Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 5, Suppl 2, 2013

Research Article

FORMULATION OF PRIFINIUM BROMIDE AND PRIFINIUM BROMIDE –DICLOFENAC SODIUM COMBINATION AS ORODISPERSIBLE TABLETS

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Received: 03 Mar 2013, Revised and Accepted: 13 Apr 2013

ABSTRACT

Oro-dispersible tablets (ODTs) are solid dosage forms that are designed to be placed in the mouth, disintegrated in the saliva, and then swallowed without the aid of additional water in less than one minute; thus, enhance patient compliance especially for paediatrics and geriatrics. The aim of this study was to develop a simple and inexpensive method of manufacturing ODTs of Prifinium Bromide (PBr) using direct compression method and study the effect of different types and concentrations of superdisintegrants (SD) and diluens on the tablets characteristics. Then a combination of Prifinium Bromide-Diclofenac Sodium (PBr-DcNa) ODTs was to be prepared using the best formula of PBr ODTs.

Different formulas of PBr were prepared using different types and concentrations of SD as well as different diluents. The resulted tablets were evaluated to select the best formula especially regarding disintegration and dissolution. Then a combination of PBr-DcNa formula was prepared using the best PBr ODTs and evaluated.

Results showed that the formula contained crosscaramellose sodium (CCS) as SD, Avicel-mannitol combination as diluents gave the best results concerning disintegration (12), dissolution where total drug release was achieved in 2 minutes , and physical characteristics of the resulted tablets. In addition, combination of the two drugs was successful. No interaction between the two drugs was detected and the combination orodispersible tablets showed high release of both drugs (> 80%) in pH 6.8 in 20 minutes.

Keywords: Orodispersible tablets, Prifinium bromide, Diclofenac sodium, Superdisintegrant, Direct compression, Combination therapy.

INTRODUCTION

Solid dosage forms are convenient to patients as they are self-administered, medication is already in a distinctive measure, and therefore, accurate dose is given. They are also easier to package, distribute, and store.[1] One of the disadvantages of solid dosage forms is that particular classes of patients including geriatrics and paediatrics have difficulty in swallowing tablets or capsules. Furthermore, conventional tablets usually take longer time for disintegration, dissolution and drug absorption.[2]In view of that, scientists have developed Oro-dispersible drug delivery system, offering the convenience of a solid dosage form with the rapid onset of action[3]

Many processes are usually applied in the development of ODT. The most widely used methods are: Freeze drying, molding and conventional methods which include: direct compression, wet granulation and dry granulation.[4]

Oro-dispersible tablet (ODT) is "A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue.[25]

Despite the advantages and the wide acceptance of ODTs in the market, many factors should be taken in consideration in their development process. Fast disintegration is the major specification of ODT which is attributed to quick access of water into tablet matrix resulting in rapid disintegration. Therefore, the basic approaches to develop ODTs include the use of highly water-soluble excipients, incorporating the appropriate disintegrating agent(s) and maximizing the porous structure of the tablet matrix.[5,6]

In addition, the physicochemical and organoleptic properties of the active drug substance such as solubility, chemical stability, and taste along with the intended dose can potentially affect the performance of ODTs.[7]

Combination therapy has been used to maximize therapeutic outcomes and enhance patients' compliance. For employers and healthcare insurers, it reveals that the combination therapy is more economic regarding packaging needed and less time consuming for the manufacture of products; which provides an industrial rationale for producing such combinations.[8]

Prifinium Bromide is an anticholinergic drug used to relieve smooth muscle spasms. Diclofenac Sodium (DcNa) is a non-steroidal anti-inflammatory drug (NSAID) with analgesic activity [26]

From a clinical therapeutics point of view, the rationale for using drug combinations to obtain a greater therapeutic effect with the combination that can be achieved with either drug alone and to obtain the same therapeutic effect as could be obtained with only one of the two drugs, but with fewer deleterious side effects or dose-limiting toxicities. Presumably, an ideal combination therapy would accomplish both of these goals.[9]

The aim of this study is to formulate directly compressible rapidly disintegrating tablets of PBr and investigates different factors affecting the formula like the effect of diluents, the type and concentration of superdisintegrant (SD) on the characteristics of the resulted ODTs, and perform physical and chemical evaluation of the prepared formulas. Also, to prepare ODTs that contain combination of PBr and DcNa for the use in diseases that need anticholinergic beside analgesic effect.

