

# Development and evaluation of taste masked orally disintegrating tablets of pioglitazone hydrochloride

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**ABSTRACT:** Orally disintegrating tablets, over the years, have become the preferred alternative to conventional tablets and capsule dosage forms because of better compliance. These are suitable for special populations like pediatrics, geriatrics, patient with dysphagia, patients with hand tremors, patients with frequent traveling, etc. The focus of this research was to mask the unpleasant taste of type 2 antidiabetic drug "Pioglitazone Hydrochloride" followed by designing an orally disintegrating tablet of the same. Taste masking was accomplished using a pH-independent polymeric dispersion of ethylcellulose i.e. "Surelease E-7-19040" in combination with a Hypromellose-based ready-to-coat film coating system i.e. "Opadry YS-1-19025-A" in a different ratio. Uncoated powder, coated granules, and prepared tablets of Pioglitazone Hydrochloride were investigated for in-vivo taste evaluation and flow as well as compression behavior, Fourier Transform Infrared spectra, scanning electron microscopy, powder X-ray diffraction, and in-vitro dissolution, disintegration properties. The study demonstrated the use of 3<sup>2</sup> full factorial design study to identify optimal ratio of pore former in Surelease and Opadry polymeric coating combination to achieve desired taste masking of unpleasant Pioglitazone Hydrochloride without any impact on immediate release characteristic of the orally disintegrating tablet formulation. It further demonstrated that, an increase in pore former concentration resulted in a lower rating by human volunteers indicating relatively more bitterness, however, an increase in percent weight gain resulted in a higher rating by human volunteers indicating efficient taste masking.

**KEYWORDS:** Taste masking; orally disintegrating tablets; coating; polymeric dispersion; direct compression.

## 1. INTRODUCTION

Among various delivery methods for drugs, oral administration is considered as most convenient to manufacture. However, patient compliance with regard to taste and ease of swallowability is one of the biggest driving factors for the success of a product [1]. It also offers uniqueness and a competitive edge, particularly in the case of over-the-counter products[2]. One of the approaches to improve patient acceptance and compliance is to mask the bitter or unpleasant taste of drugs. There are twenty-five intact bitter receptor genes in humans, with ligands discovered for twenty-one of them. However, new data reveals that bitterness is not a single, unified perception, and the notion that bitterness is simply an indication of hazardous chemicals to be avoided is an understatement[3]. Various techniques have been reported to mask the bitter taste of the drug for example use of additives such as sweeteners, flavors, and amino acids[4], the use of local anesthetic drugs such as phenol and phenolic derivatives to anesthetize the taste buds, use of traditional granulation technique[5], use of polymeric dispersion for coating of the bitter drug, preparing a complex of unpleasant API with ion exchange resins to produce a resinate and then utilizing that resinate to formulate a dosage form[6], use of  $\beta$ -cyclodextrin to form a complex with bitter tasting drug[7], use of other techniques such as Freeze-drying technique, spray congealing approach with lipids, and utilizing these combinations or complexes to manufacture new dosage form[8]. Preparation of various forms of emulsions and the addition of other excipients to mask bitter aftertaste, such as starch, gelatin[9], liposomes[10], lecithin, surfactants, polymeric membrane, or salts, among others, are used to increase the palatability of the

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medicine. The drug's disagreeable taste is concealed using one of the methods outlined above, and then a solid oral dosage form is developed.

Pioglitazone Hydrochloride (PIOH) is an oral anti-diabetic drug that works by reducing insulin resistance. It is used to treat type 2 diabetes. The crystalline powder of PIOH is odorless and white. It is somewhat soluble in anhydrous ethanol, slightly soluble in acetone and acetonitrile, essentially insoluble in water, and insoluble in ether[11]. The goal of the study was to produce a patient-friendly PIOH orally disintegrating tablet (ODT) using the FDA's Safety-by-Design principles[12]. The research also shows that the bitterness masking technique described for PIOH may be implemented easily across the pharmaceutical sector with little need for specialized equipment and at a reasonable cost. The majority of the taste-masking techniques are based on either forming a complex using ion exchange resins or  $\beta$ -cyclodextrin or applying a pH-dependent polymeric layer over the bitter-tasting substrate to mask the bitter taste of the drug. However, the current study has adopted the unique technique of applying a combination of pH-independent water-insoluble and water-soluble polymeric layers over bitter-tasting drug particles and developing an immediate drug release formulation thereof.

