

Preparation and Evaluation of Oroslipey Tablets Contain Irbesartan and Hydrochlorothiazide Combination

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Abstract

Oroslipey tablets (OSTs) is a technique used to improve swallowing of tablets for patients with dysphagia. The aim of this study was to formulate irbesartan, a hypotensive agent and hydrochlorothiazide, a diuretic as Oroslipey tablets (OST) containing 150 mg irbesartan and 25 mg hydrochlorothiazide designed for dysphagia patients. A simple and rapid method of analysis was developed and validated according to the ICH guideline using HPLC with UV detector. Tablets were prepared by direct compression and then coated with the slippery coat of three different concentrations of the slipping substance "xanthan gum" (2%, 3% and 4%) in Opadry Colorcote® and evaluated according to USP. Slipperiness test was performed using Albino rabbits. Results showed that 2% xanthan gum gave the shortest swallowing time. Also, disintegration time was increased by the coat significantly with the increase of the gum's concentration in the coat. The release kinetics study of the tested formulations (uncoated versus coated with 2% gum) gave the highest correlation for the "first-order release model" for both drugs in the absence and presence of the slipping agent which indicates that the coating did not interfere with the release kinetics of both drugs. In a conclusion, 2% xanthan gum as slipping agent was the optimum concentration used to promote easy ingestion of this tablet.

Keywords: Dysphagia, Hydrochlorothiazide, Irbesartan, Oroslipey tablets (OST), and Slipperiness test, HPLC, ICH guideline.

تحضير وتقييم الأقراص الفموية المنزقة التي تحتوي على مزيج اربيسارتان وهيدروكلور ثايازايد

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الخلاصة

الأقراص المنزقة (OSTs) هي تقنية تستخدم لتحسين بلع الأقراص لمرضى عسر البلع. يتضمن تحضيرها دمج عامل تحفيز الانزلاق في مادة الطلاء. تهدف هذه الدراسة الى صياغة عقار اربيسارتان والذي هو عامل مخفض لضغط الدم والهيدروكلور ثايازايد وهو مدرر على شكل أقراص فموية منزقة تحتوي على 150 ملغم اربيسارتان و 25 ملغم هيدروكلور ثايازايد مصممة لمرضى عسر البلع تم تطوير طريقة بسيطة وسريعة للتحليل والتحقق من صحتها وفقاً لإرشادات المؤتمر العالمي للتوافقية (ICH) باستخدام التحليل السائل عالي الكفاءة مع كاشف الأشعة فوق البنفسجية.

تم تحضير الأقراص عن طريق الضغط المباشر ثم تم تغطيتها بطبقة زلقة من ثلاثة تراكيز مختلفة من المادة المنزقة "صمغ الزانثان" (2%، 3% و 4%) في الغلاف "كولوركون" ثم تقييمها حسب دستور الادوية الامريكي.

تم إجراء اختبار الانزلاق باستخدام أرناب ألبينو وأظهرت النتائج أن صمغ الزانثان 2% أعطى أقصر وقت للبلع. كما زاد وقت تفكك الطبقة بشكل كبير مع زيادة تركيز الصمغ في الغلاف.

أعطت دراسة حركية الإطلاق للصمغ المختبرة (غير المطلوبة مقابل 2% صمغالزانثان) أعلى ارتباط لـ "نموذج الإطلاق من الدرجة الأولى" لكلا العقارين في غياب وجود عامل الانزلاق مما يشير إلى أن الطلاء لم يتدخل مع حركية إطلاق كلا العقارين.

في الختام، فإن 2% صمغ الزانثان كعامل انزلاق، هو التركيز الأمثل المستخدم لتعزيز سهولة تناول هذه الاقراص.

الكلمات المفتاحية: عسر البلع، هيدروكلور ثايازايد، اربيسارتان، الأقراص الفموية المنزقة، اختبار الانزلاق، التحليل السائل عالي الكفاءة، إرشادات المؤتمر العالمي للتوافقية

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Received: 29/9/2021

Accepted: 5/12/2021

Introduction

The term “dysphagia” is widely used to describe a symptom that is manifested as subjective perception of swallowing difficulty during the passage of a liquid or a solid bolus from the oral cavity to the stomach or obstruction perception during swallowing⁽¹⁻³⁾. Oropharyngeal dysphagia is a common type of dysphagia that refers to an oral preparatory, pharyngeal and/or oral swallowing disturbance⁽⁴⁾. Various dosage forms are developed to combat dysphagia for which medications are administered into the oral cavity even without requirement for chewing to create a systemic or local effect. Effervescent and lozenges tablets, as well as sublingual (SL), buccal, Orodispersible (ODTs), and the newly developed oroslippery (OS) tablets, are among them⁽⁵⁻⁸⁾.