MATERIALS AND METHODS

Materials

PBr, DcNa, Crospovidone (CP), Mannitol, Lactose, Dibasic calcium phosphate (DCP), Aspartam, Magnesium Stearate (MgSt) and Mint flavor were kindly supplied by Hikma Pharmaceuticals. Avicel® PH102 (AZ Chem for chemicals, Germany). VIVA Sol® Crosscarmellose Sodium, VIVA Star® Sodium Starch Glycolate and VIVA Pharm®. Banana and Pineapple flavors (Bell Flavors & fragrances, Germany). Hydrochloric Acid 37% (Biosolve chimie SARL, France), and chloroform (VWR® Prolabo, EC).

Methods

Formulation of PBr ODT

Different formulas of ODT were prepared by accurately weighing the active pharmaceutical ingredient (API) and other excepients. Composition of each tablet is given in table 1 and the batch size was 200 gm.

The weighed PBr was added to diluent(s), SD, sifted colloidal silicon dioxide (Aerosil™), in polyethylene bag and mixed manually for

about two minutes. Then flavour and sweetener were added and mixed again for two minutes. The resulted mixture was passed through sieve no. 1.5 and the sifted materials were mixed again for about two minutes. Then, sifted magnesium stearate (Mg St) was added to the previous combination and mixed for about one minute. The obtained powder blend was directly compressed into tablets on a rotary tablet press (Cadmach® compression machine, India) using 9.7mm flat bevelled bisected upper punch and plain lower punch.

Table1: The Prepared Formulas of PBr ODT

Ingredient (weight in mg)	Formula code													
	AC1	AC2	AC3	AP1	AP2	AP3	AS1	AS2	AS3	MC2	LC2	AMC2	ALC2	ADC2
PBr	15	15	15	15	15	15	15	15	15	15	15	15	15	15
CCS	10	15	20							15	15	15	15	15
CP				10	15	20								
SSG							10	15	20					
Aspatam	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Falavour	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Avicel	165	160	155	165	160	155	165	160	155			80	80	80
Mannitol										160		80		
Lactose											160		80	
DCP														80
Aerosil	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Mg stearate	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total wt.(mg)		200	200	200	200	200	200	200	200	200	200	200	200	200

CCS=Crosscaremellose, CP=Crosspovidone,SSG= sodium starch glycolate, Avicel=microcrystalline cellulose, DCP = dibasic calcium phosphate, Aerocsil™=colloidals silicone dioxide.

Physicochemical evaluation of the compressed tablets

These tests include: tablet appearance, uniformity of weight, tablet thickness, hardness and friability, wetting time, disintegration time, content uniformity and dissolution test in simulated gastric fluid (SGF)pH2.1 and phosphate buffer pH 6.8.

Wetting time was performed as follows: A piece of filter paper (Whatman® number1 filter paper 10.75 X 12.00 mm) folded twice was placed in small petridish containing 6 ml of water. A tablet was put on the paper and the time for complete wetting was measured.[10,11]

While in measurement of disintegration time, one tablet was placed in a petridish (10 cm diameter) containing 10 ml of phosphate buffer pH 6.8 at 37 ± 0.5 °C. The time required for complete dispersion of the tablet was measured.[12]

Drug content was measured spectrophotometrically at λ max. 245nm after the construction of calibration curves at pH 6.5 using phosphate buffer.(Spectrophotometer: Jasco V530, Japan). This test was performed according to the requirements of USP[13] on the selected formula as the best basing on wetting and disintegration tests.

Dissolution test was performed according to USP 32 paddle method (apparatus (Erweka DT600, Germany), where the dissolution test jar contained 900 ml of dissolution medium with temperature kept constant 37.5± 0.5 °C and 100 rpm [13]. Dissolution test was performed at pH 2.1 and pH 6.8.

Compatibility of PBr and DcNa

Thin Layer Chromatography (TLC)

Qualitative analytical TLC was performed to investigate the possibility of any interaction between PBr and DcNa by measuring the retardation factor (Rf) value of each drug separately and in combination. Three samples were prepared as follows: Sample (P) solution prepared by dissolving PBr in 0.5ml Methanol; Sample (D) solution prepared by dissolving DcNa in 0.5ml Methanol; And sample (DP) solution prepared by dissolving PBr- DcNa mixture in 1ml Methanol. Samples then applied as a spot on a 1cm distance from the origin of the silica gel plate. After evaporation of the sample solvent, the plate is placed in a sealed chamber that contains Chloroform-Methanol (9:1) mixture as a mobile phase. Development occurs as the mobile phase moves up the layer by capillary forces. Then the retardation factor (R_f) was calculated as in equation 1:

Equation 1: R_f = Distance travelled by substance/Distance travelled by solvent

Differential Scanning Calorimetriy (DSC)

Thermal analysis of PBr and DcNa, was carried out using DSC apparatus (DSC283e Mettler Toledo, Switzerland).

