Formulation and Evaluation of Optimized Zaltoprofen Lyophilized Tablets by Zydis Technique

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Abstract

"Orodispersible Tablet" a tablet that is to be placed in oral cavity where it disperses rapidly by saliva with no need for water before swallowing. Zaltoprofen (ZLP) is one of NSAIDs which is used in the treatment of rheumatoid arthritis and osteoarthritis as well as to relieve inflammation and pain after surgery, injury and tooth extraction**.** The present study was aimed to prepare rapidly dissolved lyophilized Zaltoprofen tablet with different pharmaceutical excipients and studying the factors affecting pharmaceutical properties like (solubility, disintegration time DT, dissolution, etc.) of tablets. The lyophilized disintegrating tablets (LDTs) were prepared using Zydis technique by lyophilization an aqueous dispersion of Zaltoprofen with a matrix forming agent, gelatin, and a collapse protectant, glycine. In addition to many excipients like PVPK30 was used to improve the in vitro, in vivo disintegration time and dissolution rate, mannitol as bulk forming agent. Fourteen formulations were prepared to inspect the variables that affect the disintegration time and dissolution rate. All the formulations were evaluated for their physical appearance, mechanical strength, X-ray diffraction, FTIR, DT, and in vitro drug release. The prepared tablets were optimized and formula was subjected to different measured parameters such as disintegration time, Drug content, and in-vitro drug release. Results obtained from dissolution studies and DT showed that lyophilized disintegrating tablets (LDTs) (F8,F10,F12,F13 was 45,37,21 and 17 Sec.) respectively ,while(F14) displayed considerably faster in vitro dissolution rate of (Zaltoprofen) 3 min. and DT 9 sec. The (lyophilized disintegrating tablets) were also evaluated showing the transformation into amorphous state and absence of interaction of Zaltoprofen with the components of the tablets. From visual inspection ,physical strength ,DT and release behavior obtained ,one can conclude that the formulas(F14) which contains Zaltoprofen 3.2% ,gelatin3%, mannitol 3%, glycine 1.5%, PVP K30 1.5% was the most suitable one.

Keywords : Zaltoprofen, lyophilization, PVPK30 .

تصييغ وتقيم حبوب الزالتوبرفين المحسنة والمجففة بالتجميد باستخدام تقنية ال"zydis "

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الخلاصة

يمكن تعريف الحبوب الذائبة فمويا بانها الحبوب التي ما ان توضع بتجويف الفم فانها تتفكك وتنتشر بسرعة بوجود اللعاب دون الحاجة للماء قبل ان تبلع.ويعتبر الزالتوبروفين من ادوية مجموعة مضادات الالتهاب اللا ستيرويدية المستخدمة لعلاج الروماتيزم وكدلك علاج الام ما بعد العمليات الجراحية والاصابات وقلع الاسنان. الدراسة الحالية تهدف لتحضير حبوب الزالتوبروفين سريعة الدوبان بطريقة التجفيد باستخدام(سواغ صيدلانية)مختلفة ودراسة العوامل المؤثرة مثل الدوبانية,معدل التفكك وتحرر الدواء على الخواص الصيدلانية للحبوب.قد تم تحضير الحبوب بطريقة التجفيف بالتجميد حيث تتم عملية التجفيد للمحلول المائي للزالتوبرفين مع الجيلاتين ومضاد الانهيار الكلايسين بالاضافة الى البولي فنيل بايرولدين ك ٣٠ كمادة محسنه لتفكك الحبة وكدلك معدل عملية الدوبان والمانيتول كمادة مكونة للشكل. اربعة عشر صيغة تم تحضيرها مع المعاينه والتقييم للعوامل المؤثرةعلى تفكك الحبة و معدل الدوبانية. وقد تم تقييم كل الصيغ في ما يخص شكلها الفيزياوي وقوتها الميكانيكيه وتفكك الحبة وتحرير الدواء. النتائج بعد تحضير الحبوب بتقنية (Zydis) وتحسين الصيغ تم اخضاعها لعدة تقييمات مثل وقت التفكك ونسبة احتواء الحبة من الدواء ومعدل تحرير الدواء وكانت النتائج تتضمن ان الحبوب المجففة بالتجميد للزالتوبروفين للصيغة رقم (١٤) اظهرت لنا معدل سريع لتحرير الدواء خلال الدقائق الثلاث الاولى وصلت الى ١٠٠% ووقت التفكك للحبة بلغ (٩) ثواني .تم تقييم وفحص الحبة سريعة الدوبان المجففة بالتجميد باستخدام تقنية الاشعة السينية و(FTIR) واظهرت تحول الدواء الى الصيغة اللابلورية اللامنتظمة مع غياب فرصة التداخل بين مكونات الحبة والزالتوبروفين.نستنتج من الدراسة ان الصيغة التي تحتوي على الزالتوبروفين ٣.٢%, الجيلاتين ٣% ,مانتول ٣%, كلايسين ١.٥ % وبولي فنيل بايرولدون ك ٣٠ ١.٥% كانت الصيغة الافضل .

