Formulation and Optimization of Oral Fast Dissolving Prochloperazine Maleate Tablets

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Abstract

Prochloperazine maleate (PCM) is one of the most prescribed phenothiazine. The purpose of the present research was to develop fast dissolving tablets of PCM with β-cyclodextrin inclusion complex. Tablets prepared by wet granulation with sublimation and by using different superdisintegrants type [low-hydroxypropylcellulose LH21 (L-HPC LH21), carboxymethylcellulose calcium (ECG505), crospovidone (CP)], and different type of subliming agents (urea and ammonium bicarbonate (AB)). Tablets evaluated for its % friability, disintegration time, wetting time, hardness, content uniformity, weight variation, in vitro dissolution studies. For further enhancement of disintegration and dissolution, PCM orodispersible tablet were formulated as (PF2,PF3 and PF4) using inclusion complex of drug in β-cyclodextrin at different ratios (1:1, 1:2 and 1:3) respectively. These formulation showed disintegration times between (22s and 14.6s), and drug release showed $t_{80\%}$ between (2.9% and 0.9%). Among all the formulations PF4 was considered as the best, containing PCM: β-cyclodextrin 1:3, 10% crospovidone and 25% ammonium bicarbonate which shows the shortest DT, good dissolution study and stability. The overall results suggest that the orodispersible tablet of PCM enhance the absorbable part than that of corresponding conventional tablet by using superdisintegrants and β-cyclodextrin inclusion complex of drug.

Key words: Prochloperazine maleate, Orodispersible tablet, Crospovidone, Ammonium Bicarbonate, Sublimation.

تصييغ وتعيين لحبوب فموية للبروكلوبيرازين ماليت سريعة التحلل

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الخلاصة

يعد عقار البروكلوبيرازين ماليت واحد من أكثر العقاقير استعمالا للفينوثيازين، الهدف من البحث تصييغ معقد الضمين للبروكلوبيرازين ماليت مع البيتا سايكلودكسترين كنظام دوائي سريع التحلل بالفم. الحبوب حضرت بطريقة الترطيب المرطب بواسطة التسامي عن طريق استخدام عدة مواد مفككة و هي (هيدروكسي بروبايل سليلوز، كاربوكسي مثيل سليلوز كالسيوم و كروسبوفيدون) ،وأنواع مختلفة من المواد المتسامية (يوريا و امونيوم بيكاربونيت).الحبوب قيمت عن طريق عن طريق فحص الهشاشة، وقت التفكك، وقت الترطيب، المتانة، محتوى الدواء، فرق الوزن ودراسة تحرر الدواء. لغرض زيادة الذوبانية و سرعة تحلل، البروكلوبيرازين ماليت حضرت ك (PF2,PF3,PF4) بطريقة معقد الضمين للدواء مع البيتا سايكلودكسترن بنسب مختلفة (١:١، ١:٢، ١:٣) بالتتابع . التركيبات اعطت وقت تفكك مابين(٢٢ ثانية الى ١٤.٦ ثانية) و تحرر دوائي الوقت المطلوب لـ ٨٠% من الدواء لكي يتحرر مابين (٢.٩% الى ٠.٩%). من بين كل التركيبات، PF4 اختيرت كأفضل تركيبة تحتوي بروكلوبيرازين ماليت: وبيتا سايكلودكسترين بنسبة (١:٣) ، ١٠% من الكروسبوفيدون و ٢٥% من الامونيوم بايكاربونيت لها وقت التحلل الأقصر، تحرر دوائي و استقراريه جيدة. إجمالي النتائج تقترح بان تحضير البروكلوبيرازين ماليت بشكل حبة سريعة التحلل بالفم اعطت زيادة في الامتصاص من الحبة العادية عن طريق استخدام مواد مفككة و معقدالضمين بيتاسليكلودكسترين مع الدواء.

الكلمات المفتاحية: بروكلوبيرازين ماليت ، الحبوب الفموية الذائبة، كروسبوفيدون، امونيوم بايكاربونيت، التسامي

Introduction

Tablets are solid dosage forms usually prepared with the aid of suitable pharmaceutical excipients they may vary in their size, shape, weight, hardness, thickness, disintegration, dissolution characteristics and in other aspects depending on their intended use and method of manufacture[(1)].One of the important drawback of solid dosage forms is the difficulty in swallowing (dysphagia) or chewing in some patients particularly pediatric and geriatric patients[(2)].To overcome this weakness, innovative drug delivery systems have developed known as fast dissolving tablets. Rapid breakdown or fast disintegrating tablet of the type of those intended to undergo disintegration in the mouth in contact with the saliva in less than 40 seconds [(3)]. Fast dissolving tablets are also known as mouth-dissolving tablets, melt-in mouth tablets, orodispersible tablets, rapimelt, porous tablets, quick dissolving tablets[(4)].