Each of the API was scanned individually and then the PBr-DcNa mixture was also analyzed. Each sample was weighed and subjected to heat range from 25°C to 300°C at a heating rate of 10°C/min under a (80 ml/min) flow of nitrogen.[14]

Ultraviolet (UV) spectrophotometer

PBr and DcNa were first scanned individually, and then PBr-DcNa mixture solution was scanned using UV spectrophotometer in a wavelength range of 200-400 nm.

The results were compared and analyzed to check if there is any interaction between the two compounds.

Formulation of PBr– DcNa Combination as ODTs

After investigation of the properties of different PBr formulas. The selected PBr ODT formula with the best physical and chemical evaluation results was chosen to prepare PBr – DcNa combination as ODT In which the weight of DcNa, 25 mg, was subtracted from the weight of diluents, keeping the weight of each formula constant (200 mg). The powder blend was prepared by the same method as in PBr ODT and compressed using the same machine.

Stability study

Short term stability studies were performed on the selected PBr ODTs (AMC2) at accelerated stability conditions (40 ± 2 °C and 75 ± 5 % relative humidity (RH) for three months) [10,15]

The stability study of the combination formula was carried out at (40 ± 2 °C and 75 ± 5 % RH for one month).[16,17]

The tablets were stored in airtight containers with a tight lid and were kept in the incubator (Memmert HCT 108, Germany).

This evaluation is based on detecting chemical changes of tablets by measuring drug content pre and post exposure to the extreme conditions.

RESULTS AND DISCUSSION

Physicochemical evaluation of the compressed tablets

Appearance, weight variation, hardness and friability

Physical examination of tablets of each formula after compression showed white sheen, circular bisected tablets, with no sticking, capping or broken edges.

The average weight of ten tablets from each formula of PBr ODT was measured individually. For the tablet to be accepted, each unit should lie within the range of 85% to 115% of the label claim.[13] All the tested tablets passed the uniformity of weight test as shown in table 2.

During the preparation of PBr ODTs, the weight and hardness had been considered as controlling factors (constant values), while other test parameters were considered as response variables. Evaluation of the tablets' properties depends on comparing results of the response variables for the different formulas.

As illustrated in table 2, values of hardness were all accepted for ODT and the percentage of friability was less than 1%.[18]

Wetting and disintegration time

Wetting time is considered an indicator for the porosity of tablets' structure and the hydrophilicity of their ingredients.[10] Wetting time of PBr ODT is demonstrated in table 2 and figure 1.

Effect of the type and concentration of SD [Formulas (AC1- AP3) table1]

- Formulas containing CCS showed a relatively short wetting time (12.2-19.3) seconds, this is due to the fact that CCS rapidly swells to 4-8 times of its original volume on contact with water.[19] Formulas containing SSG also showed a short wetting time (12.3-21.8 sec) by rapid uptake of water followed by rapid and enormous swelling. While formulas containing CP showed a little increase in the wetting time (22.5- 28.3 seconds) which is due to that CP draws water mainly by wicking mechanism. The flow of water in the capillaries of SD as being twisted after compression takes little longer time to reach all parts of the tablet.[20] However, the wetting time is still within the acceptable value.

- The wetting time was decreased by increasing the concentration of SD from 5% to 7.5%; however, further increase to 10% causes a slight increase in the wetting time in all the three types of SDs used. This could be due to reduction in the capillary action, which may be due to the blockade of the pores of the formulation with the increase in concentration of SD and forming of gel like structure that hinders more water sorption.

Effect of Diluents [Formulas (MC2- ADC2) table 1]

The effect of diluents on wetting time was studied by formulating (MC2) and (LC2), using mannitol and lactose, instead of Avicel®, respectively. Then a combination of Avicel® with Mannitol, Lactose and Dibasic Calcium Phosphate as diluents was also prepared. The type and concentration of SD were constants (7.5% CCS).