Dysphagia is a serious problem requires continuous treatments; new formulations will be helpful in controlling the progression of this problem and offer comfort to the patients. Modification of the available dosage forms especially the widely used oral tablets is an ongoing process in pharmaceutical industry. One new modification is by the introduction of a material that induce a slipperiness characteristic to the tablet coat which facilitate easy smooth swallowing of the tablet^(9,10)

Hypertension (HTN) affects over one billion persons globally, with a systolic BP of higher than the 140 mmHg and/or the diastolic BP lesser than the 90 mmHg. HTN is a serious health issue that is a common risk factor of cardiovascular disease (CVD) and death⁽¹¹⁾. More than 50% of hypertensive patients have additional cardiovascular risk factors. The most common additional risk factors are diabetes (15%–20%), lipid disorders (elevated low-density lipoprotein-cholesterol [LDL-C] and triglycerides [30%]), overweight-obesity (40%), hyperuricemia (25%) and metabolic syndrome (40%), as well as unhealthy lifestyle habits (e.g., smoking, high alcohol intake, sedentary lifestyle). The presence of one or more additional cardiovascular risk factors proportionally increases the risk of coronary, cerebrovascular, and renal diseases in hypertensive patients⁽¹²⁾.

Irbesartan is administered orally and competitively antagonize the angiotensin II receptors that is being used to manage the hypertension and the kidney impairment in hypertensive and diabetic individuals. Among humans' smooth muscle vascular cells, it shows high affinity to the receptor of AT1, causing a decrease of peak response for angiotensin II⁽¹³⁾. Irbesartan is a solid crystalline powder slightly soluble in water with M.Wt. 428.5 and pKa(s) 4.08, 4.29⁽¹⁴⁾.

Hydrochlorothiazide is a diuretic of the thiazide form that has been available for more than 5 decades for clinical use⁽¹⁴⁾. Hydrochlorothiazide hydrochloride is a thiazide derivative with Mwt (334.2 g/mol). It is a white crystalline powder, slightly soluble in water and freely soluble in sodium hydroxide solution.⁽¹⁵⁾ Irbesartan is available in a [fixed-dose combination](#) formulation with [hydrochlorothiazide](#), to achieve an additive antihypertensive effect. Irbesartan/hydrochlorothiazide combination preparations are marketed under various brand names.

A 25mg of HCT with 300mg IRB can exhibit synergistic antihypertensive efficacy in such a dose-dependent way with excellent tolerability in a variety of patient classes. In individuals who are not managed neither IRB nor HCT alone, the mixture lowers the BP considerably. The combination of these drugs had a beneficial impact. IRB seemed to attenuate hypokalemia, uric acid and the total cholesterol side effects that caused by HCT in many experiments⁽¹⁶⁾.

Oroslippery tablets (OSTs) aim to facilitate the swallowing of the tablets by the modification of the coat to offer slippery smooth passage of the tablet especially that of large size through pharynx and esophagus. Very few studies are available and many factors that affect the efficiency of the coat are still in need to be studied. A study of Mahdi and Marie in 2015 described coating of valsartan tablet with kollicoat immediate release (IR) (film former) and xanthan gum (slipperiness inducer) at different coating levels.⁽¹⁰⁾

Opadry Colorcone is a coating mixture powder introduced by Colorcone. It is one-step film coating system which combines polymer, plasticizer and pigment, as required, in a dry concentrate. Different types of Opadry are available depending on the type of polymer if it produces immediate release, controlled release or enteric coating.⁽¹⁷⁾

Xanthan gum is an extracellular polysaccharide secreted by the microorganism *Xanthomonas campestris*. Commercially it is manufactured by a fermentation process.

The xanthan gum polysaccharide consists of a backbone of β -(1→4) linked d-glucose molecules. Every second glucose molecule is substituted at C3 with a trisaccharide side chain consisting of β -d-mannose-(1→4)- β -d-glucuronic acid-(1→2)- α -d-mannose. It has many uses as food additives, viscosity builder and pharmaceutical uses.⁽¹⁸⁾

The aim of this study is to formulate a combination of Irbesartan and hydrochlorothiazide as oroslippery tablets by formulation of this combination as core tablets then coating with

Opadry colorcone immediate release tablets with different ratios of xanthan gum as slippery agent and evaluation of the tablets.

Materials and Methods

Materials

Irbesartan was purchased from (purity 99.5%, Jiangsu Yew Pharmaceuticals Co. Limited, China) Hydrochlorothiazide (purity 99.6% Provizer Pharma, India), sodium starch glycolate, Avicel (PH102), aspartame, mannitol, peppermint flavor, aerosol (hydrophilic grade), Na stearate, Xanthan gum and Opedry® Colorcon were all given as gift from Dar Al Dawa pharmaceutical/Jordan. Methanol (Merck) HPLC grade, tetrahydrofuran, sodium acetate (Sigma), acetic acid (Sigma), sodium hydroxide (Sigma).

Methods

Chromatographic condition

High Performance Liquid Chromatography (HPLC) was used as a method of analysis to detect and quantitate IRB and HCT in tablet intended to be prepared. After several trials the chromatographic conditions showed in Table 1 were decided and followed. The elution was isocratic were the composition and flow rate of mobile phase was constant along the run time.