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Their characteristic advantages such as administration without water, anywhere, anytime lead to their suitability to geriatric and pediatric patients, they are also suitable for the mentally ill, the bedridden and patients who do not have easy access to water[5]. Moreover, pharmaceutical companies also have commercial reasons for formulating ODTs. As a drug reach end of its patent, the development and formulation of the drug in to new dosage forms allow pharmaceutical companies to extend the patent life and market exclusivity[6]. The basic approach to the development of mouth dissolving tablets is the use of superdisintegrants such as (carboxymethyl-cellulose calcium (ECG505®) and crospovidone (CP)). An other approach used in developing ODTs is maximizing the pore structure of the tablet matrix. Freeze drying and vacuum drying techniques have been tried by researchers to maximize the pore structure of the tablet matrix[7-9].However, freeze drying is cumbersome and yields a fragile and hygroscopic product., meanwhile vacuum drying along with sublimation of volatilizable ingredient has been employed to increase tablet porosity[10].Prochloperazine maleate (PCM) is an important member of the group of phenothiazine derivative [11]. It is used as is an antiemetic, antipsychotic and tranquilizing agent[12]. It Absorbed well after oral administration with poor bioavailability (0-16%) due to extensive hepatic first pass metabolism, peak plasma concentration following a single oral dose about 6 hours[13]. The peak plasma concentration (C max) and the time taken to reach Cmax (T max) depend on the extent and the rate of dissolution of the drug, respectively. The rate of dissolution can be increased by increasing the surface area of the available drug by various method (micronization, complexation and solid dispersion)[14].The aim of this study is to prepare PCM fast disintegrating tablet using crospovidone, ammonium bicarbonate(AB) and investigation different variables that affect the physical properties of the prepared tablets.

Materials and Methods

Materials

PCM pure powder from Ratiopharm, Germany. CP, (ECG505) from 3B pharmaceutical (wuhan) international co. Ltd, China. L-HPC LH21 from sigma Aldrich, steinheim, Germany. Mg- stearate, mannitol, AB from Riedel De- Haen ag seelze, Germany. Colloidal silicon dioxide, polyvinylpyrrolidone (PVP), talc from Sigma- Aldrich, Germany. β-cyclodextrin from Himedia Laboratories PVt. Ltd. Mumbai, India. Aspartam from BDH chemicals LTD poole, England. Urea from Evans medical Ltd, Liverpool, England. nautisol® tablet from medochemie LTD,Limassol-CYPRUS (EUROPE).

Methods

Formulation of orodispersible tablets of prochloperazine maleate

The orodispersible tablet of PCM were prepared using superdisintegrants (L-HPC LH21, ECG505 and CP), subliming agents (AB, urea), mannitol as a diluent, Aspartam as a sweating agent, alcoholic solution of PVP in ethanol (10% w/v) as binder and colloidal silicon dioxide, talc with Mg-stearate as a flow promoter (table 1). The (drug , superdisintegrant, subliming agent, mannitol and Aspartam) were mixed together, and a specified volume of alcoholic solution of PVP (10% w/v) was added and mixed to form a coherent mass. The wet mass was granulated using sieve no. 10 and dried in a tray dryer at 65ºC for 10 min then screened through sieve no. 18. The dried granules were then blended in a tumbling cylindrical blender with colloidal silicon dioxide, talc and Mg-stearate and compressed in to tablets using 7 mm double punch tablet machine (Korsch, Erweka,GmbH. Kr offen bachl main Germany). Tablet from formulation F4 to F8 containing subliming agent were further dried at 80ºC until they reached constant weight[15].

Preparation of complex of prochloperazine with β- cyclodextrin

A mixture of PCM and β-cyclodextrin (1:1, 1:2 and 1:3) equal to (5:5, 5:10, 5:15) respectively, was ground in a glass container and a minimum amount of solvent (ethanol: distilled water 1/1 V/V) was add. The mixture was reacted for 90 seconds at 60ºC in the microwave oven. After the reaction was completed, an adequate amount of solvent was added to remove residual of PCM and β-cyclodextrin from glass container and filtered, after drying at room temperature for 24 hour, a white powder was attained, which was the inclusion complex of PCM and β-cyclodextrin[16].