الكلمات المفتاحية: زالتوبرفين ,تجفيف بالتجميد ,بولي فنيل بايرولدين ك٣٠.

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Introduction

A fast disintegrating or dissolving system or tablet can be defined as a solid dosage form that can disintegrate or dissolve within 30 seconds, in the oral cavity resulting in a solution or suspension without administration of water[1] .The technologies used for manufacturing fast dissolving tablets are freeze-drying, spray-drying, tablet molding, sublimation, tablet compression, and disintegration addition[2]. Lyophilization (freeze-drying) is a process in which water is sublimated from the product after freezing at a specific temperature and pressure. Lyophilization technique is used in order to improve the dissolution of the given substance and improve the oral bioavailability of the drugs with poor solubility and high permeability [3]. Zaltoprofen is BCS Class-II having low solubility and high permeability [4]. Zaltoprofen, chemically it is 2-(10,11-dihydro-10-oxodibenzo(b, f)thiepin-2-yl) propionic acid, is a derivative of 2-arylpropionic acids(2-APA), is one of non-steroidal anti-inflammatory drugs (NSAIDs) and has potent inhibitory effects on acute and chronic inflammation, according to their chemical structure or their selective inhibition of cyclooxygenase COX-1 and COX-2, Zaltoprofen is COX-2 inhibitor and selectively inhibits prostaglandin E2 (PGE2) production at the sites of inflammation with less adverse reactions on the gastrointestinal tract than other NSAIDs[5].

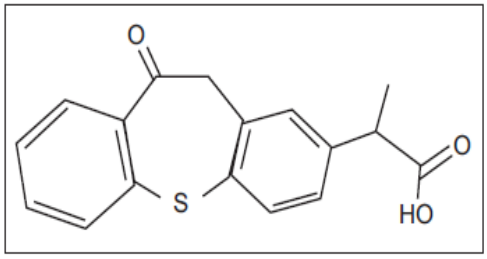

Figure (1): Chemical structure of Zaltoprofen [5]

Materials and Methods:

Materials

Zaltoprofen was purchased from Hyperchemical China, gelatin, was kindly gifted from Baghdad College of Pharmacy, mannitol, sorbitol ,glycine ,PVP K30 were purchased from M/s Provizer Pharma company India . The water used was distilled de-ionized water. All other chemicals were reagent grade.

Determination of melting point

The melting point of Zaltoprofen powder was measured according to USP method using capillary tube method using Electrical melting point apparatus. The tube was dipped in the drug powder closed from one end and placed inside the melting point apparatus, the temperature was increased gradually. The temperature at which the powder liquefied was recorded as the melting point [6].

Determination of absorption maxima (λ max)

A solution of (10 µg/ml) of Zaltoprofen in 0.1 N HCl (pH 1.2), phosphate buffer (pH 6.8), and distilled water were scanned by a UV spectrophotometer from 400-200nm, and λ max of Zaltoprofen was indicated for each solution.

Preparation of standard curves of zaltoprofen:

Calibration curves of Zaltoprofen were constructed in distilled water, 0.1N HC1 (pH 1.2), and phosphate buffer (pH 6.8), separately using UV Spectrophotometer (UV-6100 PC). Serial dilutions were prepared with different concentrations (4,8,10,12, and 14 µg/ml) from stock solution containing (20µg/ml) Zaltoprofen in 0.1N HCl (pH 1.2), phosphate buffer (pH 6.8) and(2,4,5,8,10,12,14 µg/ml) from stock solution containing (20µg/ml) Zaltoprofen in distilled water, samples were then analyzed spectrophotometerically for Zaltoprofen at its λ max. The determined absorbance was recorded and plotted versus concentration to get a calibration curve.

