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Original Article

TASTE MASKING OF PRIFINIUM BROMIDE IN ORODISPERSIBLE TABLETS

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ABSTACT

Objective: In previous work, Prifinium Bromide had been successfully formulated as oro-dispersible tablets. However, Prifinium Bromide, a quaternary ammonium compound, has a bitter taste; therefore, taste masking was necessary to produce acceptable oro-dispersible tablets and enhance patients' compliance.

Methods: In this work, several attempts had been made to mask the bitterness of this drug. β-cyclodextrin inclusion complexes, solid dispersions of the drug in ethyl cellulose and methyl cellulose as well as loading the drug on Eudragit E100 have all been used. The selected granules were used to prepare oro-dispersible tablets and were evaluated.

Results: Drug-Eudragit granules E3 prepared by mass extrusion method gave less than 10% of drug in simulated saliva fluid and almost complete release in simulated gastric fluid after 2 minutes. Therefore, it was used to prepare oro-dispersible tablets formulas. In vitro disintegration time of formula T2 was 45.5 ± 7.7 seconds showed a complete drug release of Prifinium Bromide in phosphate buffer (pH 6.8) and (94%) in SGF (pH 2.1).

Conclusion: Loading of Prifinium Bromide on Eudragit E100 using mass extrusion method was the best method to overcome the disagreeable taste of the drug. They gave the least amount of drug released in simulated saliva fluid and passed the quality control tests of tablets after formulation as oro-dispersible tablets. They also gave good taste when tested in vivo.

Keywords: Prifinium Bromide, Orodispersible tablets, Taste masking of active ingredient, Mass extrusion method, Eudragit E100, β - Cyclodextrine.

INTRODUCTION

Oro-dispersible tablets (ODTs) entered the market in the 1980s as an alternative to tablets and other conventional dosage forms**.** ODT is defined as a tablet that disperses or disintegrates in less than one minute in the mouth before swallowing. It results in quick dissolution and rapid absorption, which provide rapid onset of action. It also provides an advantage particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules [1].

There are some challenges in the formulation and production of successful ODTs like the fast disintegration, tablet strength and porosity, moisture sensitivity, amount of drug and the size of tablet in addition to the drug organoleptic properties like solubility, stability and taste [2]. For drugs having disagreeable taste, several taste masking techniques were introduced to overcome this problem. Addition of Sweeteners and flavors is a well known technique that uses artificial sweeteners instead of natural sugars. Saccharin Sodium, Aspartame, Sucralose have all been used as sweeteners [3].

Layering process is another technique used to overcome the disagreeable taste of active pharmaceutical ingredient (API) which involves deposition of serial layers of API onto the granules of an inert starter seeds such as sugar spheres or microcrystalline cellulose beads and using a polymer that's usually not dissolve in pH of saliva [4],[5]

Taste masking could also be achieved by granulation to decrease the surface area subjected to the taste buds. [6]. Spray drying, on the other hand, serves to coat the API particles with polymers as done by Dionysios, *et al*. Where Cetirizine HCl taste-masked ODT using Eudragit® RL30-D in different ratios were prepared using a fluidized bed coating machine. [7].

Complexation is used to mask the bitter taste of API by either decreasing its oral solubility on ingestion or decreasing the amount of drug particles exposed to taste buds thereby reducing the perception of bitter taste [8]. Cyclodextrin is one of the widely used complexing agent in masking taste by inclusion complexes [9].

Other approaches are coaservation phase separation [10], ion exchange resins [11], solid dispersions [12] and extrusion method [13] have all been used to mask the disagreeable taste of the API.

The aim of this study is to develop a successful method to cover the bitter taste of previously prepared Prifinium Bromide (PBr) ODT [14] by trying different techniques and the preparation of a taste masked ODT using a previously prepared formula.

MATERIALS AND METHODS

Prifinium Bromide, Mannitol, Ethocel, Aspartam, Sucralose, Magnesium Stearate and Mint flavor were kindly supplied by Hikma Pharmaceuticals. Eudragit E100 (Evonik industries, Germany). β-Cyclodextrin (Sigma- Adrich, USA).

Avecil® HFE- 102 (AZ Chem for chemicals, Germany). VIVA Sol® Crosscarmellose sodium, VIVA Star®, HPMC hypromellose (JRS Pharma GMBH & Co., Germany). Banana and Pineapple flavors (Bell Flavors & fragrances, Germany).