A shorter wetting time was observed with formulas containing Avicel® as single or in combination with other diluents; this is due to the ability of Avicel® to retain a large amount of water yet allowing this stored water to be released easily.[21]

The disintegration time (DT) is a crucial factor in the success of oro-dispersible dosage form. Therefore, the formula with the shortest *in vitro* DT was selected to be tested for dissolution tests and stability study.

The *in vitro* disintegration times of PBr ODT after incorporation of varied concentrations of super disintegrants and diluents are illustrated in table 2.

- Formulas (AC1, AC2, AC3) containing CCS as SD, in concentration (5, 7.5 and 10%) respectively, gave short and very acceptable disintegration time profile in the range of 11.3- 12.3 seconds. The cross linking of CCS allows water absorption many times its weights of water, causing increase in hydrostatic pressure that breaks the interparticular forces formed during compression. As direct compression is a dry process, the high water absorption ability of CCS serves to perform the disintegration process very quickly.[22]Increasing the concentration of CCS from 5% to 10% showed no significant increase or decrease in DT ($P < 0.05$) indicating that this range of SD concentration is acceptable in this formulation.

- Formulas (AS1, AS2, AS3) containing SSG as SD, in concentration (5%, 7.5% and 10%) respectively, showed also rapid disintegration time. Combining the effect of cross linking and hydrophilicity of starch result in rapid uptake of water that results in rapid breaking of the interparticular forces. DT of the three formulae using SSG as SD did not show significant differences from those of CCS formulas. ($P < 0.05$).

- Formulas (AP1) and (AP2) containing CP as SD in 5% and 7.5% respectively, showed little longer disintegration time. However, increasing the concentration of CP to 10 % in (AP3) showed improvement in the disintegration time with 14.3 seconds. Nevertheless, CP is reported to be efficient superdisintegrant that absorbs water by wicking mechanism.[23]

Formula AC2 containing 7.5 % of CCS as SD, has been chosen as the best formula to test the effect of other diluents.

Table 2: Weight variation, hardness and friability of the compressed ODTs.

FormulaCode	Wt. of tablet (gm)	Hardness (N)	Friability (%)	Wetting time(sec)	In vitro DT (sec)
AC1	0.209±0.05	36.3±0.57	0.46	16.97±4.38	12.3±0.6
AC2	0.208±0.04	36±1	0.22	12.27±0.84	11.3± 0.6
AC3	0.209±0.02	49.3±2.08	0.22	19.33±1.82	12±1
AS1	0.203±0.06	33±3.06	0.25	13.17±1.01	11.3±0.6
AS2	0.207±0.03	36±2	0.27	12.3±0.87	12.3±0.6
AS3	0.208±0.06	34±2	0.24	21.80±1.64	12.3±1.2
AP1	0.200±0.01	38±1	0.24	22.5±5.31	24.3±5.9
AP2	0.208±0.02	39.3±1.5	0.24	23.00±2.96	25±1
AP3	0.208±0.06	34±2	0.24	28.23±5.9	14.3±2.1
MC2	0.206±0.03	38±1	0.23	62.47±9.9	78±6.2
LC2	0.206±0.01	40.67±3.21	0.24	177.87±10.35	86±9
AMC2	0.208±0.02	35±3.05	0.52	33.40±2.08	12.7±0.58
ALC2	0.205±0.02	35±3.6	0.23	44.33±2.08	22.3±0.6
ADC2	0.202±0.04	39±3.6	0.24	25.60±1.71	13.6±1.2

Effect of diluents on DT is shown by examining the results of formulas AC2,MC2 LC2,AMC2, ALC2 and ADC2. Avicel proved to be the best diluents that helps absorption of water. However Avicel alone gives the tablets gritty structure and taste. Combination the advantage of water absorption of Avicel with the good taste and mouth feeling of mannitol that lacks high water absorption capacity gives very accepted DT of 12.7 ± 0.58 seconds.

***In vitro* disintegration time / wetting time correlation**

The wetting time was correlated with the disintegration time to see if it can be used as indicative parameter to the disintegration time. As demonstrated in figure 1 there is a direct relationship between wetting time and the *in vitro* disintegration time, with a correlation coefficient = 0.8619.