Estimation of zaltoprofen saturation solubility

Solubility studies of Zaltoprofen were carried out in distilled water; simulated gastric fluids (SGF) pH 1.2 and simulated intestinal fluids (SIF) pH 6.8 were used to study solubility behavior of Zaltoprofen. Using shake -flask method .Saturated solutions were prepared by adding excess of Zaltoprofen to the all mentioned liquids in 10 ml tube which were placed in a shaker water bath at 40 rpm for 48 hours at 25 °C. Then the samples were filtered through a 0.45 µm millipore filter. The solutions were diluted suitably, analyzed by UV-spectrophotometer at λ max of the drug. Three determinations were carried out for each sample to calculate the solubility of Zaltoprofen [7].

Formulation of zaltoprofen FDTs by lyophilization techniques

In this study, Zaltoprofen, FDTs containing gelatin as matrix forming agent, glycine as collapse protectant, sorbitol and mannitol as bulk forming agent and PVPK30 as matrix supporting agent, were prepared by lyophilization technique according to formulae given in Table 1.The percentage of excipients used was optimized during the formulation

process to obtain a withstand and elegant tablet that could be handled with ease.

To prepare different batches, all ingredients according to the formula were accurately weighed. Gelatin was first dissolved in distilled water at about 40°C stirred on a magnetic stirrer (Stuart, U.K.) until a clear phase was obtained, then glycine, PVPk30, mannitol were added separately with continuous stirring until homogenous mixture was obtained then the required Zaltoprofen amount was added Exactly (0.5 ml) of the resultant solution was poured into each of the pockets of tablet blister pack .The tablets blister pack each contained 10 tablets , then they were then transferred to a freezer at about -22 °C and kept in the freezer over night until complete freezing was established .The frozen tablets were placed in a lyophilizer for 24hr utilizing a vacuum freeze dryer (TECHSUPPORT, Korea) with a condenser temperature of - 45°C and pressure (8.6) Pascal. The lyophilized tablets were kept away from moisture at room temperature until further investigation was performed [8].

Table (1) :Composition of different zaltoprofen lyophilized tablets formulas tablets

Formula / Material	ZLP (g)	Gelatin %w/v	Sorbitol %w/v	Mannitol %w/v	Glycine %w/v	PVPK30 %w/v
F1	3.2	2				
F2	3.2	3				
F3	3.2	4				
F4	3.2	3	2			
F5	3.2	3	3			
F6	3.2	3		1		
F7	3.2	3		2		
F8	3.2	3		3		
F9	3.2	3		3	1	
F10	3.2	3		3	1.5	
F11	3.2	3		3	2	
F12	3.2	3		3	1.5	0.5
F13	3.2	3		3	1.5	1
F14	3.2	3		3	1.5	1.5
Total To make 20ml						

Preliminary screening for optimizing lyophilized tablets:

The effect of concentration of matrix forming agent

Formulas 1-3 were used to study the effect of concentration of the matrix forming agent (gelatin 1%,2%,3%) on the mechanical properties and other parameters on the prepared tablets Table 1.

The effect of bulking agent type and concentration

Formulas 4-8 were used to study the effect of the bulking agent type and concentration (sorbitol 2%, 3% and mannitol 1%, 2%, 3%,) on the mechanical properties and other parameters on the prepared tablets Table 1.

The effect of collapse protectant concentration (glycine)

Formulas 9-11 were used to study the effect of collapse protectant concentration (glycine 1%, 1.5%, 2%) on the mechanical properties and other parameters on the prepared lyophilized tablets Table 1.

The effect of matrix supporting agent

Formulas 12-14 were used to study the effect of matrix supporting agent on the mechanical properties and other parameters on the prepared lyophilized tablets Table1.

