AJPS, 2013, Vol. 14, No.2

Development and evaluation of or dispersible tablet of Propranolol Hydrochloride by sublimation technique

Mowafaq, M. G.
Department of pharmaceutics, College of Pharmacy,
University of Baghdad.

Abstract:

Propranolol Hydrochloride (PHCl) is a synthetic beta adrenergic receptor blocking agent used widely in the treatment of angina pectoris, cardiac arrhythmias and hypertension. The purpose of this study was to develop PHCl orodispersible tablet of fast disintegration in mouth with high mechanical strength to withstand handling during manufacturing and patient use.

Sublimation technique was used to prepare the orodispersible tablets of PHCl using four subliming agents; camphor, thymol, ammonium bicarbonate and menthol by direct compression method in presence of 2.5%w/w crospovidone as superdisintegrant. The product is of high porosity after sublimation of agent from the tablets. To mask the bitter taste of the drug, increase sweetness and to provide acceptable feeling in mouth, aspartame, saccharin sodium, and citric acid were added. Mannitol was used as sugar based multifunctional diluents.

The formulas powder blend was evaluated before compression for angle of repose and compressibility index while the post-compression parameters were evaluated for weight variation, content uniformity, hardness, friability, disintegration time, and drug *in vitro* release of the formulated tablets. The weight and drug content of tablets of all batches were within the acceptable limits. The *in vitro* disintegration time was less than 62.8 seconds for all batches except that containing 2.5% w/w menthol shows disintegration in 202.73 sec.

Menthol 15% w/w shows the shortest disintegration time among subliming agents with acceptable friability and hardness, thus selected as the best formula (F9). The optimized formulation showed faster release profile in comparison to the conventional tablets.

الخلاصة:

هايدروكلورايد البروبرانولول هو دواء صناعي غالق لمستقبلات بيتا الأدرينالية وتستخدم على نطاق واسع في علاج الذبحة الصدرية، عدم انتظام ضربات القلب وارتفاع ضغط الدم. وكان الغرض من هذه الدراسة هو تطوير حبوب سريعة الذوبان في الفم بدون ماء من هايدروكلورايد البروبرانولول مع مواصفات جيدة للحبوب منها تفكك سريع في الفم وقوة ميكانيكية عالية على تحمل النقل اثناء التصنيع وحين استخدامه من قبل المريض.

تم استخدام تقنية التسامي لإعداد حبوب سريعة الذوبان في الفم من هايدروكلورايد البروبرانولول باستخدام أربعة مواد متسامية وهي: الكافور، الثيمول، بيكربونات الأمونيوم وتركيزات مختلفة من المنثول بواسطة أسلوب الكبس المباشر مع وجود 2.5٪ كروسبوفيدون كمادة مفككة فائقة. كانت الحبوب المنتجة كثيرة المسامات بعد انتهاء عملية التسامي. لإخفاء الطعم المر للدواء وإضافة حلاوة وتوفير شعور مقبول في الفم أضيفت الأسبارتام، السكرين الصوديوم، وحامض الستريك. كما تم استخدام مانيتول كسكرمكمل للوزن اضافة لمنافعه الاخرى في التركيبة.

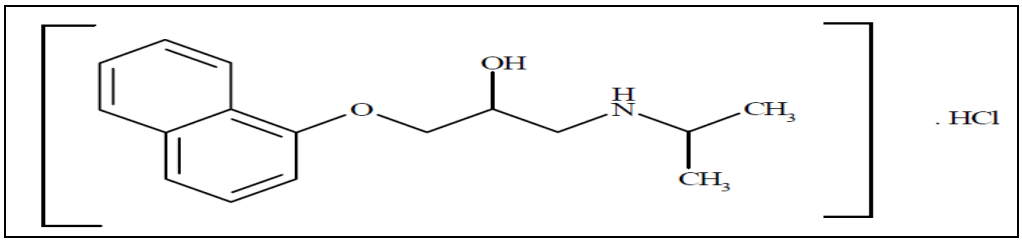
جرى تقييم مواصفات الحبوب بعد الكبس من ناحية اختلاف الوزن، وتجانس المحتوى الدوائي، والصلابة، ودرجة تكون الباودر، ووقت التفكك، وتحرر الدواء من الحبوب في المختبر.كان الوزن و محتوى الدواء في الحبوب لجميع الوجبات ضمن الحدود المقبولة. كان التفكك في المختبر أقل من 62،8 ثانية لجميع الوجبات ماعدا الوجبة التي تحتوي 2.5٪ وزن/وزن منثول حيث اظهرت الوجبة تفكك في 202.73 ثانية. اظهر المنثول 15٪ وزن/ وزن أقصر وقت تفكك بين مواد التسامي مع صلابة ودرجة تكوين باودر مقبولة، لذلك تم اختيارها كأفضل صيغة (F9). وأظهرت الصيغة المثلى المختارة سرعة اعلى في تحرر الدواء مقارنة بها من الحبوب التقليدية.