Content uniformity

The uniformity of dosage units reflects good mixing process; this is important to ensure that an effective dose in each tablet is delivered. Ten tablets of formula AMC2 were chosen randomly to perform content uniformity; the content of PBr was measured using UV spectrophotometer at λmax 245nm. The tablets pass the content uniformity test when the amount of active ingredient in each of the ten tablets lies within the range of (85-115%) of the labelled claim according to USP,[13]Table 3 illustrates these results.

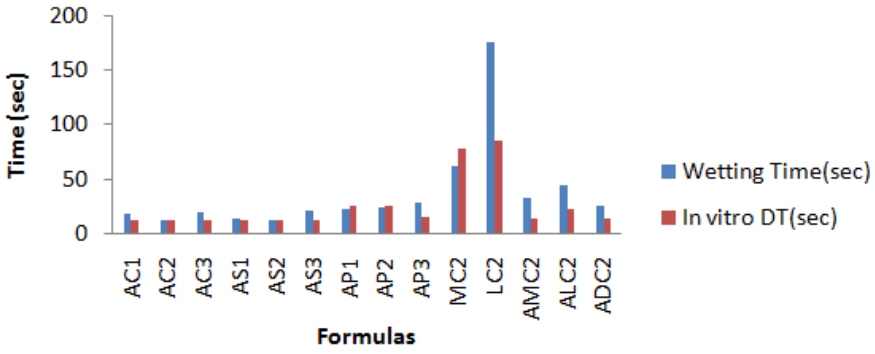

Fig. 1: Wetting time vs. DT in seconds of the prepared formulas.

Table 3: Content uniformity result of the selected formula (AMC2)

Number of samples tested	Mean content PBr	Minimum content PBr	Maximum content PBr	Standard Deviation
10	105.43%	102.87%	108.13%	2.18

***In vitro* Drug Release (Dissolution test)**

The *in vitro* drug release of the selected formula AMC2 was performed according to USP requirements to test the behaviour of PBr in ODT in the intestine using buffer pH 6.8 and in the stomach using SGF pH2.1.

Results represented in figures 2 and 3 shows the fast drug release in both media where more than 99 % of drug was released from the tablet in the first two minutes. This will ensure that the drug is soluble at the site of absorption and fulfils the aim of ODTs.

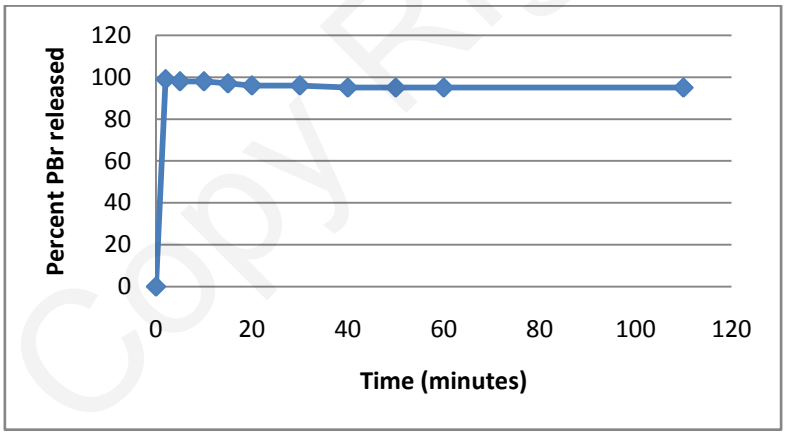

Fig. 2: *In vitro* release of PBr from formula AMC2 in phosphate buffer pH 6.8

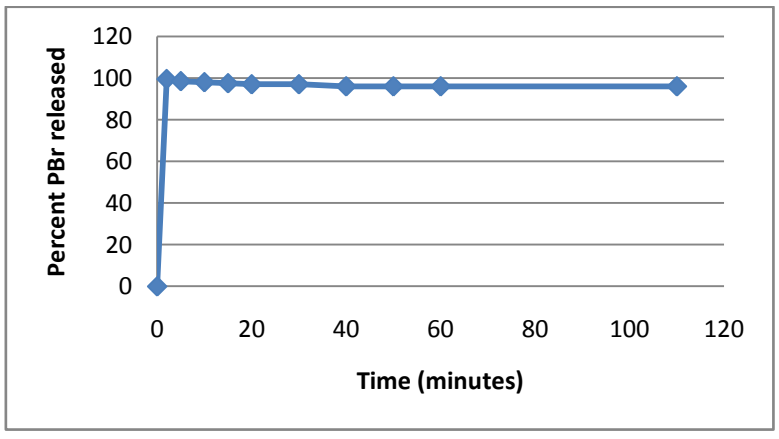

Fig. 3: *In vitro* release of PBr from AMC2 in SGF pH2.1.