Compatibility study of drug with excipients

Fourier Transform Infrared (FTIR) spectroscopy

FTIR spectroscopy analysis was done in the range of 4000-500cm^{-1} (Fourier Transform Infrared System FTIR- 8400 S Shimadzu, Japan) by mixing the optimum formula (F14) and drug alone, separately with small amount of dry KBr powder , compressed into transparent disc and spectra was recorded .These spectra were determined to ensure there was no interaction between the drug and the excipients which may occur throughout the process [9].

Powder X-ray diffraction (XRD) analysis

X-ray diffraction experiments were performed in an X-ray diffractometer using X-ray powder diffraction analyzer (6000 XRD, Shimadzu, Japan), operated with Cu K α x

radiation at 40 k V and 30 mA. The scans were conducted 5◦ to 35◦. Diffraction patterns for Zaltoprofen powder and for the optimized orally lyophilized tablet were obtained and identification of the samples was carried out [10].

Evaluation of lyophilized tablets

Weight variation

Twenty Zaltoprofen tablets were randomly taken from each batch and the weight of their average weight was determined. Then individual tablet was taken and its weight was calculated. That individual weight was compared with average weight. The weights were measured using weighing balance (Sartorius Balance Werke GMBH, Germany) [11].

Content uniformity

Three Zaltoprofen lyophilized tablets were powdered weighed and transferred into a 100 ml volumetric flask. Initially, 10 ml of methanol was added and shaken for 10 minutes. Then, the volume was made up to 100 ml with buffer 6.8. Subsequently, the solution in the volumetric flask was filtered, 1 ml of the filtrate was suitably diluted and analyzed for drug content at 243 nm using UV-spectrophotometer (UV-6100 PC) [12].

In Vivo disintegration test

The time needed for each prepared tablet to be totally disintegrated in the oral cavity was estimated from six healthy people .All subjects had been notified about the purpose behind the test. The subjects washed their mouth with purified water with distilled water. Tablets were put on the tongue and instantly the tongue softly moved and the interval for complete disintegration with -out residue was recorded [13].

In-vitro disintegration test

Disintegration time was measured in 900 ml artificial saliva (pH 6.8) according to the USP 24 method without disc at 37 ± 0.5°C temperature. The disintegration time of 6 individual tablets were recorded and the average disintegration time was reported [14].

In Vitro dissolution test

This test is intended to determine compliance with the dissolution request for solid dosage forms taken orally. In vitro dissolution studies of FD tablets were studied using USP XXIII tablet dissolution test apparatus employing a paddle stirrer. 900 ml of pH 6.8 phosphate buffer with 2% Brij35 was used as a dissolution medium. The temperature of the dissolution medium is maintained to 37 ± 0.5 ° C .One tablet from each batch was used in each test. 5 ml of the sample of dissolution medium was withdrawn by means of pipette at known intervals of time and the sample was filtered using the whattman filter paper. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. Each sample was analyzed for drug release, spectrophotometerically using UV-visible spectrophotometer (UV-6100 PC) after suitable dilutions [15].

Results and Discussion

Determination of melting point

The measured melting point for Zaltoprofen was found to be 139 °C. This result was the same to the data reported ,which reflects the purity of the powder used in the study [16].

Determination of λ max of zaltoprofen:

The UV scan (10 µg/ml) of Zaltoprofen in three different media 0.1N HCl solution, phosphate buffer (pH 6.8) solutions, and distilled water as shown in the Figures (1), (2), and (3), respectively in each media the drug showed maximum absorbance peaks at (243 nm) in the all above media as reported by the reference [17].