Compatibility study

The compatibility of PBr with each of the used polymers (ethylcellulose, methylcellulose, mixture of ethyl and methyl cellolose, β-cyclodextrin and eudragit E100) has been investigated using differential scanning calorimetry (DSC). Each of the mentioned materials was scanned individually and then the PBr -polymer loaded granules were 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 [15].

Preparation of taste-masked granules

Preparation of inclusion complex

Prifinium Bromide and β-cyclodextrin were mixed in the ratio (1:3) and (1:6) (w/w) ratio to prepare granules B1 and B2, respectively, as in table 1. Ethanol 50% added with continuous mixing until a suspension is formed. The solvent was evaporated under reduced pressure by using rotary evaporator for 45 minutes. After solvent evaporation, PBr - β- cyclodextrine granules obtained where stored in a desiccator for further use [16].

Preparation of solid dispersion

Solid dispersions were made by solvent evaporation method, in which different polymers, Avecil®, Ethocel, and Ethocel- Methocel mixtures were used in different ratios as follows:

Prifinium bromide: Avicel® solid dispersion

Prifinium Bromide and Avicel were mixed geometrically, then ethanol used as solvent added drop wise with continuous mixing using mortar and pestle. Few drops of polyvinylpyrrolidone (PVP) in ethanol 5% (w/v) was added as required. The resulted dispersion was then dried in oven for 30 minutes. The obtained granules were stored in a desiccator for further use.

Prifinium bromide: ethocel solid dispersion

Taste masked granules C_1, C_2 and C_3 prepared by mixing PBr: Ethocel (1:0.1), (1:0.2) and (1:0.3) (w/w) ratio respectively as shown in table 1. Taste masked granules were prepared by same procedure of PBr -Avicel above.

Prifinium bromide: Ethocel- Methocel Mixture solid dispersion

Gupte and his colleagues proposed the use of water-soluble and water-insoluble polymers in taste masking of highly water-soluble drugs [17]. In this study, D granules were prepared by same procedure above using Ethocel mixed with Methocel (50:50) to prepare (1:0.2) (w/w) ratio of PBr: Methocel- Ethocel mixture.

Preparation of taste masked granules by Mass extrusion method

Eudragit E100 was used to prepare taste masked granules of PBr by manual mass extrusion method [6],[10]. Fixed amount of drug was mixed geometrically with different amounts of powdered Eudragit E100 in (1:1, 1:3, 1:4 and 1:5) ratios in the mortar and pestle. Then acetone was added to each mixture with continuous mixing. Thin gel was obtained from the mixture of the drug and Eudragit E100 which was manually extruded using a syringe.

After extrusion of the gel, acetone was removed by evaporation overnight and subsequently the solidified gel in the shape of strings was crushed into granules using a mortar and pestle and sieved to get a uniform size of drug- Eudragit E100 granules.

Taste masked granules E1, E2, E3 and E4 containing PBr: Eudragit E100 in ratios (1:1, 1:3, 1:4 and 1:5) respectively, were obtained as shown in table 1.

Evaluation of taste-masked granules

Drug release in Simulated Saliva Fluid (SSF)

Using phosphate buffer pH 6.2, 0.25 g of prepared granules were dissolved in 100 ml of phosphate buffer and filtered using syringe filter 0.45µm. Then, with appropriate dilution, the amount of drug release after 2, 5, 8 and 12 minutes was measured by UV spectroscopy at λmax 245nm. The percentage of drug release was calculated by equation1:

$$\text{Equation1: \% Drug release} = \frac{\text{Amount of soluble drug in buffer}}{\text{Total amount of drug in granules}} * 100$$

Drug release in Simulated Gastric Fluid (SGF)

Using 0.1N HCl, adjusted with diluted NaOH, to prepare simulated gastric fluid (SGF) pH 2.1 the same method as in SSF was performed to evaluate drug release from the taste masked granules in acidic media.

Table 1: Composition of Taste –Masked Granules

Ingredients	Taste Masked granules (mg)										
	A	**B1**	**B2**	**C1**	**C2**	**C3**	**D**	**E1**	**E2**	**E3**	**E4**
PBr	15	15	15	15	15	15	15	15	15	15	15
Eudragit E100								15	45	60	75
Methocel							1.5				
Ethocel				1.5	3	4.5	1.5				
β-cyclodextrin		45	90								
Avicel	80										

Preparation of Orodispersible tablets

The taste masked granules which gave the best evaluation results were weighed equivalent to 15 mg/tablet of PBr and were mixed with other diluents, superdisintegrant and sifted colloidal silicon dioxide (Aerosil™) in polyethylene bag and mixed manually for about 2 minutes. The flavor and sweetener were then added and mixed again for 2 minutes.