Compatibility of PBr and DcNa

Thin Layer Chromatography (TLC)

According to the analytical TLC chromatogram shown in figure 4 and table 4, the retardation factor R_f value of pure drugs PBr and DcNa were almost the same as in PBr- DcNa combination. This also indicates the absence of chemical interaction between PBr and DcNa.

DSC analysis

The DSC studies were carried out to investigate the possibility of any interaction between PBr and DcNa. Thermal analysis of PBr and DcNa is shown in figure 5 in which endothermic peaks for pure PBr and pure DcNa were obtained; these peaks correspond to the melting points of PBr and DcNa, respectively.[23,24]

In PBr- DcNa combination, two endothermic peaks were obtained corresponding to the melting point of the two compounds with no additional peaks, which indicates no interaction between the two compounds has taken place.

Ultraviolet (UV) spectrophotometer

The presence of two peaks in the UV absorption spectrum of solution containing PBr-DcNa combination at λmax 245nm and λmax 275nm indicates the presence of PBr and DcNa, respectively with no additional peak indicating no chemical interaction between them as shown in Figure 6 (c).

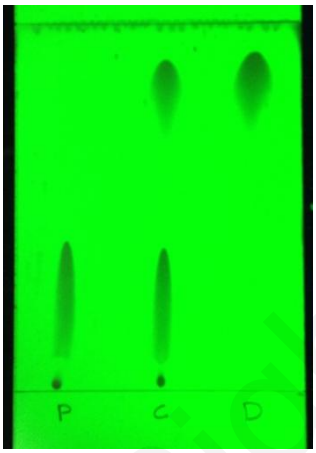

Fig. 4: Analytical thin layer chromatography chromatogram under UV 254nm light using silica gel as adsorbant and Chloroform- Methanol (1:2) mixture as the mobile phase. (P= PBr, C= PBr- DcNa Combination, D= DcNa)

Table 4: R_f values of BPr and DcNa separately and in combination

Drug	R_f value
PBr	0.227
DcNa	0.77
PBr in PBr-DcNa mixture	0.227
DcNa in PBr-DcNa mixture	0.73

Fig. 5: DSC thermogram of DcNa, PBr- DaNa combination and PBr.