The present work demonstrated the technique to formulate taste-masked ODT's of PIOH, by applying a polymeric layer on bitter-tasting drug particles as a physical barrier to mask the unpleasant taste of the drug. The polymeric dispersion evaluated in the study was a combination of pH-independent, water-insoluble polymeric dispersion with pH-independent, a water-soluble polymer as a pore former [13]. Three different ratios of water-insoluble to water-soluble polymer were optimized using a  $3^2$  full factorial design approach [14]. Coated PIOH granules were evaluated for powder properties, *in-vitro* drug release studies, and *in-vivo* taste evaluation. The optimized formulation was also evaluated for DSC(Differential scanning calorimetry), FTIR Fourier-transform infrared spectroscopy, PXRD (Powder X-ray diffraction), and SEM(Scanning electron microscopy) for solid-state study as well as surface properties. These coated PIOH granules were then used to develop ODT's and formulations were evaluated for pre-compression properties like bulk density, tapped density, Carr's index, Hausner's ratio, angle of repose, and post-compression properties such as thickness, hardness, friability, *in-vitro* disintegration time, drug content, *in-vitro* drug release studies, and *in-vivo* taste evaluation studies.

## 2. RESULTS

### 2.1. Development of taste masked PIOH granules

#### 2.1.1 Use of $3^2$ full factorial design to optimize pore former and percent weight gain ratios:

A  $3^2$  full factorial design was employed to study the effect of two formulation variables i.e. pore former concentration (A) and percent weight gain (B) on the dependent variable (taste evaluation score by human volunteers)[15]. Details of the design study are given in Table 1. In this design, two factors were evaluated, each at three levels, and experimental trials were performed for all nine possible combinations. The results of human volunteer rating, drug content, and percent drug release of coated PIOH formulations are given in Table 2.

Multiple regression analysis was performed for selected variables and taste efficiency and the equation was generated (Equation 1).

$$\text{Human volunteer score} = 47.53 - 9.13A + 11.95B \quad (1)$$

The values of the correlation coefficient ( $R^2 = 0.8446$ ) indicate a good fit. Taste evaluation rating by human volunteers and percent drug release in 1 minute is given in Table 2.

**Table 1.** 3<sup>2</sup> full factorial design study for coated PIOH granules

Batch no	Coded values		Actual values	
	X1(Pore former percentage)	X2 (Percent weight gain)	X1(Pore former percentage)	X2 (Percent weight gain)
-	Control sample		Uncoated API	
F1	-1	-1	10	20%
F2	-1	0	10	35%
F3	-1	+1	10	50%
F4	0	-1	15	20%
F5	0	0	15	35%
F6	0	+1	15	50%
F7	+1	-1	20	20%
F8	+1	0	20	35%
F9	+1	+1	20	50%

**Table 2.** Coated PIOH granules – Drug content, *In-vivo* taste evaluation rating, and Percent drug release

Formulation	Drug content (%)	<i>In-vivo</i> Taste evaluation ratings by human volunteers	Percent drug release in 1 minute (%)
F1	98.4 ± 0.77	4.43 ± 1.47	67.33 ± 1.34
F2	97.8 ± 1.23	4.85 ± 1.25	44.30 ± 1.56
F3	98.8 ± 0.82	7.50 ± 1.43	39.40 ± 0.99
F4	96.4 ± 0.75	3.60 ± 1.26	78.67 ± 1.12
F5	97.3 ± 1.17	4.50 ± 1.70	63.50 ± 1.74
F6	97.1 ± 0.92	6.60 ± 1.20	48.67 ± 1.29
F7	99.1 ± 1.26	3.10 ± 1.37	85.33 ± 1.39
F8	97.7 ± 1.06	4.00 ± 1.05	78.40 ± 1.54
F9	98.6 ± 1.11	4.20 ± 1.75	61.33 ± 0.95

### Influence of pore former on taste and drug release:

The model is significant reflecting both the factors with less than 0.05 values. The negative sign of pore former (A) signifies, that the higher the concentration of the pore former, the higher would be the drug release. Therefore, a more bitter sensation leads to a lower rating in human volunteers.

As shown in Table 2, at a constant 20% weight gain and varying concentrations of pore former the taste evaluation rating by human volunteers was found to be 3.10, 3.60, and 4.43 at 20, 15, and 10% concentrations of pore former respectively. While at 35 %, it was 4.00, 4.50, and 4.85. Whereas, at 50% target weight gain, it was 4.20, 6.60, and 7.50. The results indicated palatability of coated PIOH granules improved with increased percent weight gain and reduced pore former concentration.