The resulted mixture was passed through sieve no. 1.5 and the sifted materials were mixed again for about 2 minutes. Then, sifted magnesium stearate was added to the previous combination and mixed for about 1 minute. The percent of each ingredient was according to the standard formula prepared previously. The obtained powder blend was directly compressed into tablets on a rotary tablet press (Cadmach® compression machine, India) using 9.7mm flat beveled bisected upper punch and plain lower punch.

Evaluation of taste-masked tablets

The tablets were evaluated for appearance, hardness, friability, content uniformity, disintegration and dissolution. Some modification on the formula has been made according to the results of some tests. Then stability of the best formula was tested in accelerated conditions (40±2 °C and 75±5% relative humidity RH).

***In vivo* Disintegration time and taste evaluation**

This test was performed on the selected formula using six healthy volunteers, who were informed precisely about the purpose of the study and the possible adverse effect of the API. Then three tablets were randomly chosen and the time required for complete disintegration of the tablet in the mouth, without biting and without drinking water, was measured. The volunteers were informed to spit the tablet and wash their mouth thoroughly.

The taste was evaluated and assigned a numerical value in a 1 to 5 scale according to the following scale 1: Distasteful. 2: Slightly Distasteful. 3: Fair. 4: Slightly Tasty. 5: Tasty [18].

RESULTS AND DISCUSSION

Compatibility study

During the preparation of complex, solid dispersion and the organogel and due to the use of solvent system each time, a possibility of chemical or physical interaction may arise. One of the known efficient methods to detect such an interaction is the DSC analysis. The following figures illustrate the DSC analysis of the taste masked granules that contain PBr and the polymers ethyl cellulose (Fig.1), mixture of ethyl and methyl cellulose (Fig.2), β-cyclodextrin (Fig.3), and Eudragit E100 (Fig.4). Thermograms show no additional peaks indication lack of chemical interaction between the drug and the polymers during granules preparation.

Evaluation of taste masked granules in SSF

The taste masked granules prepared using the above approaches in taste masking were evaluated in SSF (phosphate buffer pH 6.2) for drug release. The taste masked granules were designed to avoid

contact of the drug with taste buds; therefore a low drug release in saliva was desired.

PBr - β- cyclodextrins inclusion complexes were prepared, (B1) and (B2) in a ratio of (1:3) and (1:6), respectively. β- cyclodextrins has a cone like structure that is able to incorporate a drug molecule within its cavity bonded by a Van der Waals forces forming inclusion complex that do not dissociate in saliva but are biodegradable in intestine releasing the drug and then be eliminated from the body unchanged [19].

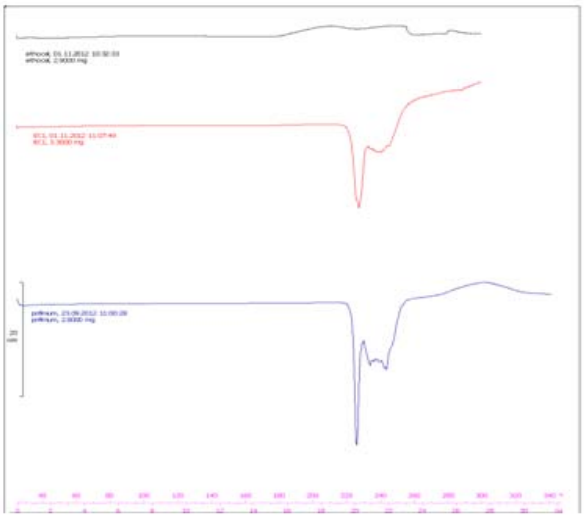

Fig. 1: DSC thermogram of Ethylcellulose (Ethocel), C1 (PBr-ethylcellulose granules) and PBr