Table 1. Chromatographic conditions used in method development

Component	Type
HPLC	Server (LC-Thermo) with by LC Solution Software
Detector	UV detector.
Wavelength	265 nm
Mobile Phase	methanol-tetrahydrofuran: acetate buffer pH 6.5 (47:10:43) v/v/v.
Flow Rate	1ml/min
Injection Volume	20 µl
Total Run Time	9 min
Column	Supelcosil C18 (150 mm × 4.6 mm, 5 nm part..size)
Column Temp.	Room temp (25°C).

The method was validated by measuring Linearity, precision, accuracy and recovery for both drugs measured simultaneously. Linearity of IRB was measured by measuring concentrations range (10, 20, 40, 80, 140, 180) µg/ml and of HCT (1, 12, 24, 36, 44, 50) µg/ml. Regression and correlation coefficient was calculated. Inter and intra-day precision of the method were determined by the analysis of 6 samples (calibration conc.) with 3 replicates and calculation of percent coefficient of variation (%CV). While recovery of drugs was calculated by analysis of powder mixture

(before compression). Conc. of IRB used were (35, 50, and 65 µg/ml) and for HCT also, (31, 45, and 58 µg/ml) µg/ml) using different degrees of dilution. All tests were performed and evaluated according to the ICH guideline.

Formulation of core tablet

A standard formula was prepared as in Table 2. One hundred tablets were prepared and evaluated. Then other batches were prepared for coating

Table 2. Composition of IRB-HCT combination core tablet

Ingredient	Amount (mg) /tab.
Irbesartan (IRB)	150 mg
Hydrochlorothiazide (HCT)	25 mg
Sodium starch glycolate	20 mg
Avicel (PH102)	150 mg
Mannitol	47 mg
Aerosil (hydrophilic grade)	4 mg
Na stearate	4 mg
Total weight	400 mg

One hundred (100) tablets - batch of the formula was prepared. All ingredients were weighed, and mixing process was performed manually by wide mouth conical flask. First all materials were sieved through mesh no. 36 to get rid of any particulate materials. Then all constituents except the lubricant were put the flask and rotated manually in one direction for 20 min. After that the lubricant was sieved in 60 mesh size and added to the mixture and mixed for 1-2 min⁽¹⁹⁾.

The obtained powder blend was directly compressed into tablets using tablet press (Erweka, single punch compression machine) using oval shape upper punch and die⁽²⁰⁾. One hundred tablets of the formula were compressed

Evaluation of the prepared tablets

Uniformity of weight

Weight variation of the prepared tablets were performed by weighing, randomly selected, twenty tablets individually from each formula using electrical sensitive balance (Shimadzu, Japan) and the average weight ±SD was calculated⁽²¹⁾.

Tablet thickness

Thickness of tablets was measured using thickness caliper (Mitutoyo® CD-15B, England) for 10 randomly selected tablets. Average thickness in mm ±SD was recorded⁽²²⁾.

Hardness and friability

The breaking force (hardness) was measured using hardness taster (Dr. Schleuniger Pharmatron 8M, Switzerland). The test was performed in the beginning, during and at the end of the tablet production to ensure a fixed hardness over the production process. Friability of the tablets was determined using (Erweka® TA 100 friability tester, Germany). Twenty tablets were initially weighed (Wt1) and transferred into Friabilator. The Friabilator was operated at 25 rpm for 4 mins. The tablets were weighed again (Wt2). The percentage (%) of friability was then calculated using equation 7:

$$\text{Percentage of friability} = \frac{W_1 - W_2}{W_1} \times 100 \%$$

Where W1 is weight of 20 tablets before placing in Friabilator and W2 is the weight of 20 tablets after taking out of Friabilator⁽²³⁾.

Disintegration time

Disintegration time was determined using the disintegration apparatus USP (Electrolab, Bangalore, India) in D.W maintaining the temperature at $37 \pm 1^\circ\text{C}$. Six tablets were used. Each tablet was put in each vessel and time of disintegration was recorded in minutes \pm SD⁽²⁴⁾.

Assay of APIs in the tablets

Twenty tablets were taken randomly from the prepared tablets and crushed to fine powder. A powder weight was taken equivalent to 150 mg IRB and to 25 mg HCT. Mobile phase of the validated method was used to solubilize the drug each time to 50 ml total volume. Solution was filtered through 0.45 μm membrane filter to get clear solution. Suitable dilutions were made to get concentration of IRB 50 $\mu\text{g/ml}$ and 40 $\mu\text{g/ml}$ HCT

and each drug content was calculated from its calibration curve⁽²⁵⁾.

Coating process

Tablets were coated using Opadry colorcone® to which added the slipping agent in different concentrations and other additives. Table 3 shows the coating formulations.

Three liters of each coating formula was prepared. Solid materials were all weighed and put aside. A mixture of solvent system (60:40) water: ethanol (90%) was prepared in 3500 ml hard glass beaker and put under electrical stirrer. 2750 ml solvent system was put first then gradually adding the solid material while starting low speed stirring until the whole quantity is added. The stirring speed was then increased until fixed onto 1000 rpm for 40 min. Then the speed was gradually decreased to avoid air bubbles and stopped. Volume was completed to 3 L and additional 15 min of stirring were added to ensure homogenization. The coating dispersion was freshly prepared before each coating run⁽¹⁷⁾.