Preparation of tablet containing a complex of pcm with β- cyclodextrin.

From the best evaluated formula of PCM orodispersible tablet (F8, table1) regarding to shortest disintegration time (DT) in mouth, good friability and accepted hardness selected to become PCM orodispersible table (PF1). PCM was prepared as inclusion complex with β-cyclodextrin in different ratios (1:1, 1:2 and 1:3) and formulated orodispersible tablets (PF2, PF3 and PF4) respectively using the same

component utilized to formulate PCM PF1(table 2) without β-cyclodextrin complexation in order to study the effect of the inclusion complex on the physical properties of the prepared PCM orodispersible tablets.

Table 1: Composition of different batches of ODTs of prochloperazine maleate

Formula ingredients (mg)	Formula no.							
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**
Prochloperazine maleate	5	5	5	5	5	5	5	5
L-HPC LH21	13(10% w/w)							
ECG505		13(10% w/w)						
Crospovidone			13(10% w/w)	13(10% w/w)	13(10% w/w)	13(10% w/w)	13(10% w/w)	13(10% w/w)
Ammonium bicarbonate				13(10% w/w)		19.5(15 % w/w)	26(20% w/w)	32.5(25 % w/w)
Urea					13(10% w/w)			
*Aspartam	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
*Colloidal silicon dioxide	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
**Talc	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6
*Mg-stearate	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3
Mannitol Q.S to	130mg	130mg	130mg	130mg	130mg	130mg	130mg	130mg

* 1% of (Aspartam , colloidal silicon dioxide, Mg stearate) were used.
** 2% of talc was used**.**

Table 2: Composition of different batches PCM: β- cyclodextrin inclusion complex orodispersible tablets

Formula ingredients (mg)	Formula no.			
	PF1	**PF2**	**PF3**	**PF4**
Prochloperazine maleate	5	5	5	5
β - cyclodextrin		5	10	15
Crospovidone	13 (10% w/w)	13 (10% w/w)	13 (10% w/w)	13 (10% w/w)
Ammonium bicarbonate	32.5 (25% w/w)	32.5 (25% w/w)	32.5 (25% w/w)	32.5 (25% w/w)
Aspartam	1.3	1.3	1.3	1.3
Colloidal silicon dioxide	1.3	1.3	1.3	1.3
Talc	2.6	2.6	2.6	2.6
Mg- stearate	1.3	1.3	1.3	1.3
Mannitol Q.S to	130mg	130mg	130mg	130mg

Evaluation of the prepared granules

Angle of repose. The angle of repose was measured by passing the prepared granules through a sintered glass funnel of internal diameter 27mm on the horizontal surface. The height (h) at the heap formed was measured with a cathetometer, and the radius(r) of the cone base was also determined. The angle of repose (φ) was calculated from Eq.1[17].

Tan φ= h/r ……(1)

Compressibility (Carr's) index. An accurate weight of formula granules was poured into a volumetric cylinder to occupy a volume ($V_\circ$) and then subjected to a standard tapping procedure onto a solid surface until a constant volume was achieved (V_f). The Carr's index was calculated using Eq.2.[17].

$$\text{Compressibility} = \frac{V^\circ - Vf}{V^\circ} \quad \ldots\ldots\ldots(2)$$

Evaluation of the prepared orodispersible tablets

Weight Variation. Randomly, 20 tablets were selected after compression and the mean weight was determined. None of the tablets deviated from the average weight by more than ± 7.5%[18].

Uniformity of content. The content of PCM was performed by taking five tablet and assayed individually. The requirement for this test is to met if the amount of ingredient in each of the five tablets lies within the range of 95-102% of the label claim.[17].

Wetting time. A piece of tissue paper (12×10.75cm) folded twice was placed in a Petri dish (internal diameter 9mm) containing 10ml of buffer solution simulating saliva, pH 6.8, and nigrosine. A tablet was placed on the paper and the time taken for complete wetting was noted. Three tablet from each formulation were randomly selected and the average wetting time was recorded[19].

Hardness. The crushing strength of the tablets was measured using a Monsanto hardness tester. Three tablets from each formula batch were tested randomly and the average reading ± SD was recorded.

Friability. Twenty tablet were weighed and placed in a Roche friabilator and the equipment was recorded at 25 rpm for 4min. The tablets were taken out, dedusted, and reweighed. The percentage friability of the tablets was calculated using Eq.3[18].

$$\%\ \text{friability} = \frac{\text{Initial weight - final wieght}}{\text{Initial weight}} \times 100 \ldots.(3)$$

In-vivo disintegration time. Five healthy human volunteers were selected and their written consent was obtained. Each volunteer randomly took one tablet and kept on the tongue. The time in seconds taken for complete disintegration of the tablet on the tongue was noted. It is expressed in seconds. Before the test, mouth was washed with DW. Three trials were performed with 10-day interval between trials[20].