Introduction:

The traditional forms of dosages such as tablets, capsules, granules, pills, and powder may not obtain the complete therapy due to low patient compliance [1]. Swallowing difficulty is associated with nearly 35% of general population [2]. It is observed with some situations such as pediatric, geriatric, unconscious, bedridden, and developmentally disabled patients [3, 4]. Furthermore patients who are travelling when water is not available nearby and some patients who refuse to administer therapy as psychological patients. The researches about solid oral dosage forms in the last few years results in development of oral disintegration tablets.

Oral disintegrating tablets overcome the difficulties which face the traditional dosage forms [5, 6]. An Oral disintegration tablets is a solid dosage form that disintegrates and dissolves in the mouth without water within 60 seconds or less [7]. The European Pharmacopoeia defines the term "or disperse" as a tablet that can be placed in the mouth where it disperses rapidly before swallowing[8]. Most pharmaceutical manufacturers prefer ODTs in comparison to other drug delivery system due to simplicity in prod uction and drug registration [9, 10].

Another property of orodispersible tablets is the possibility of increased bioavialbility due to rapid disintegration of tablet inside the mouth; drugs may be absorbed in the buccal, pharyngeal, and gastric regions [11]. Propranolol hydrochloride is a synthetic beta-adrenergic receptor-blocking agent chemically described as 2-Propanol,1-[(1-methylethyl)amino]-3-(1-naphthalenyloxy)-, hydrochloride,(±)-. It has the following structural formula.



Propranolol hydrochloride is a stable, white, crystalline solid which is readily soluble in water and ethanol. Its molecular weight is 295.80 [12]. PHCL is non-selective beta-blocker with no intrinsic sympathomimetic activity (ISA) [13] that is widely used in the treatment of angina pectoris, cardiac arrhythmias and hypertension [14].

The purpose of this works was to prepare or dispersible tablets of PHCl using different subliming agent by direct compression method.

Material and Methods

Materials

Propranolol hydrochloride powder was purchased from IPCA laboratory Ltd Selvassa, India. Crospovidone (CP) was purchased from 3B pharmaceutical (Wuhan) international Co. Ltd, china. Magnesium stearate, mannitol, and ammonium bicarbonate were purchased from Riedel-De-Haen AG seelze, Germany. Camphor and menthol were purchased from Evans Medical Ltd, Liverpool, England. All other materials were of analytical grade.

Methods Formulation of orodispersible tablets of Propranolol Hydrochloride

The composition of different batches is shown in table (1). All the ingredients (except lubricants and glidant) were passed through mesh No.44 meshes separately, Then weighed and mixed in geometrical order for about 10 min. Then lubricants and glidant (magnesium stearate,

talc, and cab-o-sil) were added to the mixture and mixed for about 2min. Finally an amount of the blend was evaluated before direct compression into tablets of 200 mg using 8mm round flat single punch tablet machine (MANESTY, Type F3, and Liverpool, England).

Sublimation was performed from tablets contain subliming agents at 60ºC until a constant tablet weight was achieved [15].
A minimum of 50 tablets was prepared for each batch.

Table-1: Different formulas used in preparation of orodispersible tablets of PHCL

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Propranolol hydrochloride	40	40	40	40	40	40	40	40	40
Camphor	10								
Ammonium bicarbonate		10							
Thymol			10						
Menthol				5	10	15	20	25	30
Crosspovidone	5	5	5	5	5	5	5	5	5
Aspartame	6	6	6	6	6	6	6	6	6
Saccharin Sodium	3	3	3	3	3	3	3	3	3
Citric acid	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4
Sodium Bicarbonate	4	4	4	4	4	4	4	4	4
Mg Stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3
Cab-O-Sil	2	2	2	2	2	2	2	2	2
Mannitol QS	200	200	200	200	200	200	200	200	200

Precompression parameters

Angle of Repose

Angle of repose was determined using fixed high cone method [16]. The powder blend was poured through funnel that can be raised vertically until a maximum cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose was calculated using the formula; **Tan θ = h/r**

where, θ is the angle of repose, h is height of pile; r is radius of the base of pile.