Due to small number of tablets prepared, the coating pan was loaded with placebo tablets (made of compressed avicel) to make tablets rolling over and the optimization of coating parameters easier⁽¹⁷⁾. The tablets prepared for the animal study were smaller in size (50 mg wt.) in addition to the placebo bulk. The bed was pre-heated to 40°C using dryer and thermometer, the coating pan was loaded with the tablets and switched on. Few tablets were taken after 60, 80 and 100 min for inspection and weighing. The coating process was stopped after 100 mins. where the weight gain was 3 % (average 11-14 mg)⁽²⁶⁾.

Table 3. The experimental design and formulas of the slipping coat.

Material	Control formula (CF)(%)	Coating formula 1 (CF1)(%)	Coating formula 2 (CF2)(%)	Coating formula 3 (CF3)(%)
Opadry	12	12	12	12
Xanthan gum (Slipping agent)	0	2	3	4
Peppermint flavor	0.5	0.5	0.5	0.5
Aspartame (sweetener)	0.1	0.1	0.1	0.1
Total solid concentration	12.6	14.6	15.6	16.6

Evaluation of the coated tablets

Weight gain by coat

Weight uniformity test was repeated on coated tablets and the average weight gain by coating process was calculated.⁽²⁷⁾

Thickness of coated tablets

Thickness of coated tablets was measured to check the increase in tablet thickness due to

coating process. 10 tablets were chosen randomly, and the thickness was measured by (Mitutoyo® CD-15B, England). Average thickness \pm SD was recorded and compared with the thickness of the uncoated tablet statistically.⁽²²⁾

Disintegration time

Disintegration time was repeated for the coated tablets, average time \pm SD was recorded for

each formula and compared statistically to the standard uncoated formula. (24)

Slipperiness test

Four albino rabbits were used in this test. (Ethical approval dec. 6/7 20-21, Al-Ahliyya Amman University). Each one received 3 tablets of the specified concentration of the slipping agents. Rat 1 received tablets coated with Opadry without slipping agent, rat 2 received coated tablets with 2% Slipping agent, Rat 3 received tablets of 3% slipping agent and Rat 4 received tablets of 4% slipping agent. The rabbits were given water to drink immediately prior the test to avoid dry mouth. Then a tablet is put on his tongue and time is recorded as zero time, then the hand is put gently on his throat to sense the swallowing of the tablet. This moment is recorded as time from zero. Three readings were taken for each tablet tested, average \pm SD was estimated. (10)

Drug release and dissolution

The dissolution test conditions were chosen according to the USP monographs and published works of both drugs. USP App II with 0.1 N HCl (900 ml) as a dissolution media, 75 rpm stirring rate and the temperature of 37 ± 0.5 °C were chosen as dissolution conditions. Time points: 5, 10, 15, 20, 30, 45, 60 min. Six (6) tablets were put each in a jar and 5 ml samples were withdrawn and replaced by fresh media to keep sink condition, Samples were taken at time points; 5, 10, 15, 20, 30, 45, and 60 min., filtered through $0.45 \mu\text{m}$ and suitably diluted by mobile phase and analyzed using the validated method developed and data was reported as average conc. \pm SD of each reading. Then percent drug dissolved vs time was plotted as the dissolution profile. Dissolution test was performed on the uncoated formula and the coated formulas. (28)

Results and Discussion

Method development and validation

IRB absorbs at 270 nm (29) and HCT has maximum absorption at 238 and 271 nm (30). These values differ slightly according to the method. Here, 265 nm was chosen as suitable λ for best results where a good absorption of both occurs and both peaks appeared in the same chromatogram clearly using the specified mobile phase. HCT was eluted first with RT = 3.0 min, then next IRB with RT= 6.5 min. Figure 1 shows one chromatogram of IRB and HCT and the clear separation of the two APIs.

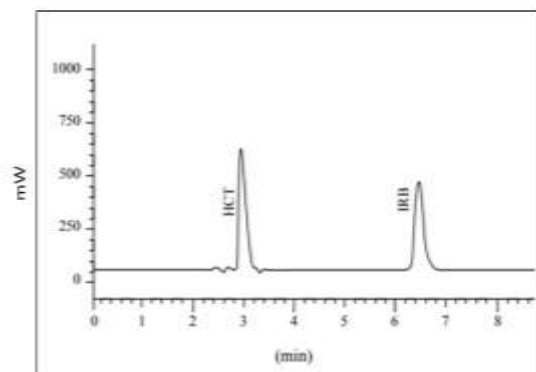


Figure 1. Chromatogram showing peaks of HCT (30 $\mu\text{g/ml}$) and IRB (80 $\mu\text{g/ml}$)

IRB and HCT showed linearity in the specified concentrations with correlation coefficient equals to 0.999 for both drugs and relative standard deviation (RSD) less than 2.00. Calibration curves are shown in figure 2 (A and B).