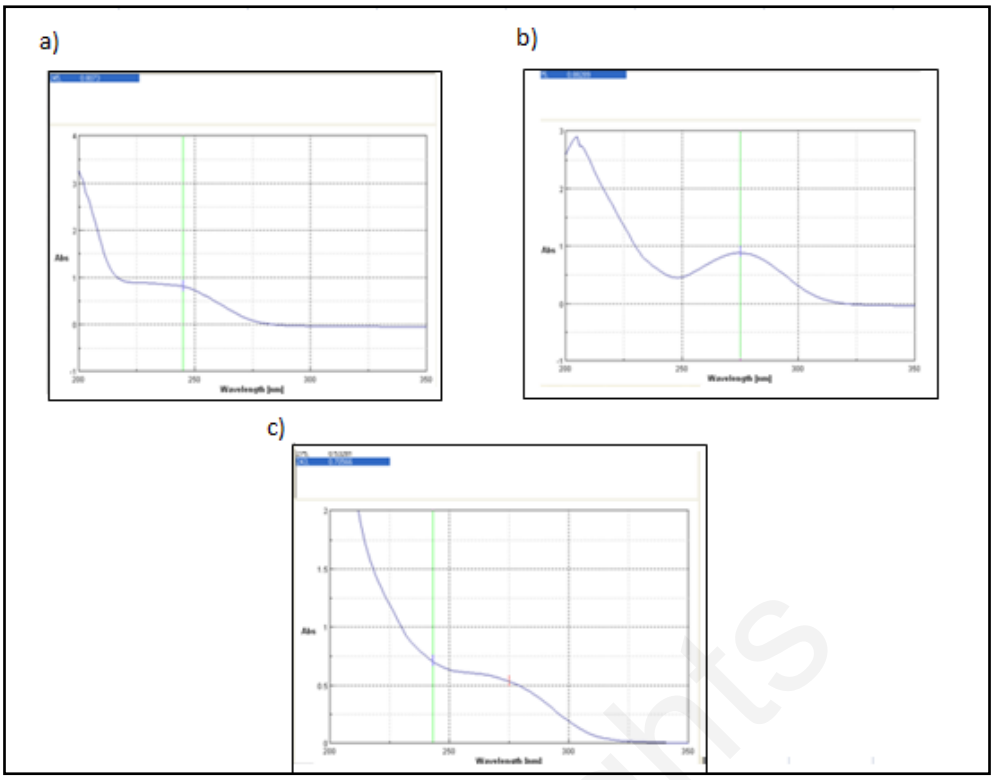

Fig. 6: UV spectrum analysis of a) PBr b) Dc Na c) Combination of PBr and Dc Na

Evaluation of PBr-DcNa ODT

The combination formula in which DcNa was added to formula AMC2 was evaluated. The tablets passed weight variation test with average hardness 30± 0.9 Newton and friability 0.75%. They also passed content uniformity test for both drugs (PBr percent content 85.2%, max. 108.64 % with SD= 8.5% while for DcNa, min 86.67%, max. 104.13% and SD= 6.3%)

In- vitro Disintegration time

The combination formula showed DT about 5 minutes which is relatively long as ODT. Thus, the amount of SD was increased to 10 % to give disintegration time 56 sec.

DcNa is sparingly soluble in water[18], this justifies the long disintegration time of the tablets containing DcNa. It might interfere with the quick wetting and water absorption mechanism. Increasing the amount of SD could overcome this elongation.

In-vitro Drug Release (Dissolution test)

Dissolution of PBr was tested in SGF pH 2.1 and dissolution of both drugs was tested in pH 6.8 because DcNa shows very low solubility in acidic media.

Results of dissolution tests showed that almost total release of PBr occurred within 20 minutes in SGF pH 2.1 and in phosphate buffer pH 6.8 and more than 85% of DcNa was released at pH 6.8 which is acceptable for oral tablets. This difference is attributed to the higher solubility of PBr.(figures 7 and 8)

Stability Study

The results of stability study indicated that there was no decrease in PBr content in ODT (formula AMC2) compared to initial reading (102.8 %). These results indicated that PBr was stable during three months of exposure to accelerated conditions (40 ± 2 °C and 75 ± 5 % RH) for three months (Figure9). The results also indicated that PBr and DcNa (combination formula) were stable during one month of exposure to 40 ± 2 °C and 75 ± 5 % RH for 31 days (Figure 10).

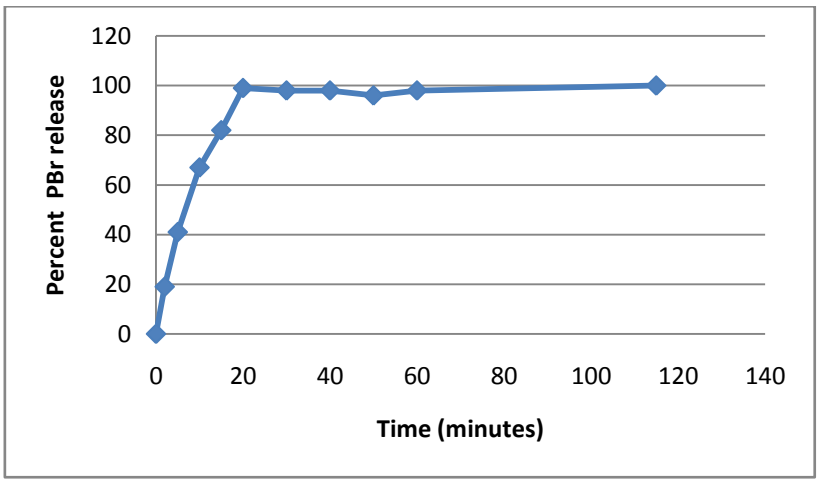

Fig. 7: *In vitro* drug release of PBr in the combination formula in SGF (pH 2.1)