Determination of solubility of prochloperazine maleate: β- cyclodextrin inclusion complex

The solubility of PCM powder and different ratios (1:1,1:2,1:3) of PCM: β- cyclodextrin complexes powders were determined using the shaking-flask method by placing excess amounts separately in 30ml vial then 20ml of phosphate buffer (pH 6.8) was add. The vial were sealed well and covered with opaque aluminum foil then incubated together in a shaking water bath at 25ºC for 72hours.100µl of each Samples were withdrawn for 3 days at 24 hours interval, then filtered and diluted to 3ml, then diluted samples along with standard calibration curve were analyzed by UV spectrophotometer at λmax 255 nm to determine the dissolved quantity of PCM and PCM: β- cyclodextrin at different ratios[21].

FTIR studies

The studies were done for the PCM , β-cyclodextrin powders alone and PCM: β-cyclodextrin (1:1, 1:2 and 1:3) complexes powder using shimadzu 8300 Fourier transform infrared (FTIR) spectroscopic analysis to ensure the inclusion between PCM and β-cyclodextrin using potassium bromide disc method in the range of 4000-500cm^{-1}.

Dissolution studies

In-vitro dissolution studies were performed using type Π (paddle) dissolution apparatus (Copley UK) at 50 rpm, and 900ml of phosphate buffer (pH6.8) was used as dissolution medium at 37±0.5ºC. Five milliliters aliquot of the dissolution was withdrawn at (1, 2, 4, 6, 8,10, 15, 20, 25, 30). The absorption of filtered solution was measured by UV-Visible spectrophotometer at λmax 255nm and the percent drug release was determine. The dissolution rate was studied for the prepared formulation and conventional tablet. The time required for 80% of the drug to be release ($t_{80\%}$) and percent drug remaining in 2 min ($D_{2min\%}$) were estimated to compare the dissolution result. The $t_{80\%}$ and D_{2min} were determined by fitting the dissolution data to a four parametric logistic model using the marquardt-levenberg algorithm (sigmaplot Π SPSS)[22].

Comparison of dissolution profiles

The similarity factor (f_2) given by SUPAC guideline for modified release dosage form was used as a basis to compare dissolution profile. The dissolution profiles of products were compare using a similarity factor (f_2). This similarity factor is calculated by following equations [23].

$$f2 = 50 \times \log\left\{\left[1 + \frac{1}{n}\sum_{t=1}^{n}\left|Rt - Tt\right|^2\right]^{-0.5} \times 100\right\} \ldots..(4)$$

where n= is the number of dissolution time points

Rt the reference profile (nautisol) at the time point t

Tt the test profile at the same point.

Generally f_2 value greater than 50 (i.e. from 50-100) ensure equivalence of the two curves.

Stability studies

The stability study was carried out on optimized formula (PF4). The tablets were stored at 40±2ºC/75±5% relative humidity (RH) using stability chamber for one mouth, then the samples were evaluated for various physical tests and drug release study[24].Moreover, the FTIR spectra of PCM: β- cyclodextrin (1:3) powder, physical mixture and optimum formula (PF4) as a tablet were obtained using FTIR-potassium bromide discs in the range of 4000 cm^{-1} to 500 cm^{1} to detect any drug –excipients interaction[25].

Statistical Analysis

The results of the experiments are given as a mean samples ± standard deviation (SD) and were analyzed according to t-test and one way analysis of variance (ANOVA) using Sigma Plot 11 software at the level of ($p<0.05$).

Results and Discussion

Evaluation of the prepared orodispersible prochloperazine maleate tablets

The weight variation(percent weight within the pharmacopial limits of ±7.5% of the average weight) and content uniformity tests (99.75±0.2) of the prepared PCM orodispersible tablets complied with USP specification.