Figure (1) UV scan of Zaltoprofen in 0.1N HCl solution

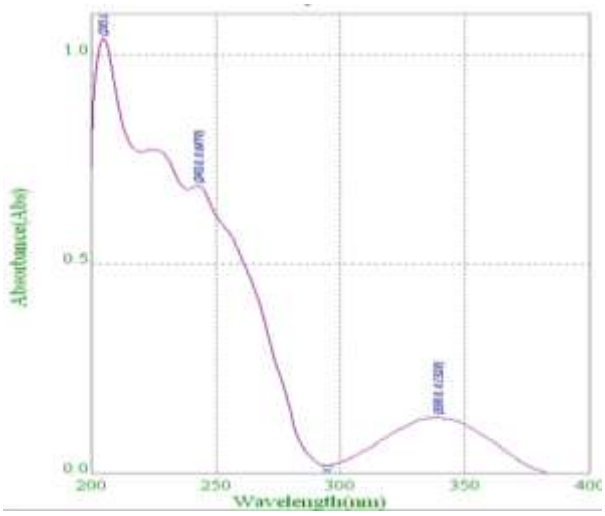

Figure (2): UV scan of Zaltoprofen in phosphate buffer (pH 6.8) solution

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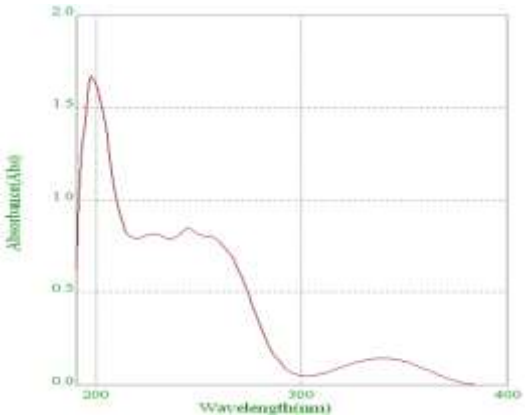

Figure (3): UV scan of Zaltoprofen in distilled water

Determination of calibration curves of zaltoprofen:

Figures (4), (5), and (6) show the calibration curves of Zaltoprofen in 0.1N HCl, phosphate buffer (pH 6.8) and distilled water respectively. A straight line was obtained as a result of plotting the absorbance versus concentration. For each media which indicates that it follows Beer- Lambert's law within the concentrations used [18].

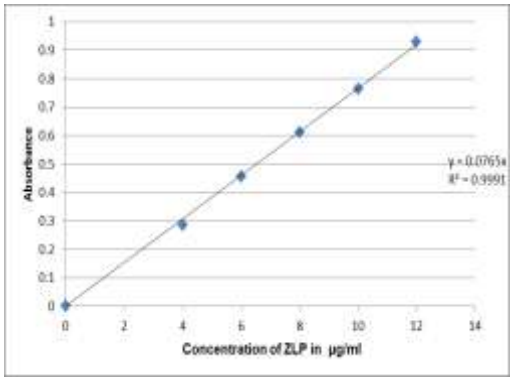

Figure (4): Calibration curve of zaltoprofen in 0.1N HCl

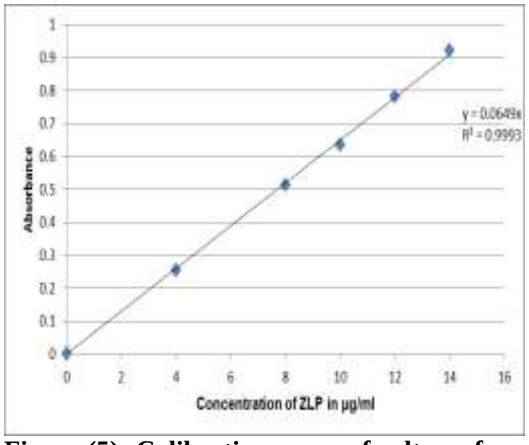

Figure (5) :Calibration curve of zaltoprofen in buffer 6.8

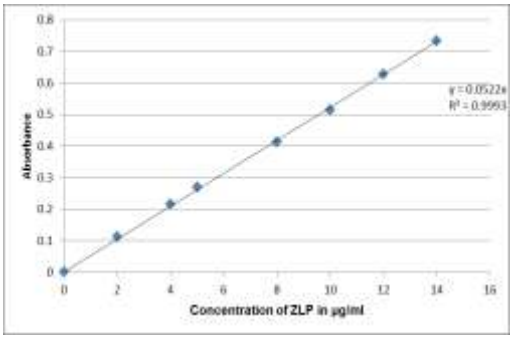

Figure (6) :Calibration curve of Zaltoprofen in deionized water

Solubility Studies

The solubility profile of Zaltoprofen was determined in various solvents as shown in Table (2). The results show that Zaltoprofen showed significantly ($p<0.05$) higher solubility in phosphate buffer pH 6.8 than in 0.1 HCL and in DW .In addition to that it's known that Zaltoprofen is acidic compound with pKa of 5 [19]. Therefore; the solubility of acidic compound increases as the pH is above pKa value, this increase in pH may alter the ratio of ionized to non-ionized species which can be predicted by application of Henderson-Hassel Balch equation [20].