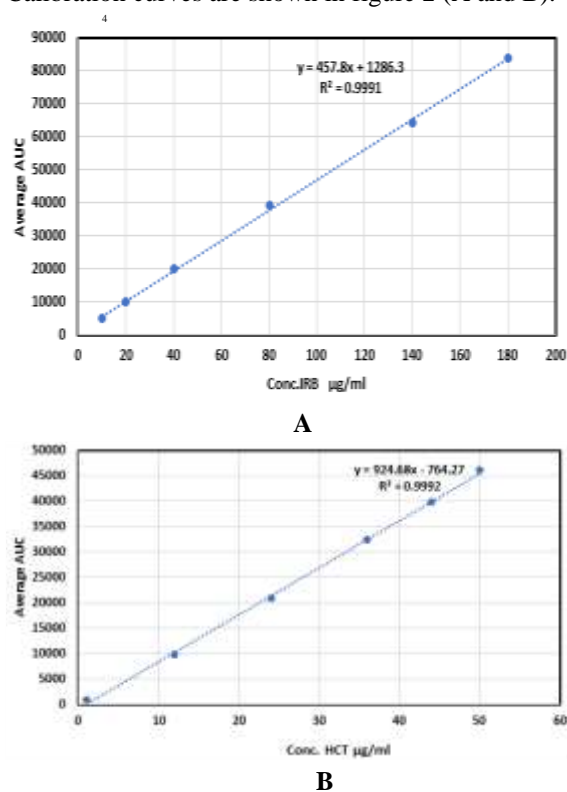


Figure 2. Calibration curves of Irbesartan (A) and Hydrochlorothiazide (B)

Inter and intra-day precision results gave the mean value of percent accuracy between 97.7 - 101.1% for both IRB and HCT and the %RSD is below 2%, which means an accepted criterion according to the ICH guideline. Recovery of IRB from the formula was 99.3% with RSD 0.46 and that of HCT was 98.0 with RSD equals to 0.9.

Formulation design and powder preparation

The master formula was prepared using sodium starch glycolate as disintegrant, avicel and mannitol as bulking agents. The powder mix was

prepared, and no segregation of materials was detected. This may be related to close particle size achieved by sieving before mixing process. No clogging or attachment of powder to the flask walls was observed except minor dusting.

Physical evaluation of the prepared tablets

The obtained tablets were inspected visually. Tablets were good shaped with sharp edges, shiny, smooth with bright white color. No cracks, no capping or peeling were observed. Considering uniformity of weight, the average weight of ten tablets was measured individually according to the specification of the USP ⁽²¹⁾. Tablets weigh less than 180 mg might have less than $\pm 10\%$ of weight variation. Tablet's weight 180-325 mg would accept $\pm 7.5\%$ while tablets weigh more than 325 mg would accept $\pm 5\%$ of its weight variation. No tablet should weigh more or less than double the allowed percent variation. Average theoretical weight of the tablets is 400 mg, and it follows the third category All tablets were in the USP specifications, and this reflects the efficiency of compression process. Results are shown in Table 8. Thickness of tablets are shown in table 8. Coating will add to the tablets and would be measured again to detect how much thickness the coat would add.

Hardness and friability

Hardness of tablets should be enough to handle coating process and satisfy the properties of

Table 6. Results of assay of IRB and HCT in the prepared uncoated tablets

Tablets APIs	Theoretical Concentration ($\mu\text{g/ml}$)	Average Area measured n=3	Actual Concentration ($\mu\text{g/ml}$)	Percent content (%)	Precision (RSD)
IRB	50.0	21047.42	48.90 \pm 1.2	97.8	0.8
HCT	40.0	37735.6	41.1 \pm 0.9	102.75	0.7

Tablet coating

The coated tablets with the slipping coat were prepared as described earlier. The 3 batches were re-evaluated physically before performing the slipperiness test. The coated tablets were examined visually. They showed good appearance, uniform white color with no peeling or mottling. Tablets are shown in Figure 3.

Weight gain by coating

Film coating should not add much weight to the tablets. Weight gain was checked during or before finishing the process. However, re-weighing the tablets after coating and drying was done. Results gave increase in the weight about 3.25%. Thickness was also increased due to the coating process. Results showed increase in thickness about 1.3 % as illustrated in Table 7.

immediate release tablets and allow disintegration and dissolution. Friability of tablets should not exceed 1% according to the USP which is like regular tablets. After several trials in compression of the formula, the hardness was kept on 5 Kg and friability was below 1%. Results of weight uniformity, hardness, friability and disintegration test are shown in table 5. Disintegration time of the uncoated tablets was 5.6 ± 0.8 min, this result is compatible with the specification of USP of immediate release tablets.