Effect of superdisintegrant type

The assessment of disintegration time for the ODT is difficult using the tests for conventional tablets due to its rapid disintegration rate even in a small volume of water, In addition to the strong agitation used during this test, and consequently, the DT obtained from the conventional disintegration tests appear not to be reflective of the DT in human mouth[26].Thus, in vivo disintegration time was used in this study. The superdisintegrants alleviate most of the problems associated with long tablet disintegration time; also, the use of the superdisintegrants in ODT is possible as the tablet shows optimum physical properties. Formulas F1-F3 were prepared to study the effect of type of superdisintegrant, L-HPC LH21, ECG 505 and CP, on the in vivo DT of the prepared PCM orodispersible tablet. The results shown in (table 3) indicate that CP has the shortest in vivo DT(58 seconds) followed by ECG 505(63.6 seconds) then L-HPC LH21(71.7 seconds).the tablet that contain CP have shortest wetting time (73.3 seconds) which may attributed to strong wicking among the other superdisintegrants. This result is in agreement with the result obtained by Jinichi *et al*[27].Although all the three formulas (F1-F3) had acceptable flowability and compressibility as shown in (table 4) as well as had acceptable hardness and friability, from these results CP was selected as the best superdisintegrant and (10%) used in formulas F4-F8 to investigate other formulation variables.

Table 3: Evaluation of the prepared orodispersible tablets of Prochloperazine maleate (each value represented as mean ± standard deviation, n=5).

Properties	Formula no.							
	F1	F2	F3	F4	F5	F6	F7	F8
Wetting time (seconds)	158 ±1.4	139 ±4.9	73.3 ±2	55.6 ±0.6	162 ±1	69 ±3.2	63 ±2	55.6 ±1.5
In vivo DT (seconds)	71.7 ±3.2	63.6 ± 3.2	58 ±2.6	33.3 ± 2.8	52.3 ±0.8	29 ± 1	24.6 ± 1.5	22 ± 2.3
Hardness (kg/cm^2)	4.3 ± 0.6	4.9 ± 3.7	4.3 ± 2.4	4.07 ± 0.5	2.1 ± 0.7	3.1 ± 0.5	3.6 ± 0.4	3.3 ± 0.5
Friability w/w(%)	0.62	0.8	0.44	0.61	1.1	0.75	0.81	0.85
Drug content (w/w%)	99.2 ±102	100.2 ± 1.2	101.3 ±0.3	98.5 ± 0.9	95.3 ± 2.8	99.7 ± 2.1	100.2 ± 0.7	101.7 ± 0.3

Table 4: Micrometrics properties of ODTs of Prochloperazine maleate (each value represented as mean ± standard deviation, n=3).

Formula no.	Angle of repose	Carr's angle	Flow character
F1	32.7±4.4	13.5±1.4	Good
F2	24.5±0.9	11.9±2	Excellent
F3	21.8±3.7	10.8±0.4	Excellent
F4	25.3±1.2	16.3±0.1	Excellent
F5	20.7±0.8	13.1±1.4	Excellent
F6	20.07±0.9	13.7±0.9	Excellent
F7	28.6±2.7	14.4±0.9	Excellent
F8	24.7±2.9	15.1±1.3	Excellent

Effect of subliming agent type

Results for F4 and F5 which were utilized to study the effect of subliming agent type (urea and AB). Using AB as a subliming agent produce significant ($p< 0.05$) increase in hardness(4.07 kg/cm^2) and decrease in friability (0.6%) of tablets in comparison with urea (2.1 kg/cm^2, 1.1%) respectively, that produce mechanically weak tablets. While urea containing formula showed excellent flow properties, but poor hardness and friability. Also it didn't exhibit complete sublimation which can be predicted by stinging taste of urea by putting the tablets in the mouth of volunteers for in vivo DT measurement. Thus AB was preferred over urea as subliming agent in their study.

Effect of subliming agent concentration

Formulas F3,F5,F6,F7 and F8 were designed to study the effect of concentration of AB as subliming agent on the properties of ODT of prochloperazine maleate. The results showed that the concentration of AB didn't result in large changes in the flow character of the prepared granules, and all formula had acceptable flow characters. But it was seen that as the concentration of the subliming agent increased, there was a gradual decrease in vivo DT to reach 22 seconds for 25% AB used. The reduction in DT may be attributed to the increase in porosity of the tablet so easily picking up the disintegrating medium and bringing about rapid tablet disintegration and shorter wetting time[28].