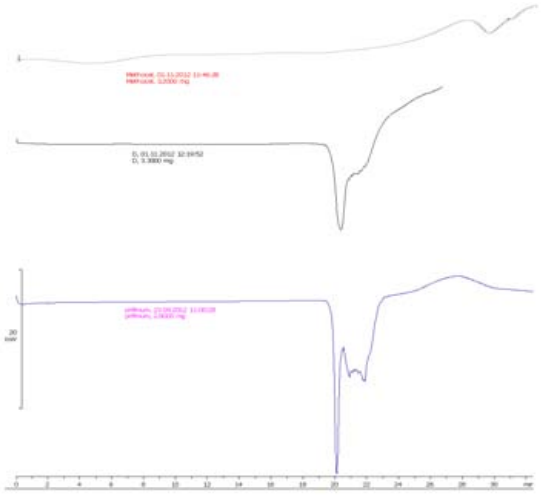

Fig. 2: DSC thermogram of Methylcellulose (Methocel), D (PBr-methylcellulose- ethylcellulose granules) and PBr.

According to the evaluation of taste-masked granules shown in table 2, the inclusion complexes were unstable or not completely formed which results in a rapid release of the drug. The taste masked granules B1 and B2 showed 48% and 97% drug release, respectively, in SSF after 2 minutes. This may be due to the fact that PBr has a strong hydrophilic area on the charged nitrogen atom that might be unable to be adapted by the inner surface of β- cyclodextrin cone that is a hydrophobic area. Further studies may be needed to investigate different possibilities of drug- β- cyclodextrins interaction. So far, this method was found to be ineffective to control the bitter taste of PBr.

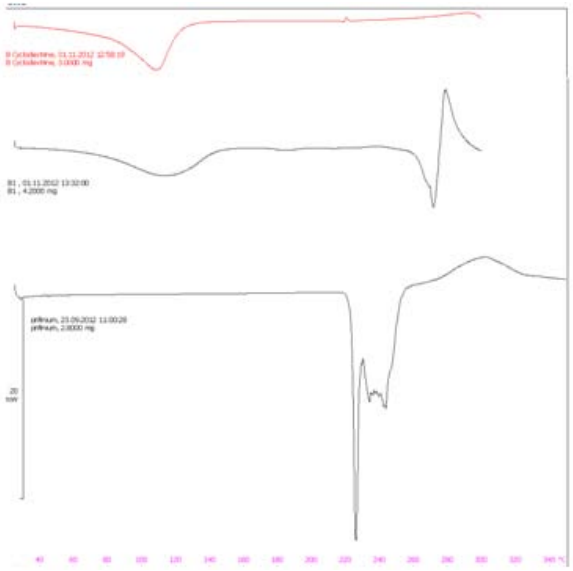

Fig. 3: DSC thermogram of β- cyclodextrin, B1 (PBr- β-cyclodextrin granules) and PBr

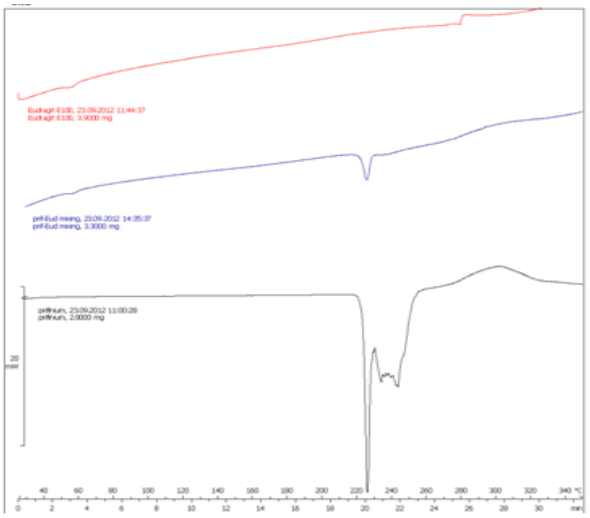

Fig. 4: DSC thermogram of Eudragit E100, E3 (PBr-Eudragit E100 granules) and PBr

Solid dispersions of PBr with the chosen polymers did not show efficient depletion of drug release in SSF. In all types prepared there was lack of sufficient bonding mechanisms between drug and the polymer which resulted in quick drug release in SSF. Thus, they would be inefficient to escape the mouth during and after disintegration of the tablet. This could be due to the fact that PBr is highly water soluble and may require an efficient coating technique to cover the particles completely and avoid contact with taste buds (Table2).