Compressibility (Carr's) index

An accurate weight of powder blend was poured into a measuring cylinder to occupy a volume ($V_\circ$) and then subjected to a standard tapping procedure on to a solid surface until a constant volume was achieved (V_f). The Carr's index was calculated using following equation [16].

Compressibilty

Index= (tapped density-bulk density/ tapped density) x100= 100x (V_0-V_f)/V_0

The values indication of angle of repose and compressibility index is shown in table-2.

Table-2: Flow property analysis parameters indication

Angle of Repose (degrees)	Compressibility index%	Flow property
25-30	≤10	Excellent
31-35	11-15	Good
36-40	16-20	Fair
41-45	21-25	Passable
46-55	26-31	Poor
56-65	32-37	Very poor
>66	>38	Very, very poor

Evaluation of the prepared orodispersible Propranolol Hydrochloride tablets

Weight variation

Twenty tablets were selected at a random basis from each batch and average weight was calculated. Then individual tablets were weighed and the individual weight was compared with the average weight to assess the weight variation of the tablets. The batch to be accepted, none of the tablets should deviate from the average weight by more than ±7.5%.

Uniformity of content

Ten tablets were weighed and powdered; 200 mg from it was transferred to a 100 ml volumetric flask, 5 ml of dilute HCl was added, and it was allowed to stand and swirled occasionally. About 70 ml of methanol was added, shaken well and the volume was made up. It was mixed and a small portion of the solution was centrifuged. A suitable volume of this was then diluted with methanol to obtain a solution containing 40 µg of propranolol hydrochloride per ml. The extinction of 1 cm layer of the resulting solution was measured at a maximum of about 290 nm using methanol as the blank solution [17]. The requirement for this test is met if the amount of drug in each of the ten tablets lies within the range of (85-115) % of the label claim proving that no loss or degradation of the drug during preparation.

Wetting time

The method was applied to measure tablet-wetting time. A piece of tissue paper (12cm x10.75cm) folded twice was placed in a Petri dish (Internal Diameter=9cm) containing 10ml of buffer solution simulating saliva pH 6.8 and amaranth. A tablet was placed on the paper and the time taken for complete wetting was noted. Three tablets from each formulation were randomly selected and the average wetting time was recorded **[18]**.

Hardness

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

Friability

Tablet friability was measured using Erweka Friability Tester at 25 rpm for 4 minutes. The weight of twenty tablets before and after completion of the test was recorded and friability was calculated by the following formula [19]:

Percent Friability = (Initial weight-Final weight)/ Initial weight x 100

***In vitro* Disintegration Time**

The disintegration time (DT) was determined using the disintegration test apparatus BP. The disintegration time was defined as the time in seconds taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measure in second using

artificial saliva as disintegration medium. Six tablets were placed individually in each tube of disintegration test apparatus. The values reported are mean ± SD [20].

***In Vitro* Drug Dissolution Test**

In vitro dissolution studies were performed only for the Optimum formula and PHCL (reference tablet, 40mg) by using type I (Basket) dissolution apparatus (Copley dissolution 8000, Copley scientific, U.K.) at 100 rpm, and 500 ml of 0.1 M HCL was used as a dissolution medium. Temperature of the dissolution medium was maintained at 37°C ± 0.5℃. Five ml aliquot of the dissolution medium was withdrawn at specific time intervals and it was filtered. Absorption of filtered solution was read by UV- visible spectrophotometer (Carry win UV, Varian, Australia) at λ_{max}= 290nm and drug content was determined from a standard calibration curve [17] .The mean of three determinations was used ± SD.

The percent of drug dissolved in 12 minutes was considered for comparing the dissolution results.

Palatability test

A panel of three persons was employed to assess the mouth feeling of the selected formula of PHCl orodispersible tablets. The human test was performed according to the guidelines of WMA Helsinki declaration (Ethical principles for medical research) [21]. The comments of the panel members were recorded.

Statistical analysis:

The mean ± standard deviation of the experiments results were analyzed using one way analysis of variance (ANOVA).

Results and discussion:

PHCL tablets were prepared by direct compression method. Nine formulations were prepared using four different subliming agents with 2.5% w/w CP as superdisinegrants. All batches of the tablets were evaluated for various pre and post- compression parameters. Table 2 shows the data obtained from the pre-compression evaluation of tablets which includes angle of repose, and Carr's index while post compression parameters such as weight, drug content, hardness, friability, wetting time, and disintegration time were evaluated.