Table (2): Solubility of zaltoprofen in various solvents

Solvents	**Solubility (%w/w) Mean ± S.D.***
Distilled water	0.01346 ± 0.0015
HCl 0.1 N	0.01216 ± 0.0015
Buffer 6.8	3.1155 ± 0.264

*S.D. standard deviation from mean. n=3

The effect of concentration of matrix forming agent (Gelatin)

Suitable selection of polymer is the corner stone to get a freeze dried tablets with acceptable mechanical properties and rapid release rates [21].It was found that the prepared lyophilized tablets based on gelatin as binding agent showed better physical inspections compared with the tablets made from PVP K30 alone which were found to be unacceptable during the manual handling process. So, gelatin had been further optimized as matrix forming agent using 3% w/v with PVP K30 1.5%.

In parallel to most of the other dosage forms, even in case of fast disintegrating tablets, the overall description of the mechanism of disintegration include

weakening of the intermolecular bonds upon penetration of the disintegration medium in the tablet's excipients resulting in complete disintegration of the tablet [22].With increase in gelatin concentration (F3- 4%) ,the so formed network is anticipated to become more stable and extensive owing to increase in the fiber cross links and inter chain H-bonds [23], so consolidated a pernicious effect on the disintegration time of the tablets due to increase in intermolecular attraction between the binder molecules resulting in retardation in disintegration time profile .From other side, beyond a certain concentration, the gelatin matrix becomes so extensive and synonymously less porous that the interaction with disintegration medium resulted in formation of thick cohesive gels that were difficult to disintegrate . This oversight could be more expressed by documented phenomenon of formation of rough three dimensional (3D) gel network of gelatin at high concentration [24].

The decrement in mechanical properties of FDTs prepared with 2% gelatin (F1) could be assigned to the fewer number of crosslinks formed between the gelatin strands as the concentration decreases non porous tablet will form.

The use of 3% w/w gelatin as a binder showed enhanced mechanical properties of the prepared tablets .Thus, incorporation of matrix supporting agent PVP K30 was as a reasonable solution to improve DT as shown in Table 3.

The effect of type and concentration of bulking agent

Sorbitol used in (F4,F5) showed unsuitable visual inspection (shape) with hard surface texture of prepared tablets this may explain the combination of gelatin–mannitol was found to be better over gelatin–sorbitol (isomer of mannitol) in terms of tablet shape, appearance, surface texture and disintegration time and it could be attributed to superior hydrophilicity of mannitol over others(sorbitol) [25].

The formulas (F6,F7,F8) were prepared with different mannitol concentrations (1% , 2% , 3%) , according to the study of their physical properties ,the results showed that (F8) have a good physical handling and appearance while (F6 ,F7) failed to pull off from blister packs because of fragility ,then after optimization applied on the (F8) to improve the DT and manual handling to progress forward until reaching a suitable formula .

Excipients used in lyophilization are materials used to ease freeze drying of various biological components, which are usually inert ingredients like sugars , they are also used to preserve the solid matrix against collapse .Freezing system also influences the extent of crystallization and polymorphism of important formulation adjuvant drug, such as mannitol [26]. Crystallization is favored in a formulation when mannitol functions as a bulking agent. Mannitol can gain some advantages like lyophilization at high temperatures and thus shorten freeze drying cycles, and elegant product without defects caused by material collapse. Mannitol used as a stabilizer leads to a system that behaves like a physical mixture, allowing interactions only at the phase boundary. Bulking agents are used to give product elegance (i.e., acceptable appearance) as well as adequate cake, mechanical strength to avoid product blow-out. Bulking agents simply function as fillers to increase the density of the product cake [27,28] .