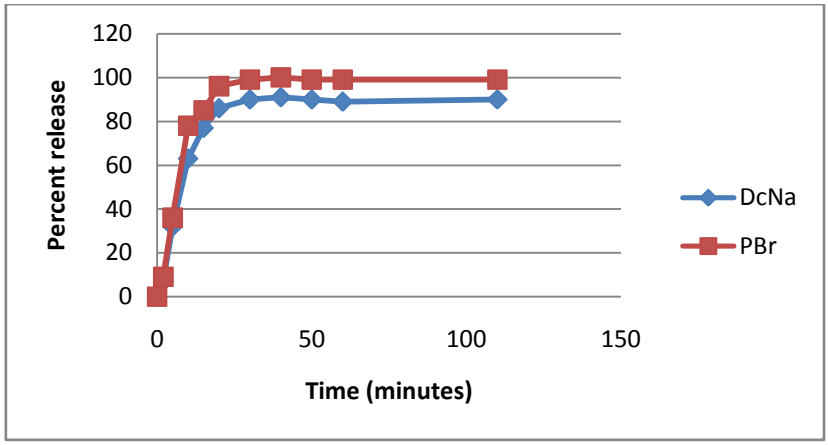

Fig. 8: *In vitro* drug release of PBr and DcNa in combination formula in phosphate buffer pH 6.8

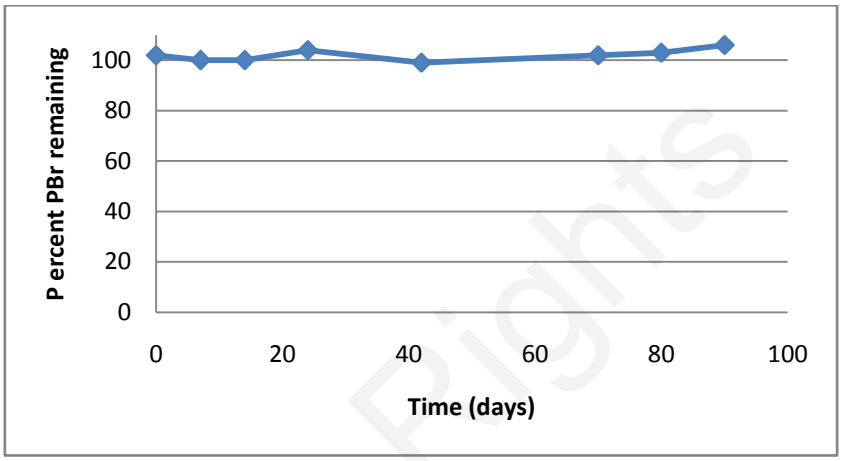

Fig. 9: Percentage of PBr remaining in formula AMC2 after exposure to 40 ± 2 °C and 75 ± 5 %RH for 3 months.

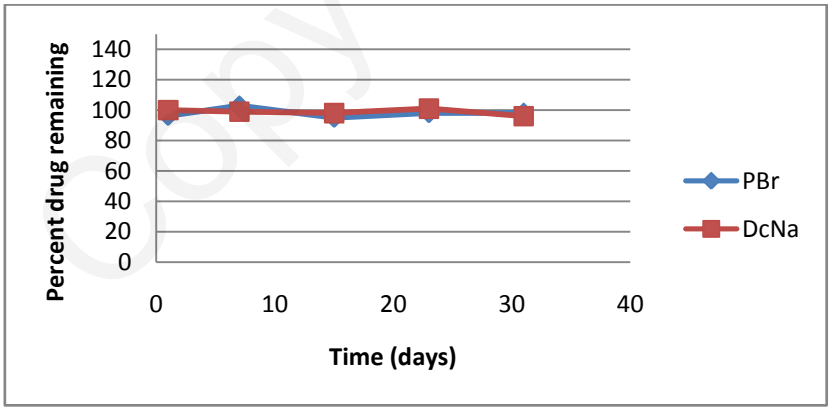

Fig. 10: Percentage of PBr and DcNa remaining in combination formula after exposure to 40 ± 2 °C and 75 ± 5 % RH for 31 days.

CONCLUSION

Prifinium Bromide was successfully formulated as ODT by direct compression method using CCS as SD, and combination of Avicel® and Mannitol as diluents. The *in vitro* DT of the best selected formula (AMC2) was 12.7 ± 0.58 seconds. The percentage of PBr released after two minutes was 99.96 % ± 0.05 in phosphate buffer pH 6.8.

Combination of PBr and DcNa was successfully formulated as ODT with disintegration time 56.3± 2.1 seconds and about 80 % of PBr and DcNa was released in phosphate buffer pH 6.8 within 20 minutes.

ACKNOWLEDGEMENT

The authors would like to thank Al-Hikma Pharmaceuticals in Jordan for their cooperation and support of this work.

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