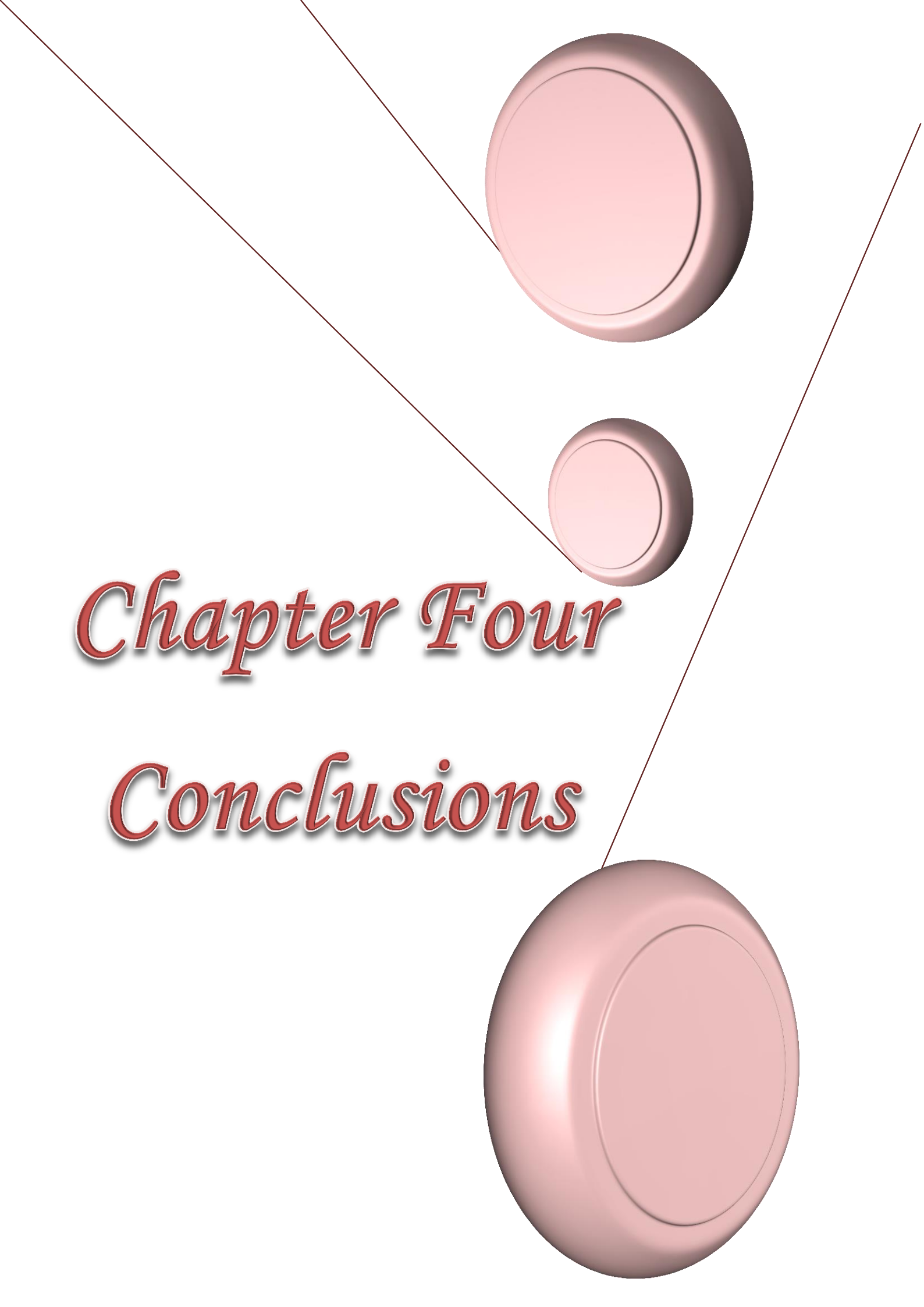
Figure(56): Accelerated degradation of optimum valsartan OSTs (F34) at different temperatures



Figure(57): Arrhenius plot of optimum valsartan OSTs (F32)



Figure(58): Arrhenius plot of optimum valsartan OSTs (F34)


Chapter Four
Conclusions

4. Conclusions and recommendations

4.1 Conclusions

Based on the results of our experiment, we can conclude the following points:

1. All the prepared core tablets were found to have suitable hardness, thickness, with an acceptable friability and weight variation.
2. There were no significant differences between the core and coated tablet hardness while a significant improvement in the friability was observed after coating.
3. Increasing the viscosity of the coating dispersion that was observed by increasing kol. or xan. concentration gave a significant increase the OSTs weight and thickness comparing to OSTs coated with lower concentrations.
4. Increasing HPMC concentration from 2% to 6% enhances disintegration and drug release from the prepared OSTs.
5. Corn starch was not effective as a disintegrating agent for the prepared OSTs.
6. CCS in concentration (6%) was found to be the best superdisintegrant by giving faster disintegration and release for the prepared OSTs.
7. As a diluent, mannitol was preferred over SDL in providing faster disintegration and release.
8. Direct compression was better than wet granulation in the preparation of the OSTs.
9. HPMC (6% w/w) and avecil (2% w/w) considered to be most suitable binders than PVP (2% w/w).

10. Kol. (film forming polymer in the oroslippery coat) in a concentration of (15%w/w), was the ideal in providing a suitable disintegration, release and slipperiness in addition to its most efficient taste masking effect.

11.The optimum concentration of xan. as a slipperiness inducing agent in the coat was (0.3 % w/w), giving the prepared OSTs the desired disintegration and release profile with an acceptable slipperiness and taste masking efficiency.

12. Double coating was preferred over single and triple coating in prolonging DT without significantly affecting the release profile in addition to the adequate slipperiness and taste masking properties.

13. Formulas F32 and F34 containing HPMC and avecil respectively, double coated with coating dispersion consisting from (15% kol.+ 0.3% xan.) were selected as the optimum formulas for valsartan OSTs, with a higher DT but similar release profile to the conventional marketed tablet (Diovan®) in both phosphate buffer pH 6.8 and HCl pH 1.2 with a similarity factor (f_2) more than 50 and difference factor (f_1) less than 15.

14. The selected valsartan OSTs showed an acceptable content uniformity agreed with the USP requirements.

15. The FTIR studies showed no incompatibilities between the drug and other excipients of the OSTs.

16. Accelerated stability study showed that the expiration day of F32 and F34 were equal to 3.28 and 3.18 years respectively.

17. The overall result of this study is the implementation of a new technology by the application of a slippery coat on a tablet surface to overcome the physical and psychological barriers of the tablet, offering an easily swallowed tablet with immediate release profile in the GIT.

Furthermore; it provides a new easy to handle tablet dosage form that is more resistant to light and humidity than ODTs, with a higher flexibility for drug and dose selection and lower taste masking difficulties comparing to buccal, SL and ODTs.