PBr-Eudragit E100 granules prepared by mass extrusion method 1:4 (E3) gave the least drug release in SSF (less than 10%) with higher release when less ratios were used, and no further decrease when higher ratios were used. (Table 2) That's why E3 granules were chosen as the best granules that can control the bitter taste of PBr in mouth. While the formation of gel in mass extrusion method might result in much better drug dumping in the polymer network and also the dependency of solubility of Eudragit E100 on pH change from saliva (6.5-6.8) to acidic in stomach resulted in ability of these granules to escape the saliva media with less than 10% release of drug.

Table 2: Percent PBr Release from Taste Masked Granules in SSF.

Time (min)	% PBr release from A	% PBr release from B1	% PBr release from B2	% PBr release fromC1	% PBr release from C2	% PBr release from C3	% PBr release from D	% PBr release from E1	% PBr release from E2	% PBr release from E3*	% PBr release from E4
0	0	0	0	0	0	0	0	0	0	0	0
2	100	49	97	72	40	35	25	37	49	10	9
5	100	49	95	99	76	66	63	48	48	15	19
8	100	51	115	100	88	83	104	50	49	16	28
12	100	52	105	99	90	85	95	50	50	20	29

Evaluation of taste masked granules in Simulated Gastric Fluid (SGF)

The behavior of E3 taste masked granules in stomach was detected by measuring the percentage of PBr release in SGF. The percentage of drug release in SGF and a comparison with the drug release in SSF is illustrated in fig.5. The results indicated a fast release 40 % of PBr in SGF, compared with only 9.6% of PBr in SSF after 2 minutes and more than 80% within 12 minutes. Therefore E3 taste masked granules was chosen to formulate taste masked PBr ODT.

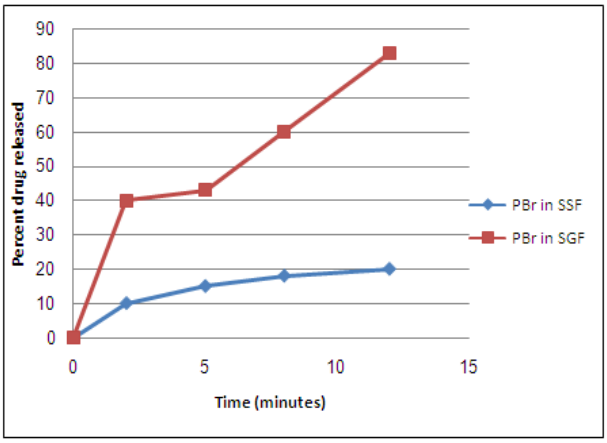

Fig. 5: Percentage of PBr release from E3 taste masked granules in SSF and in SGF.

Physicochemical evaluation of the Taste masked PBr ODTs

***In vitro* Disintegration time**

Formula T1 was prepared using E3 Taste masked granules with (1:4) ratio of (PBr: Eudragit E100) showed a long disintegration time of 160 ±5.1 seconds, which is not acceptable for ODT (Table 3) in comparison with 15 seconds of the standard formula with no taste masked granules. This may be due to the incorporation of PBr-Eudragit E100 granules, which contain polyvinyl pyrolidone (PVP) as a binding substance. After compression, there may be an increase in the bonding forces among particles causing a disruption of the porous structure and capillary characteristics of the compact powder. This may results in the long the disintegration time in formula T1.

In order to decrease the disintegration time, T1 was compressed with a decrease in compression force. A shorter disintegration time of 50 ±5.6 seconds was achieved. However, the tablet yielded was too friable and did not pass the friability test.

Therefore, Formula T2 with an increase in the percentage of crosscarmellose sodium (CCS) from 7.5% to 10% was prepared. Also other modification was made by increasing the flavor to enhance the taste acceptability. Disintegration time of T2 was 45.5 ± 7.7 seconds (Table 4) and with a hardness of 19.6N, tablets passed the friability test. Therefore, this formula was successful in meeting all the requirements of ODT and was further investigated for dissolution test, content uniformity, in vivo disintegration time test, in vivo taste evaluation and stability tests.

Content uniformity, according to USP [20], of T2 gave accepted results with minimum 85.13%, maximum 94.07 %, mean = 88.56% of claimed label with SD = 2.89%.

Table 3: Taste –masked formulas

Formula Code	PBr (gm)	CCS (gm)	EudragitE100 (gm)	Avicel (gm)	Mannitol (gm)	Aerosil™ (gm)	Flavor (gm)	Aspartam (gm)	MgSt (gm)	Total Wt. (gm)
T1	15	15	60	47	47	2	2	10	2	200
T2	15	20	60	42.5	42.5	2	6	10	2	200
Standard Formula	15	15	-	80	80	2	2	4	2	200

Table 4: Evaluation of Taste masked ODTs.