Table 5. Results of physical evaluation of the uncoated tablets

Test	Results (Average \pm SD)
Weight Uniformity test (mg) N= 20	403 \pm 6.2
Hardness (Kg)	5.0 \pm 0.1
Friability (%)	0.3
Disintegration time (min)	5.6 \pm 0.8 min

Assay of active ingredient in the tablets

Results of assay of APIs in the prepared tablets are presented in table 6. Percent drug recovery of IRB and HCT was high and close to 100% knowing that the guideline allows 90-110% drug content in the dosage form.

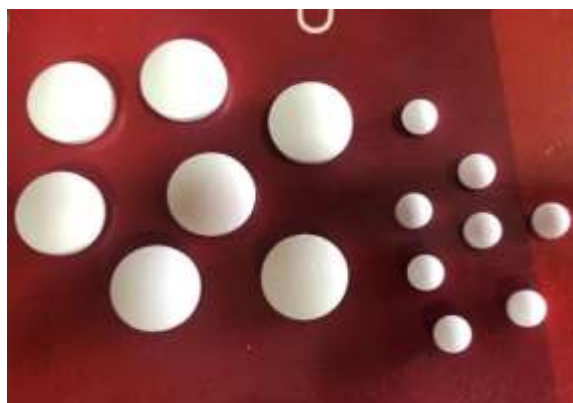


Figure 3. The coated tablets and the animal model

Disintegration time

Disintegration test was repeated for the coated tablets to investigate effect of coat and slipping agent on the physical characteristics of the tablets. Disintegration time was elongated by coating due to extra wetting time needed by the coat. Increasing the percent of xanthan gum resulted in increase in disintegration time as shown in Table 7. Xanthan gum is an extracellular bacterial exopolysaccharide synthesized by *Xanthomonas campestris*. The unique properties of xanthan gum make it widely used in different applications. It is highly soluble in water, stable

over a wide range of temperature, acidic and alkaline conditions⁽³¹⁾. Xanthan gum is a stabilizer used in suspensions and cosmetics that helps “binding” materials together. Possibly this “net” formed by the gum within the film resulted in increase in disintegration time of the coated tablets, although all values are still accepted according to the USP. Statistically, disintegration time increased significantly ($p < 0.05$) of all coated formulas compared to the uncoated formulas. And the disintegration time was increased significantly in CF1, CF2 and CF3 compared to CF^e (without Xanthan gum).

Table 7. Weight gain and disintegration time of the coated formula.

Formula code	Average weight (mg)	Disintegration time (min: sec)
Uncoated formula ^s	402 ± 3.2	1:00 ± 2 Sec
CF (0%) ^e	406.8 ± 2.5	1:10 ± 2 Sec
CF1 (2%)	408 ± 3.2	1:30 ± 3 Sec
CF2 (3%)	407.2 ± 3.1	2:20 ± 4 Sec
CF3 (4%)	405.5 ± 2.3	3:00 ± 3 Sec

Slipperiness test

Results of slipperiness test are listed in Table 8. The properties that enable the application of xanthan gum in pharmaceutical industries are emulsifying, thickening, stabilizing, film forming and gelling nature⁽³¹⁾. Here, xanthan gum is used as “slipping agent”. This characteristic is obtained due to its nature of fast wetting and forming a thin stable layer within the film that have that slippery nature when mixed with saliva. The coated tablet without slipping agent (CF) took the longest time in swallowing and swallowing was difficult and the animal was helped to swallow it. All coated formulas with the slipping agent gave significantly shorter time of swallowing than CF ($p < 0.05$). CF1 gave the shortest slipping time among the three concentrations used (30 ± 1 sec) and it was significantly shorter than CF2 (37 ± 2 sec) and CF3 (40 ± 2 sec) ($p < 0.05$). Increasing the concentration of xanthan gum from 2% to 3 and 4 %, did not enhance the slipperiness of the tablets, on the contrast it resulted in elongation of time. Although xanthan gum is described as (non-gelling agent), Other studied described xanthan gum as gel inducing agent⁽¹⁶⁾ but increasing concentration was observed to form “over wet” sticky tablet which in turn faced a slight difficulty in swallowing it. Figure 5 show the performance of the test. In conclusion, 2% xanthan gum with Opadry immediate release coat is the best concentration used to enhance swallowing of this tablet.⁽¹⁰⁾

Table 8. Results of slipperiness test on Rabbit

Formula code	Percent of slipping agent	Slipping time (sec)
CF	0%	80±5
CF1	2%	30±1
CF2	3%	37±2
CF3	4%	40±2



Figure 4. Performing slipperiness test in albino Rabbit

Dissolution of IRB and HCT

Figures 5 and 6 show the dissolution rate profile of the uncoated formula and CF1 which gave the best result in slipperiness test in animal. Both APIs were released from the uncoated ablets (>75 % in 45 min). When they were coated, the dissolution profile was highly like that of the uncoated (also >75 % in 45 min). Taking the 30 min as a comparative point, non-significant

difference ($p > 0.05$) was observed between the release of both APIs from the coated formula CF1 with respect to the coated formula (Table 9). This indicates that the coat didn't have a negative effect on the drug release. It neither enhanced nor delayed drug release. The only effect was an elongation in the disintegration time which resulted in these slight differences in amount of drug released with time. Mahdi and Maraie, 2015 showed also that 0.3% xanthan gum does not affect the release of valsartan from OST using different ratios of coating materials⁽⁹⁾.