The effect of collapse protectant concentration (glycine) on the mechanical properties

Glycine has a polar surface and therefore has a high affinity to water which generate aqueous channels that make the diffusion of the dissolution media into the tablet more quickly ,which enhance the in vivo disintegration of the prepared tablets and subsequently promote the dissolution rate .These results are documented for some amino acids which act as disintegration accelerators .The addition of glycine especially at concentration 1.5% (F10) improved the wetting time in comparison with formula(F9,F11),this due to its polar surface free energy which composed of about 75 % of its component. The polar character of glycine has a power affinity to water and generate aqueous channels that enhancing the tablets wettability [29]. Also glycine represents highly water soluble amino acid (25 g /100 ml), the solubility of amino acid in water affects the wetting of tablet, which increased the ability of water penetration into capillary of tablet matrix. A significant increase in DT as the concentration of glycine increased (direct relationship) (F11). So the increment in glycine concentration will deteriorate the DT (145 second) in comparison with formula of lower glycine concentration (F9,F10) 68, 37 seconds respectively, this due to low water holding capacity (lower and slower swelling nature of the powder)[30].

Table(3):Physical Appearance ,*in vitro* , *in vivo* D.T. and content uniformity For Lyophilized prepared tablets

Formula	Pull off	Uniformity	Physical Handling	In-vitro D.T.	In vivo D.T.	Content Uniformity (%)
F1	-ve	-ve	Brittle			-
F2	-ve	+ve	Good			96.7±0.85
F3	-ve	-ve	Hard			-
F4	-ve	-ve	Brittle			-
F5	-ve	-ve	Brittle			-
F6	-ve	+ve	Brittle			-
F7	-ve	+ve	Brittle			-
F8	+ve	+ve	good	45	57	99.5±0.78
F9	+ve	+ve	Accepted	68	79	97.7±0.84
F10	+ve	+ve	good	37	42	96.4±0.59
F11	+ve	+ve	Hard	145		-
F12	+ve	+ve	Good	21	26	99.8±1
F13	+ve	+ve	Good	17	23	100.5±0.89
F14	+ve	+ve	Good	9	12	100.1±0.97

Note:Pull off means remove the tablet from blister.
+ve means easy to pull off the tablet from blister pack, uniform tablet shape.
-ve means tablet stick to blister pack(difficult to pull off) , not uniform tablet shape.

Fourier transformed infrared spectroscopy (FTIR)

The most widely reported spectroscopic techniques for solid state characterization is FTIR. The spectra of pure Zaltoprofen powder shown in figure (7) and that of the selected lyophilized tablet (F14) spectra figure(8) display no significant shifting in the position of the characteristics peaks of the main functional groups ,so these results indicated the absence of the probabilities for interaction between the Zaltoprofen and the polymers used in the preparation of lyophilized tablets [31].

Figure (7) : FTIR spectrum of pure Zaltoprofen

Figure (8) : FTIR spectrum of lyophilized tablet (F14)

Powder X-ray diffraction analysis (PXRD) of pure Zaltoprofen and selected formula (F14)

The x-ray diffraction pattern of pure Zaltoprofen powder shows characteristics zaltoprofen diffraction peaks at 2θ diffraction angles of 4°, 13.5°, and 20.2° referring to presence of crystalline structure as in figure (9). The diffraction study of optimized zaltoprofen oral lyophilized formula (F14) showed absence of main drug diffraction peaks at (4°, 13.5°, and 20.2°) with decrement in the intensities of sharp peaks referring to present amorphous form as in figure (10) .