Formula Code	Weight Uniformity	Hardness (N)	Friability	In vitro disintegration time (sec)
T1	Failed	37.3± 2.5	Pass	160.7± 5
T2	Pass	20.6 ± 1.5	Pass	45±7
Standard Formula	Pass	35± 3.05	Pass	12.7± 0.58

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

Formula T2 was tested for in vitro dissolution to detect the release of PBr in pH 6.8 and in pH 2.1. After 10 minutes, it showed a complete drug release of PBr in phosphate buffer (pH 6.8) as demonstrated in fig. 6. Also in SGF (pH 2.1) high drug release was shown in same time (94%) as displayed in fig. 7. This indicates almost complete drug release in both simulated gastric and intestinal conditions.

Stability study of Taste masked ODTs

The results of stability study (formula T2) indicate that there was no decrease in PBr contents in Taste masked ODT compared to initial reading. These results indicate that PBr is stable during exposure to 40 ± 2 °C and 75 ± 5 % RH for 31 days.

And that loading of the drug on the polymer had no effect on the stability of tablets in these conditions for the specified time (Fig. 8).

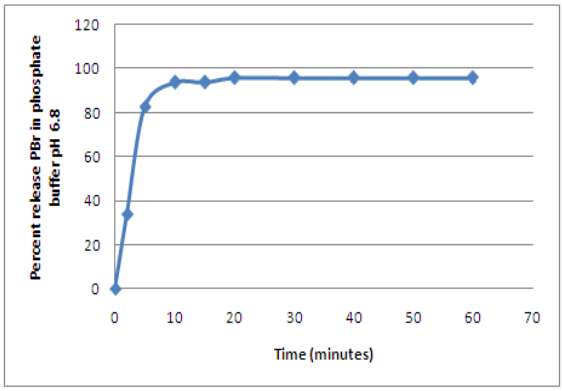

Fig. 6: *In vitro* drug release of PBr from T2 taste masked ODT in phosphate buffer pH 6.8

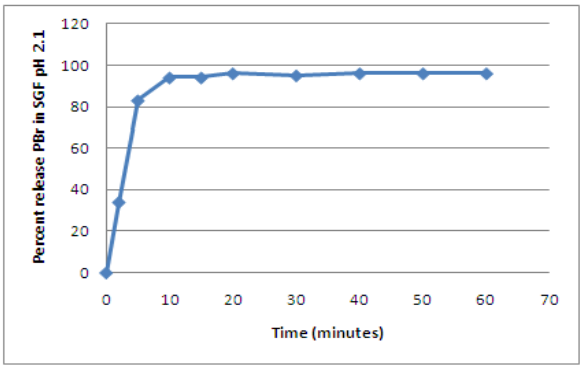

Fig. 7: *In vitro* drug release of PBr from formula T2 in SGF.

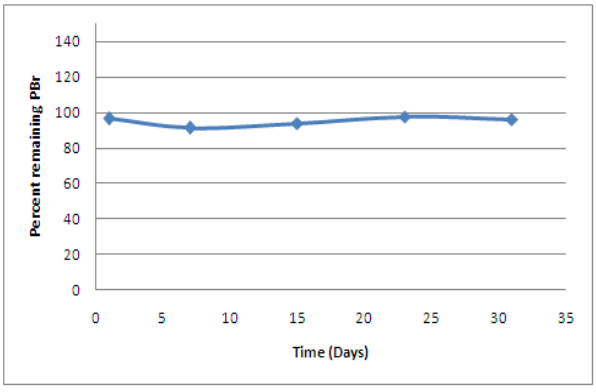

Fig. 8: Percentage remaining of PBr in formula T2 after exposure to 40 ± 2 °C and 75 ± 5 % RH for 31 days.

In vivo Disintegration time and taste evaluation

The results of disintegration time of six volunteers were obtained and the average of 40.7± 10.7 seconds for complete disintegration was recorded which is considered acceptable time for orodispersible tablets. For taste evaluation, the volunteers had considered formula T2 as accepted taste with 25% Tasty, 62.5% Slightly Tasty and 12.5% Fair taste with none scored Slightly Distasteful or Distasteful.

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