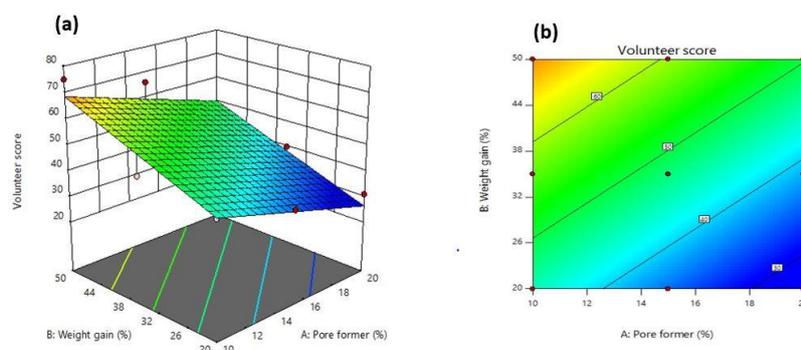
Percent weight gain (B) confirms that the higher the weight gain, the slower is the drug release, therefore less is the bitter sensation and the higher is the acceptance in the human volunteers.

As shown in Table 2, at a constant 10 % of pore former concentration and varying percent weight gain, the taste evaluation rating by human volunteers was found to be in the range of 4.43 – 7.50, which portrayed high acceptability. At a constant 15 % of pore former concentration and varying percent weight gain, the taste evaluation rating by human volunteers was found to be in the range of 3.60 – 6.60, which depicted a reasonable impact of the pore former on masking the bitterness of PIOH. While at a constant 20 % of pore former concentration and varying percent weight gain, the taste evaluation rating by human volunteers was found to be in the range of 3.10 – 4.20, which resulted in the low acceptability.

The difference in pore former concentration and percent weight gain resulted in a significant difference in drug release for all the nine formulations at the first time point of one minute as shown in Table 2, at the lowest concentration of pore former (10%), all the formulations resulted in relatively slower drug release at the first time point of 1 minute ranging from 39.4%, 44.3%, and 67.33% and at the highest level of

pore former (20%), all the formulations resulted in relatively faster drug release. However, all the formulations released more than 90% drug in 10 minutes.

The study reflected that the ratio of polymer to pore former of 90:10 out of the three different ratios' (90:10, 85:15, and 80:20) used, along with the 50 % target weight gain (formulation F3) showed an optimum balance for the taste evaluation and percent drug release at 1-minute time point. However, according to the design study, pore former had a significant negative impact whereas percent weight gain had a significant positive impact on the response as reflected in equation 1 and Figure 1.



**Figure 1.** (a) Surface plots showing the effect of PIOH formulation variables on Human volunteer score and (b) Counter plots showing the effect of PIOH formulation variables on Human volunteer score

### 2.1.2 Development of PIOH ODT

An optimized batch of coated PIOH granules (formulation F3) was chosen for the development of ODT of PIOH by direct compression method. The formulation was chosen based on its ability to mask the unpleasant taste and desired retardation at the first time point of 1 minute followed by a complete release at the latter time points. During the development of PIOH ODT, to achieve the desired mouth feel and shorter *in-vitro* disintegration time, three different Diluents (Microcrystalline cellulose, Mannitol, and Lactose monohydrate) and three different concentrations of super-disintegrant i.e. Crospovidone (2%, 4%, and 6%) were evaluated. All these formulations were evaluated for disintegration time and palatability in healthy human volunteers and the results are indicated in Table 3.

*In-vitro* disintegration of tablets from all the nine formulations of PIOH ODT (formulation ODT1 to ODT9) was found in the range of  $2 \pm 1$  to  $20 \pm 1$  seconds. For the development of ODT's, the disintegration time is one of the important quality attributes which needs critical consideration. The disintegration time of formulations with microcrystalline cellulose as a filler and different concentrations of crospovidone (2, 4, and 6%) was in the range of  $16 \pm 1$  to  $20 \pm 1$  seconds. Formulation with mannitol as a filler and different concentrations of crospovidone was in the range of  $2 \pm 1$  to  $8 \pm 1$  seconds and disintegration time for formulations with lactose monohydrate as a filler and different concentrations of crospovidone was in the range of  $12 \pm 1$  to  $17 \pm 1$  seconds. Formulation with mannitol as a filler and concentration of crospovidone at 6% for PIOH ODT (formulation ODT6) resulted in the lowest disintegration time of  $2 \pm 1$  seconds.