Effect of β- cyclodextrin complexation

Formula PF2, PF3 and PF4 were prepared to study the effect of β- cyclodextrin complexation on the DT and dissolution rate of the prepared PCM orodispersible tablets and the results compared to the PCM orodispersible tablets without β- cyclodextrin complexation PF1. The solubility of PCM alone and different PCM: β- cyclodextrin ratios (1:1, 1:2 and 1:3) were determined. The result showed that the enhancement order of solubility was found 1:3>1:2>1:1> PCM powder, since, the solubility enhance from 0.52mg/ml of PCM alone to (0.98, 1.4 and 1.8mg/ml) for (1:1,1:2 and 1:3) inclusion complex respectively. β- cyclodextrin result in improvement in dissolution by enhance the solubility of PCM[29].The flowability of PCM orodispersible tablets PF1, PF2, PF3 and PF4 did not showed a large changes in the flow character of the prepared granules and all had acceptable flow character as shown in (table 5) as well as had acceptable hardness and friability. The inclusion complex of PCM: β-cyclodextrin in 1:3 ratio (PF4) gave highly improvement in vivo DT (14.6 seconds) compared to PF1 without β- cyclodextrin complexation (22 seconds) as shown in (table 6).

Table 5 : Flow characters of the prepared Prochloperazine maleate: β-Cyclodextrin inclusion complex orodispersible tablets (each value represented as mean ± standard deviation, n=3).

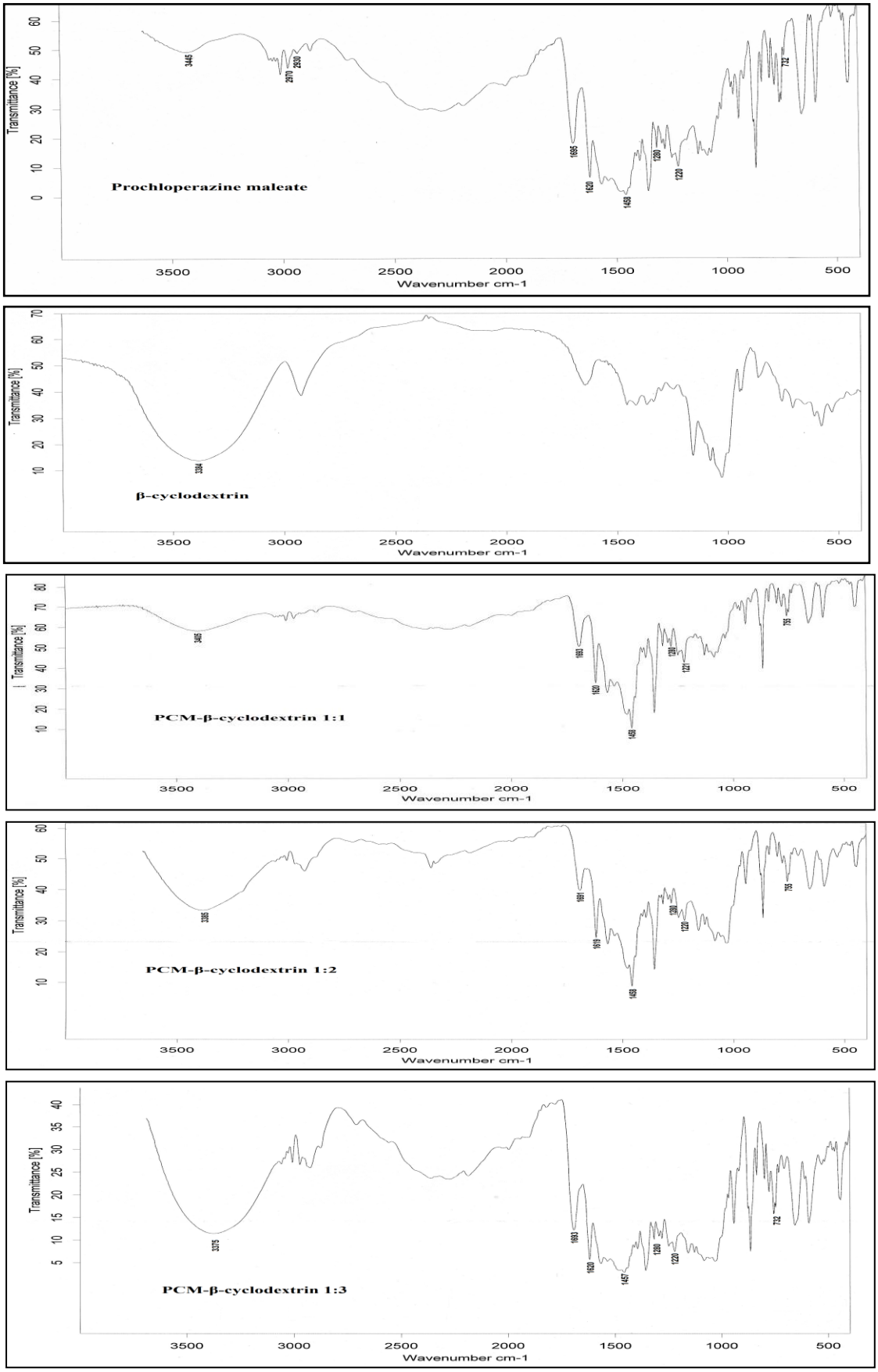
Formula no.	Angle of repose	Carr's index	Flow character
PF1	24.7 ±2.9	15.1 ±1.3	Excellent
PF2	27.3 ±2.3	13.3 ±1.8	Excellent
PF3	26.6 ±2.5	13 ±2.1	Excellent
PF4	25 ±1.7	13.2 ±3.1	Excellent