Studying the release kinetics of IRB and HCT from the tested formulas (uncoated and CF1) gave the highest correlation (R) of "first order release model" for IRB (uncoated): 0.987, HCT (uncoated): 0.975 and for CF1, IRB 0.979 and HCT 0.982. This indicates that the coat also did not interfere with release kinetics of both APIs and the idea of "Immediate Release tablet dosage forms

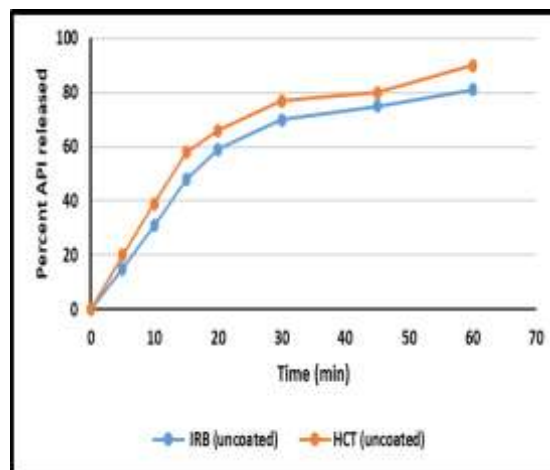


Figure 5. Dissolution profile of IRB and HCT of uncoated tablets at 0.1 N HCl, 37°C and 75 rpm showing T₃.

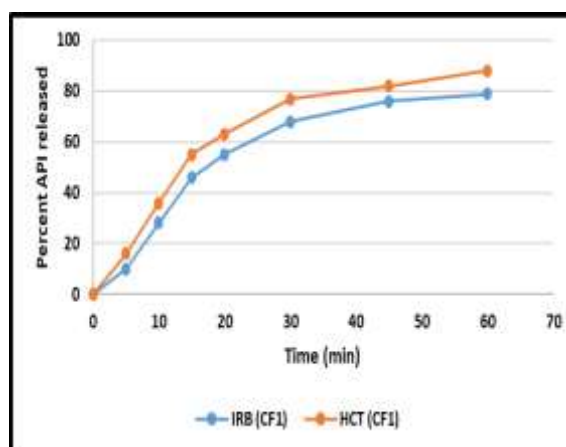


Figure 6. Dissolution profile of IRB and HCT of formula CF1 at 0.1 N HCl, 37°C and 75 rpm showing T₃₀.

Table 9. T₃₀ of release of IRB and HCT from the uncoated formula and CF1

T ₃₀ (Percent API released in 30 min)	Percent API released in 30 min T _(30%)	t-test result
IRB from Uncoated tablet	70 ± 2.0 %	
IRB from CF1	68 ± 3.0 %	P > 0.05, non-significant compared to the uncoated
HCT from Uncoated tablet	77 ± 2.0%	
HCT CF1	77 ± 2.5.0%	P > 0.05, non-significant compared to the uncoated

Conclusion

A successful, simple, valid method of analysis for simultaneous determination of IRB and HCT was developed using HPLC with UV detector. All coated formulas with the slipping agent gave significantly shorter time of swallowing than CF ($p < 0.05$). CF1 gave the shortest slipping time among the three concentrations used (30 ± 1 sec) and it was significantly shorter than CF2 (37 ± 2 sec) and CF3 (40 ± 2 sec) ($p < 0.05$). Increasing

the concentration of xanthan gum from 2% to 3 and 4 %, did not enhance the slipperiness of the tablets, on the contrast it resulted in the elongation of time. In conclusion, 2% xanthan gum with Opadry immediate release coat is the best concentration used to enhance swallowing of this tablet.

Acknowledgment

The authors would like to thank Al-Ahliyya Amman University, Amman-Jordan for supporting this work. Thanks are extended to Dar Al Dawa pharmaceuticals in Jordan for their help and support.