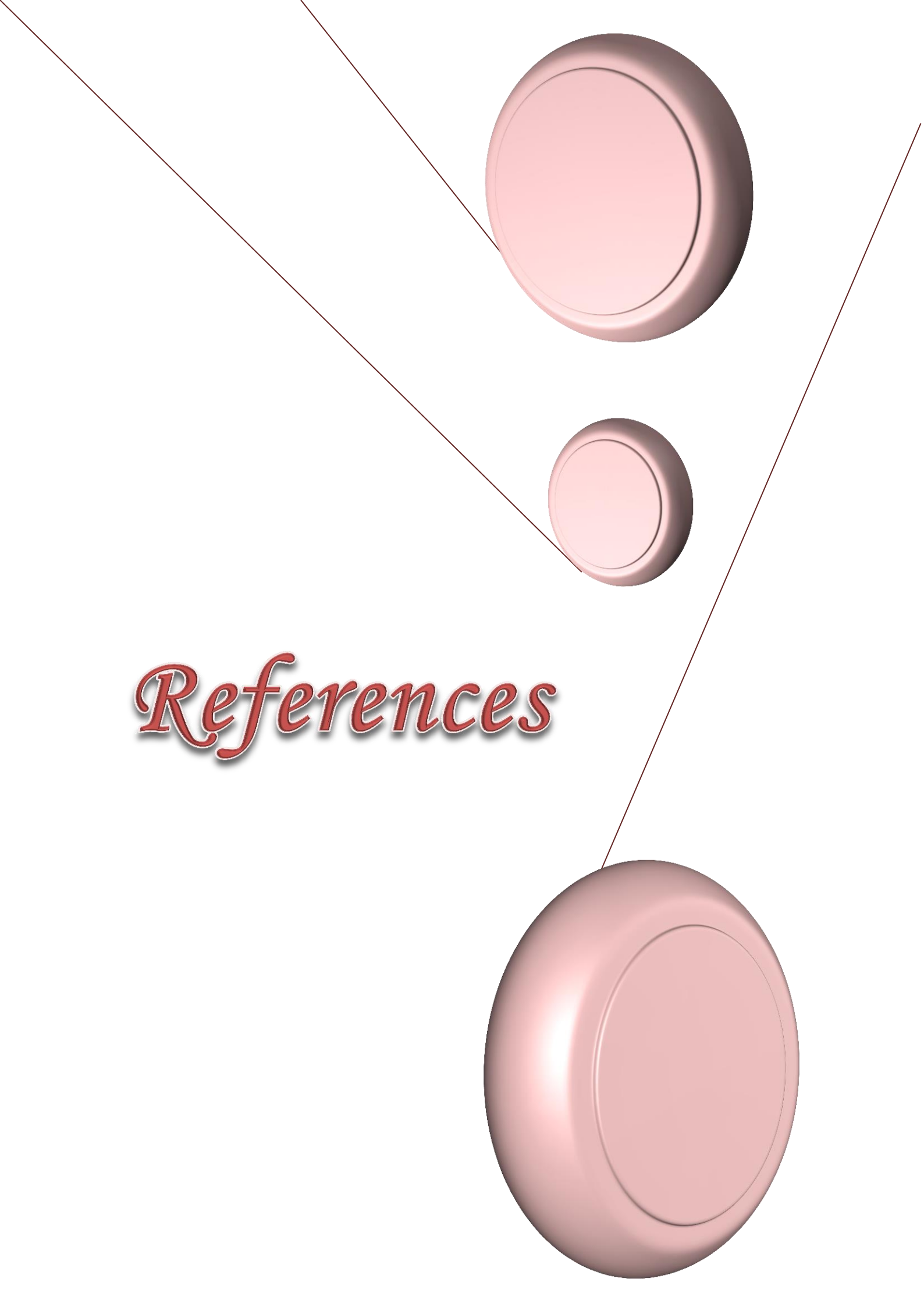
4.2 Recommendations

For future study, the following points are recommended:

1- Videofluoroscopic swallowing study (VFSS) can be performed on the prepared valsartan OSTs in comparison to the marketed conventional tablets.

2- Measurement of the coefficient of the friction of valsartan OSTs as an indicator of slipperiness.

3- Clinical studies to ensure the patient's compliance and comfort upon using OSTs.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الخلاصة

صعوبات البلع (عسر البلع) مشكلة شائعة في حوالي 50٪ من السكان مما يجعل من عملية بلع الحبوب تجربة غير سارة وخاصة بالنسبة للأطفال، وكبار السن والمرضى الذين لا يستطيعون تحمل مياه الشرب أو في حالة عدم وجود الماء. لقد تم تطوير العديد من الأشكال الدوائية للتغلب على هذه المشكلة مثل الحبوب الفموية وحبوب ما تحت اللسان والحبوب الفموية سريعة التشتت, على الرغم من ذلك, تمتلك هذه الاشكال عدد من المعوقات مثل، القيود في مجال اختيار الدواء و الجرعة ، والصعوبات في اخفاء الطعم بالإضافة الى مشاكل الهشاشة والاسترطابية والحساسية من الضوء بالنسبة للحبوب الفموية سريعة التشتت.

تتضمن هذه الدراسة تصميم حبوب جديدة سهلة البلع للفالسارتان (160 ملغ), دواء لمعالجة ارتفاع ضغط الدم ذو طعم معدني مر, وذلك بتغليف سطح الحبوب بغلاف خاص يمكن الحبة على الترطيب بسهولة بمجرد التماس مع اللعاب مما يساعد على انزلاقها الى المعدة مع المحافظة على شكلها الكامل وطعمها المقبول دون الحاجة الى شرب الماء ودون التأثير على سرعة تحرر الدواء, لهذا سميت تلك الحبوب بالحبوب الفموية الانزلاقية.