The results of flowability studies of the powder blend reveals acceptable flowability and compressibility for tablet production represented by the angle of repose and Carr's index values respectively listed in table (3).

Table-3: Precompression parameters of PHCL orodispersible formulas

Formula NO.	Angle of repose (°)	Carr's index	Flow character
F1	29.37±0.31	15.25±0.44	Good
F2	31.03±0.57	20.61±0.63	Fair to pass
F3	27.37±0.43	14.25±0.41	Good
F4	26.24±0.18	13.88±0.57	Good
F5	27.47±0.52	15.75±0.18	Good
F6	28.65±0.71	12.57±0.62	Good
F7	26.41 ±0.62	15.70±0.72	Good
F8	28.29±0.83	12.40±0.39	Good
F9	24.57±0.24	14.61±0.84	Excellent

The post-compression parameters of all prepared tablets are reported in table (4) indicate that the hardness in the range of 3.94–4.3 kg/cm^2 which is an appropriate value according to specification of tablets in British pharmacopeia. The loss in total weight of the tablets due to friability was in the range of 0.34-0.76%. The drug content in different batches was in the range of 98.13-100.74% which indicates uniformity of the drug mixing and low percent of loss through preparation.

Table-4: post compression parameters of prepared PHCL orodispersible tablets

Formula No.	In vitro DT(sec)	Wetting time(sec)	Hardness(kg/cm^2)	Friability
F1	53.35±0.98	61.88±0.85	4.20±0.12	0.53
F2	49.62±0.74	59.75±0.46	4.05±0.09	0.56
F3	62.88±0.51	57.61±0.71	4.14±0.06	0.54
F4	202.73±1.89	266.75±1.86	4.16±0.04	0.34
F5	48.01±0.22	58.68±0.73	4.04±0.18	0.49
F6	42.68±0.75	53.35±0.64	4.15±0.17	0.57
F7	40.54±0.28	48.01±0.36	3.94±0.08	0.61
F8	36.27±0.44	42.68±0.39	4.30±0.03	0.65
F9	21.34±0.25	26.67±0.22	4.17±0.16	0.76

Wetting time is an important parameter shows the efficiency of swelling in presence of water which found to be in range of 26.67-266.75 sec. The results of *in vitro* disintegration time indicate that the subliming agent in formulas shows efficiency in the following order; menthol > ammonium carbonate >camphor> thymol.

Different concentrations of menthol show that the disintegrations time decreases as the menthol concentrations increases with optimum of 15% w/w in formula (F9).

Formula (F9) was selected as best formula, thus subjected for dissolution studies in comparison to conventional tablet as shown in figure (2). The results of dissolution study (figure2) show that the release of PHCL from selected formula and conventional tablet shows release 100 and 81.8% respectively at 12 minutes which consequently indicates that enhancement of release was obtained for the selected formula. Two persons record good taste for the selected formula in palatability test while third one records very good taste.

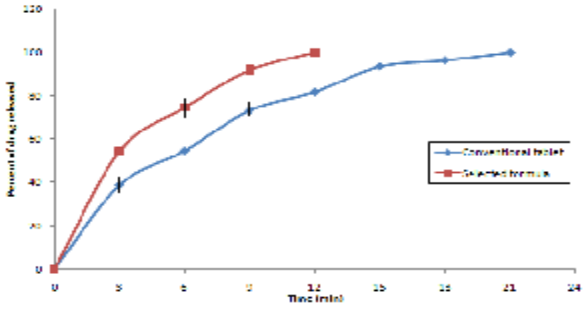


Figure-2: Dissolution profile of PHCL from selected formula and conventional tablet

Conclusion:

Formulation of ODTs of PHCL by sublimation technique using 15%w/w menthol in the presence of 2.5% w/w CP exhibited fast disintegration time with good mechanical properties which is promising for preparation of inderal orodispersible tablets after further studies of stability and *in vivo* studies.

References:

1- Debjit, B.; Chiranjib, B.; Krishnakanth, P. and Margret, C. Fast dissolving tablet: an overview. Journal of Chemical and Pharmaceutical Research. 2009. Vol. 1 (1). Pp: 163-177

2- Saravana, K.; Chandra, SKB.; Jayachandra, R. and Nagaveni, P. Design, development and characterization of mouth dissolving tablets of cefixime. Int. J. Pharm & Ind. Res. 2011. Vol.1 (2). Pp: 115-121

3- Reddy, L.; Ghosh, B. and Rajneesh. Fast dissolving drug delivery system; a review of the literature. Indian J. Pharm sci. 2002. Vol. 64. Pp: 331-336.