Authors Contributions

All the authors have contributed equally

Conflict of Interests

Declared none

References

- Khan A, Carmona R, Traube M. Dysphagia in the Elderly. *Clin Geriatr Med* 2014; 30: 43–53.
- Abdel Jalil A A, Katzka D A, & Castell DO. Approach to the patient with dysphagia. *Am J Med* 2015;128(10): 17-23.
- Chang MC, Lee C, Park, D. Validation and Inter-rater Reliability of the Modified Videofluoroscopic Dysphagia Scale in Dysphagic Patients with Multiple Etiologies. *J Clin Med*. 2021; 10(13): 2077-0383.
- Vieira JM, Andrade CC, Santos TT, Okuro PK, Garcia ST, Rodrigues MI, Vicente AA, Cunha RL. Flaxseed gum-biopolymers interactions driving rheological behaviour of oropharyngeal dysphagia-oriented products. *Food Hydrocoll* 2021; 111 : 106257.
- Taylor S, Glass BD. Altering dosage forms for older adults. *Australian prescriber* 2018; 41(6): 191–193.
- Perrie Y, Badhan RK, Kirby DJ, Lowry D, Mohammed AR, Ouyang D. The impact of ageing on the barriers to drug delivery. *J Control Release*. 2012;161(2):389-398.
- Mc Gillicuddy A, Crean AM, Sahn LJ. Older adults with difficulty swallowing oral medicines: a systematic review of the literature. *Eur J Clin Pharmacol* 2016;72(2):141-151.
- Mc Gillicuddy A, Crean AM, Sahn LJ. Older adults with difficulty swallowing oral medicines: a systematic review of the literature. *Eur J Clin Pharmacol*. 2016;72(2):141-151.
- Mahdi Z H, Maraie N K. New Easily Swallowed Tablets with Slippery Coating for the Antihypertensive Drug Valsartan. *UK J Pharm Biosci* 2015; 3(5): 9.
- Almajidi YQ, Maraie NK. An overview on oroslippery technique as a promising alternative for tablets used in Dysphagia. *Res J Pharm Technol* 2019;12(9): 4545–4549.
- Haldar R N Global Brief on Hypertension: Silent Killer, Global Public Health Crisis. *Indian J phys med Rehab* 2013;24(1): 2–2.
- Williams B, Mancia G, Spiering W, Agabiti RE, Azizi MB, Clement DL, Coca A, de Simone G, Dominiczak A., et al. ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the Management Of Arterial Hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypert* 2018; 36:1953–2041.
- Burnier M, Forni V, Wuerzner G, et al. Long-term use and tolerability of irbesartan for control of hypertension. *Integr Blood Press Control* 2011; 4: 17–26.
- National Center for Biotechnology Information (2021). PubChem Compound Summary for CID 3749, Irbesartan. Retrieved November 4, 2021 from <https://pubchem.ncbi.nlm.nih.gov/compound/Irbesartan>
- Derosa G, Ferrari I, Cicero AFG. Irbesartan and hydrochlorothiazide association in the treatment of hypertension. *Curr Vasc Pharmacol* 2009; 7: 120–136.
- <https://database.ich.org/sites/default/files/Q2%28R1%29%20Guideline.pdf>.
- Rumman T, Alani I, Hassan S. Coating potential of a new modified starch coating for immediate release oral tablets. *Am Coat Assoc* 2015; 12: 167–175.
- EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), Mortensen A, Aguilar F, et al. Re-evaluation of xanthan gum (E 415) as a food additive. *EFSA J*. 2017;15(7):e04909. Published 2017 Jul 14.
- Sulaiman, T., and S. Sulaiman. “Review: excipients for tablet manufacturing with direct compression method”. *Journal of Pharmaceutical And Sciences*, Vol. 3, no. 2, Nov. 2020; pp. 64-76.
- Lieberman HA, Lachman L, Schwartz JB. *Pharmaceutical Dosage Forms: Tablets*. 2nd ed., Vol. 1. USA: Marcel Dekker; 1989.
- USP37-NF32 (2014) United States Pharmacopeia 37: National Formulary 32.
- Kumar, Davinder & Singh, Jasbir & Antil, Mamta & Kumar, Virender.. Quality control of tablets: A review. *International Journal of Universal Pharmacy and Bio Sciences*. July-August 2016,5(4).
- USP: https://www.usp.org/sites/default/files/usp/document/harmonization/gen-chapter/g06_pf_ira_32_2_2006.pdf
- USP: <https://www.usp.org/sites/default/files/usp/document/harmonization/gen-chapter/april-2019-m99460.pdf>
- Irbesartan on : <https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=2a7cc4e3-bf9e-6d21-e054-00144ff8d46c&type=display>.
- Dubey, Atul et al. “Improvement of tablet coating uniformity using a quality by design

- approach.” AAPS PharmSciTech 2012; 13(1): 231-46.
27. Dubey, Atul et al. “Improvement of tablet coating uniformity using a quality by design approach.” AAPS PharmSciTech 2012; 13(1) : 231-46.
28. Suryadevara V, Lankapalli SR, Sunkara S, Sakhamuri V, Danda H. Dissolution rate enhancement of irbesartan and development of fast-dissolving tablets. Egypt Pharmaceut J 2016;15:150-7.
29. Anupama B, Kurumaddali A, Bhargav SN, et al. UV spectrophotometric method for irbesartan. Int J Res Pharm Chem 2012; 2: 20–21.
30. Sayyed ZM, Shinde SA, Chaware VJ, et al. Development and Validation of UV-Spectrophotometric Method for Simultaneous Estimation of Amlodipine Besylate and Hydrochlorothiazide in Combined Dosage Form Including Stability Study. J Pharm Sci Biosci Res 2015; 5: 487–493.
31. Lopes B, Lopes L, Silva B, & Carvalho M, Schnitzler E, Lacerda, L. Xanthan gum: Properties, production conditions, quality and economic perspective J Food Nutr Res 2015; 54:185-194.



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