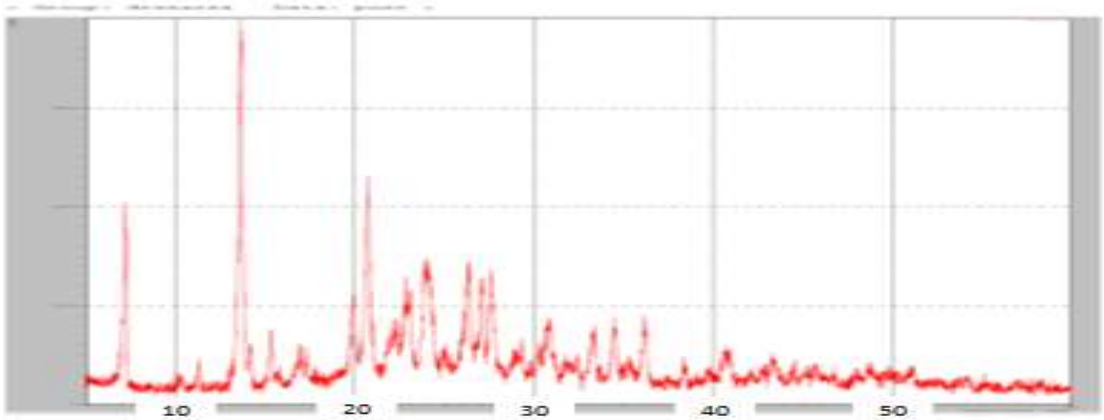

Figure (9) :X-ray diffraction pattern of Pure Zaltoprofen powder

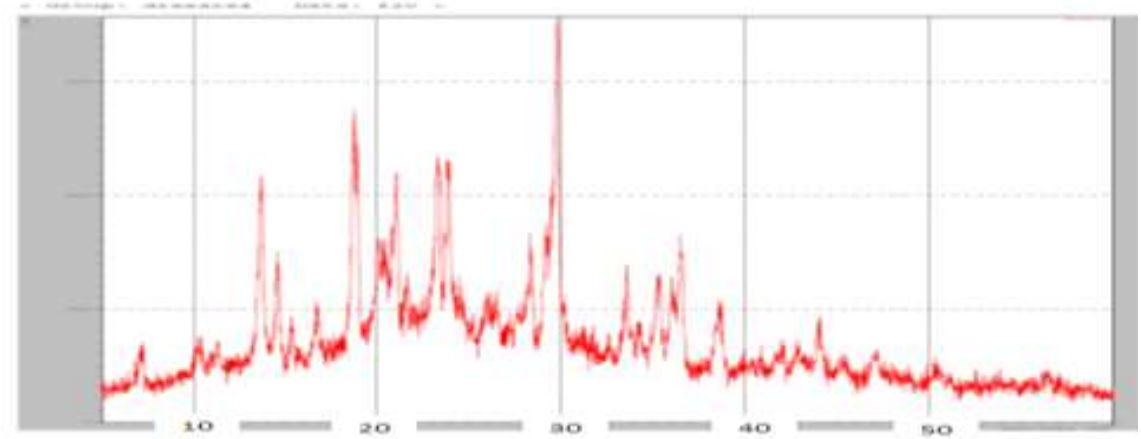

Figure (10): X-ray diffraction pattern of Selected formula (F14)

In-vitro dissolution study

The *in-vitro* drug release characteristics of Zaltoprofen lyophilized tablets (F14) were performed in phosphate buffer 6.8 (2% Brij 35) as a medium for dissolution .The cumulative ratio of Zaltoprofen release in 2 minute (D2) was 81.6% and t80% was 1.96 minute as shown in figure (11).

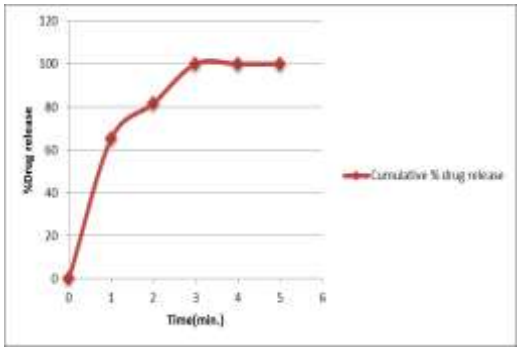

Figure (11) : *in vitro* drug release profile of(F14) in phosphate buffer pH 6.8 with 2% (Brij 35) at 37 ± 0.5°C (Results are expressed as mean , n=3)

Conclusion

Based on results obtained from the study one can conclude that, Zaltoprofen was successfully formulated as lyophilized flash tablet using Zydis technique by incorporation of gelatin 3% as a matrix forming agent which give a suitable manual handling, mannitol 3% was the best bulk forming agent compared with the others (sorbitol) ,so Gelatin–mannitol combination offered proper manual handling and retained the intactness of ODTs . In addition to the polar character of glycine has a high affinity to water and generate aqueous channels that enhance the tablets wettability .From all above, F14 was the best formula to prepare Zaltoprofen lyophilized tablet.

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