4- Atsushi, W.; Takehisa, H.; Masayasu, S. and Keiji; Y. Development and pharma ceutical properties of a new oral dosage form of theophylline using sodium caseinate for the possible use in elderly patients. International Journal of Pharma ceutics. 1995. Vol. 117 (1). Pp: 23-30

5- Chue, P.; Welch, R. and Binder, C. Acceptability and disintegration rates of orally disintegrating risperidone tablets in patients with schizophrenia or schizo affective disorder. Can J Psychiatry. Oct. 2004. Vol. 49 (10). Pp: 701-3

6- Ganesh, S. *et al*. New generation of or dispersible tablets: recent advances and future prospects. International Journal of Advances in Pharmaceutical Sciences. 2011. Vol. 2. Pp: 17-28

7- Tanmy, G.; Amitava, G. and Devi, P. Areview on new generation orodisper sible tablets and its future prospective. Int J. Pharm Pharm Sci. 2011. Vol. 3 (1). Pp: 1-7

8- Koizumi, K.; Watanabe, Y.; Monita, K. and Utosuchi, N. New method of preparing high porosity rapidly saliva soluble compressed tablets using mannitol with camphor, a subliming material. Int J. Pharm. 1997. Vol.152. Pp: 127–31.

9- Jaysukh, J.H.; Dhaval, A. and Kantilal RV. Orally disintegrating tablets: a review. Trop J Pharm Res. 2009. Vol. 8 (2). Pp: 161

10- Shobhit, K.; Satish, K. and Pramod, KS. A review on recent trends in oral drug delivery- fast dissolving form ulation technology. Advan. Biol. Res. 2012. Vol. 6 (1). Pp: 06-13

11- Yourong, F.; Shicheng, Y.; Seong, HJ; Susumu, K. and Kinam, P. Orally fast disintegrating tablets: developments, technologies, taste-masking and clinical studies. Therapeutic Drug Carrier Systems. 2004. Vol. 21(6). Pp: 433– 475

12- Sweetman, S. and ed.Martindale, the complete drug reference. London: Pharmaceutical Press. 2007. Vol. 1241-1242.

13- Katzung, B. Basic and clinical pharmacology. Lange Medical Books/ McGraw-Hill, 8th edition. 2001. Vol. 155-178. Pp: 245-264.

14- Rao, P.R.; Reddy, M.N.; Ramakrishna, S. and Diwan, P. Comparative in-vivo evaluation of propranolol hydro chloride after oral and transdermal administration in rabbits. European Journal of Pharmaceutics and Bioph armaceutics. 2003. Vol. 56. Pp: 81-85.

15- Koizumi, K.; Watanabe, Y.; Morita, K.; Utoguchi, N. and Matsurnoto, M. New method of preparing high porosity rapidly saliva soluble compressed tablets using mannitol with camphor,

asubliming material. International Jour nal of Pharmaceutics. 1997. Vol.152. Pp: 127-131.
16- British Pharmacopoeia Commission. Powder flow. London, UK: British Pharmacopoeia Commission. Appen dix XVII N. 2007.
17- Shivanand, P.; *et al*. Development and in vitro evaluation of propranolol hydrochloride based gastro-retentive floating tablet. Der Pharmacia Lettre . 2010. Vol. 2 (1). Pp: 75-86
18- Hisakadzu, S. and Yunxia, B. Preparation, evaluation and optimization of rapidly disintegrating tablets. Powder Technology. 2002. Vol. 122. Pp: 188-198.
19- Rahul, C.; Zahra, H.; Farhan, A.; Alan, MS. and Afzal, RM. The role of formulation excipients in the develop-ment of lyophilized fast-disinte grating tablets. European Journal of Pharmaceutics and Biopharmaceutics. 2009. Vol.72. Pp: 119-129.
20- Mohsin, A. A.; Nimbalakr, N. E.; Sanaullah, S. and Aejaz, A. Formu-lation and evaluation of mouth dissolving tablets of amitriptyline hydrochloride by direct compression technique. Interna tional Journal of Pharmacy and Pharmaceutical Sciences. 2010. Vol. 2(1). Pp: 204 - 210.
21- World Medical Association Declara tion of Helsinki. Ethical principles for medical research involving human subjects. Adopted in the 18th WMA General Assembly and subsequent amendments. 1964.