Table 6 : Physical properties of the prepared Prochloperazine maleate: β-Cyclodextrin inclusion complex orodispersible tablets (each value represented as mean ± standard deviation, n=3).

Formula code Properties	PF1	PF2	PF3	PF4
Wetting time (second)	55.6 ±5.1	45.6 ±3.5	34 ±3.6	24.6 ±1.1
In vivo DT (second)	22 ±2.3	19.3 ±3	17.3 ±3	14.6 ±1.5
Hardness (Kg/cm^2)	3.3 ±0.5	3.5 ±0.5	3.6 ±0.2	3.8 ±0.3
Friability (%)	0.86	0.75	0.6	0.6
Drug content (%)	97.2 ±0.2	100 ±0.2	101 ±0.2	100.8 ±0.3

FTIR studies

The FTIR spectra Fig.1. demonstrated a shift of OH band of PCM from 3445.2 cm^{-1} to (3405.2, 3385, 3375) cm^{-1} for complexes at different ratios (1:1,1:2 and 1:3) respectively which confirm complex formation the change in the rest of the spectrum are not significant.



Figures 1: FTIR spectra of PCM, β-cyclodextrin, and different ratios of PCM: β-cyclodextrin (1:1, 1:2, 1:3) inclusion complex powder

In- vitro dissolution studies

For all oral solid dosage forms, dissolution study serve as a control test. The same is true for ODTs. This is because batch-to-batch consistency can be assured, and data of the tablets are frequently predictive of the bioavailability of the product. The result of dissolution studies of formula PF1,PF2,PF3,PF4 and conventional PCM (Nautisol®) tablet in (table7) and Fig.2 indicate that the dissolution rate is increased in the following order PF4>PF3>PF2>PF1>(PCM tablet), since, the $t_{80\%}$ were (0.9, 1.5. 2.9, 3.7 and 9.5) respectively. and the calculated f_2 value for the prepared PF4 ODTs tablet when using (Nautisol®) as references were 13% this value indicate clearly the high significant difference among two formulation.

Table 7 : *In-vitro* dissolution parameters of PCM: β-cyclodextrin inclusion complex in phosphate buffer (pH 6.8)

Formula code	$t_{80\%}$ (minute)	$D_{2\ min}$ (%)
PF1	3.7	65.2
PF2	2.9	71.4
PF3	1.5	83.2
PF4	0.9	91.25
Nautisol®	9.5	46.3