لقد أعدت خمسة وثلاثين صيغة دوائية تحتوي على الفالسارتان بالإضافة الى ثمانية من الصيغ الخالية من الدواء لغرض اختيار اجود الصيغ وافضلها, وذلك عن طريق غمر الحبوب المعدة سابقا في مزيج الغلاف المتكون من kollicoat IR (كمادة مكونة للغلاف) بالإضافة الى xanthan gum (كمادة مساعدة على الانزلاق). ولقد تم تقييم هذه الحبوب الانزلاقية بالنسبة لعدد من المتغيرات المتعلقة اما بالحبوب الاساسية (بما في ذلك أنواع وتراكيز المواد الرابطة والمواد المفككة وأنواع المخفف بالإضافة الى طريقة الإعداد), او المتغيرات المتعلقة بمزيج الغلاف (مثل تراكيز المواد المكونة للغلاف او المادة المساعدة على الانزلاق بالإضافة الى مستويات التغليف).

لقد تم تقييم هذه الصيغ الدوائية لمختلف الخصائص الفيزيائية مع تقييم سرعة تفكك وتحرر الدواء في خارج الجسم بالإضافة الى تقييم خاصية اخفاء الطعم

(الوقت اللازم للإحساس بالمرارة) في داخل الجسم, في حين تم إجراء تقييم في خاصية الانزلاق (الوقت اللازم للبلع) على الصيغ الخالية من الدواء.

كشفت النتائج ان الصيغ الدوائية (32,34) المتكونة من الحبوب التي تحتوي على (6%) HPMC (32) والتي تحتوي (2%) Avecil (34) كمواد رابطة و (6%) Crosscarmellose كمادة مفككة مع mannitol كمادة مخففة, والمصنعة بطريقة الضغط المباشر, والمحاطة بغلاف مزدوج متكون من (15% kollicoat IR+ 0.3 %xanthan gum) كانت هي الصيغ المثالية, وذلك لامتلاكها الوقت المناسب للانزلاق (8±2.88 ثواني) بدون أي تحرر للطعم المر (58 ± 1.06ثانية) او أي تفكك للحبة (5.57 ± 1.36, 5.55 ± 0.98 دقيقة للصيغتين 32 و 34 على التوالي). وبالإضافة إلى ذلك تمتلك تلك الصيغ الدوائية المختارة القدرة على التحرر الفوري للدواء بالإضافة الى امتلاكها على عوامل تشابه اكثر من (50) وعوامل اختلاف اقل من (15) مقارنة مع الحبوب المسوقة الاعتيادية (Diovan®). كما وجد ان تاريخ النفاذ لهذه الصيغ (3.28 , 3.18) سنوات للصيغتين 32 و 34 على التوالي.

النتيجة العامة لهذه الدراسة هي تصنيع حبوب جديدة سهلة البلع حاوية على الفالسارتان التي تمتلك خاصية الانزلاق والممكن استعمالها كبديل مناسب للحبوب الفموية وحبوب ما تحت اللسان والحبوب الفموية سريعة التشتت وذلك لامتلاكها المرونة في اختيار الدواء بالإضافة الى قدرة الحمل الدوائية العالية, علاوة على احاطتها بغلاف خاص يحميها من الذوبان او التفكك في الفم مما يساعد على اخفاء الطعم مع الاحتفاظ بنمط التحرر الفوري في المعدة. كما يساعد وجود هذا الغلاف الخارجي على زيادة تحمل الحبوب للصدمات والرطوبة والضوء بالمقارنة مع الحبوب الفموية سريعة التشتت.

جمهورية العراق
وزارة التعليم العالي والبحث العلمي
الجامعة المستنصرية
كلية الصيدلة

تحضير, تقييم وتحسين حبوب سهلة البلع ذات غلاف انزلاقي (حبوب فموية انزلاقية) للفالسارتان

اطروحة مقدمة الى

فرع الصيدلانيات ولجنة الدراسات العليا في كلية الصيدلة/ الجامعة المستنصرية كجزء من متطلبات الحصول على درجة الماجستير في علوم الصيدلة (الصيدلانيات)

من قبل

زينب حسن مهدي

(بكلوريوس صيدلة 2007)

بإشراف

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