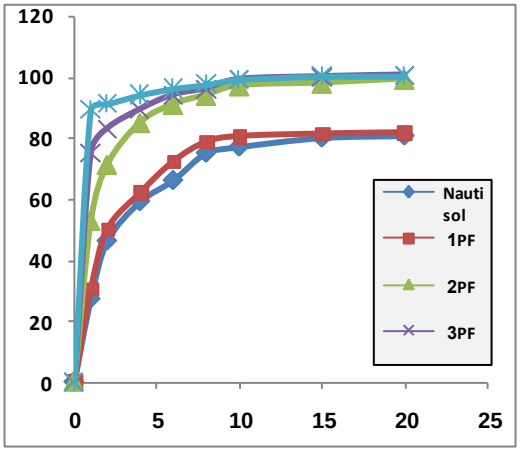
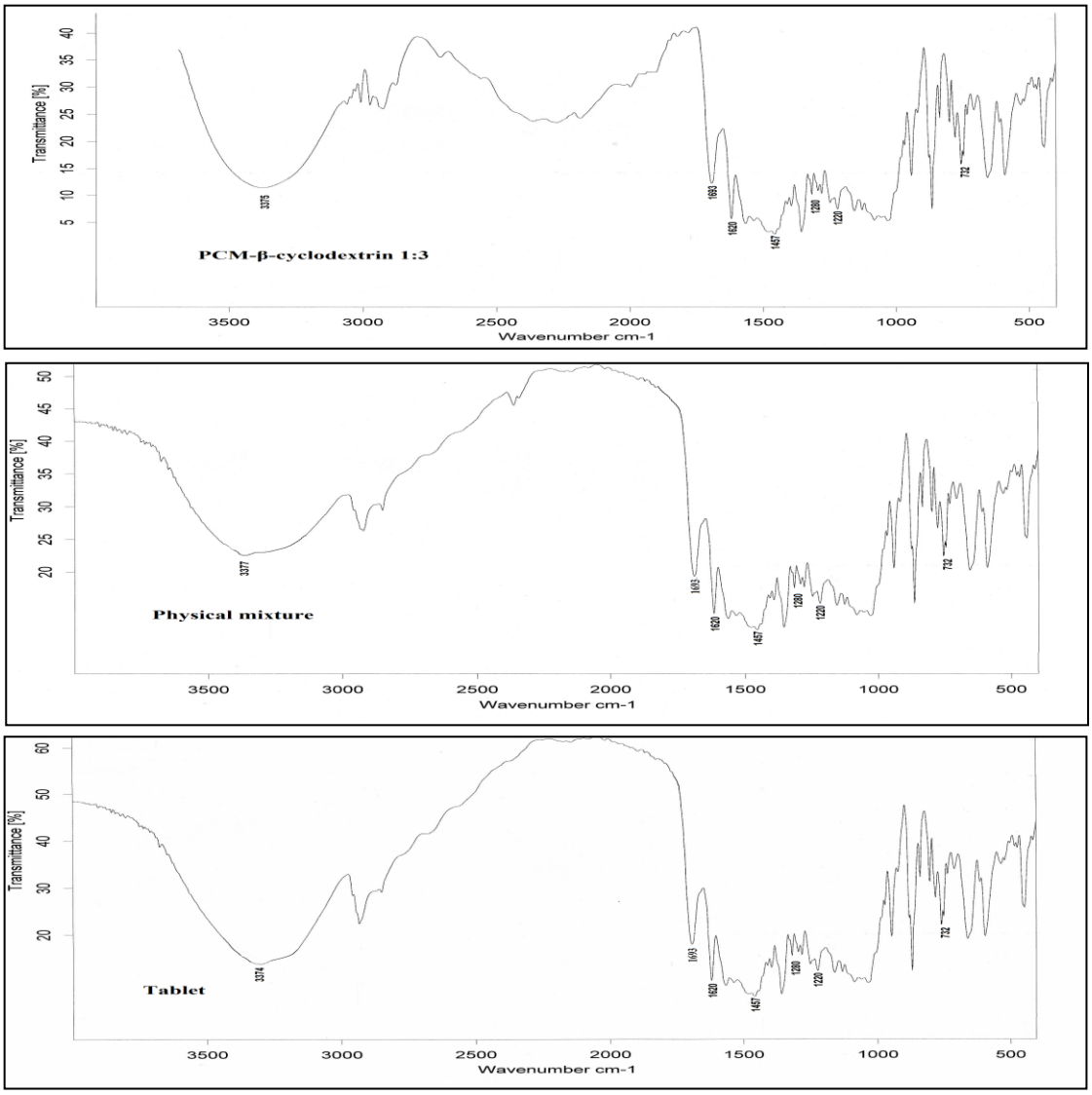


Figure 2: The dissolution profile of the prepared Prochloperazine maleate ODTs (PF1, PF2, PF3, PF4) in phosphate buffer (pH 6.8) at 37ºC ± 0.5 ºC.

Stability study

In term of overall parameter, formula PF4 was considered as the selected formula, thus it was subjected to stability studies. Comparison of FTIR spectra of PCM: β-cyclodextrin (1:3) inclusion complex, in the physical mixture and selected formula of ODT of prochloperazine maleate Fig.3. There by indicating that there is no interaction drug with the components of the formulation, moreover, the short term stability studies of the selected formula (PF4) show no changes in tablet hardness, friability, drug content, in vivo DT and dissolution rate at the end of the stability study period.



Figures 3: FTIR spectra of PCM-β cyclodextrin (1:3), physical mixture and the selected formula PF4 of ODT of PCM

Conclusion

Overall, the results suggest that suitably formulated orodispersible tablets of prochloperazine maleate containing 10% CP as a superdisintegrant and 25% AB as a subliming agent by wet granulation method with sublimation and β-cyclodextrin inclusion complex can be achieved. The optimum selected formula (PF4) has satisfactory physical resistance, fast in vivo disintegration time, high dissolution rate and good stability.

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