*In-vivo* taste evaluation score on human volunteers for all the nine formulations of PIOH ODT (formulation ODT1 to ODT9) was in the range of 2.6 to 8.9 as shown in Table 3. Formulation of ODT6 with mannitol as a diluent and crospovidone at 6% concentration had the highest preference which means these samples were more acceptable to human volunteers with regards to overall palatability and taste.

**Table 3.** Physical properties of PIOH ODT formulations

Formulation Code	Thickness (mm)	Hardness (kg/cm <sup>2</sup> )	Friability (%)	Weight variation (%)	Disintegration Time (Sec)	Drug Content (%)	Cumulative drug release in 30 min	Taste evaluation score
ODT1	2.38 ± 0.02	4.8 ± 0.14	0.15 ± 0.1	99.45 ± 0.65	20 ± 1	98.46 ± 0.34	98.9 ± 0.78	2.6 ± 1.43
ODT2	2.43 ± 0.02	5.0 ± 0.11	0.14 ± 0.13	100.03 ± 0.32	18 ± 1	97.93 ± 0.59	97.45 ± 0.89	2.8 ± 1.57
ODT3	2.39 ± 0.01	5.0 ± 0.14	0.11 ± 0.09	99.28 ± 0.43	16 ± 1	99.45 ± 0.86	97.78 ± 0.56	3.1 ± 1.13
ODT4	2.40 ± 0.02	4.9 ± 0.13	0.29 ± 0.11	100.5 ± 0.72	8 ± 1	101.38 ± 0.89	98.33 ± 0.59	7.6 ± 0.91
ODT5	2.41 ± 0.01	4.8 ± 0.11	0.28 ± 0.12	100.8 ± 0.45	5 ± 1	99.1 ± 0.43	99.56 ± 0.45	8.5 ± 1.37
ODT6	2.42 ± 0.02	4.8 ± 0.16	0.22 ± 0.1	99.2 ± 0.29	2 ± 1	98.95 ± 0.67	98.89 ± 0.34	8.9 ± 1.17
ODT7	2.39 ± 0.01	5.2 ± 0.12	0.13 ± 0.12	99.65 ± 0.38	17 ± 1	101.51 ± 0.62	97.39 ± 0.90	5.3 ± 1.40
ODT8	2.41 ± 0.02	5.0 ± 0.18	0.17 ± 0.13	99.1 ± 0.78	15 ± 1	97.66 ± 0.66	97.29 ± 0.68	5.8 ± 1.21
ODT9	2.40 ± 0.02	5.2 ± 0.13	0.12 ± 0.12	100.34 ± 0.57	12 ± 1	98.23 ± 0.78	98.39 ± 0.77	6.2 ± 1.16

### 2.1.3 Powder properties of PIOH granules and PIOH lubricated blend

Powder properties of coated PIOH granules obtained for formulations F1 to F9 were found to be satisfactory with desired flow characteristics. The bulk density of uncoated PIOH powder was 0.36 g/cc, however, for coated PIOH granules, it was found to be in the range of 0.33 g/cc to 0.51 g/cc. Tapped density of uncoated PIOH powder was 0.58 g/cc, whereas, for coated PIOH granules, it was found to be in the range of 0.44 g/cc to 0.62 g/cc. Hausner's ratio of uncoated PIOH powder was 1.53, and for coated PIOH granules, it was found to be in the range of 1.15 to 1.33. Carr's index of uncoated PIOH powder was 34.48, however for coated PIOH granules, it was found to be in the range of 13.72 to 25. This indicated the flowability of granules as fair to passable compared to uncoated powder.

However, pre-compression properties of the lubricated blend of all the PIOH ODT formulations (ODT 1 to ODT 9) were found to be satisfactory as shown in Table 4. The angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio was found to be in the range of 17.4 to 23, 0.45 to 0.57 g/cc, 0.56 to 0.7 g/cc, 16.07 to 21.31, 1.19 to 1.27 respectively indicating flow as fair to passable.

### 2.1.4 Drug content of PIOH granules and PIOH ODT

Drug content of all the nine formulations of coated PIOH granules (F1 to F9) was found to be satisfactory, in an excellent match with the label claims, and in a good agreement followed by method suitability ranging from 96.4 ± 0.75% to 99.1 ± 1.26% as shown in Table 2. Whereas, the drug content of all the nine formulations of PIOH ODT (formulation ODT1 to ODT9) was in the range of 97.66 ± 0.66% to 101.51 ± 0.62% as shown in Table 3 which was in accordance with the pharmacopeial requirement.

### 2.1.5 Tablet properties of PIOH ODT

The properties of PIOH orally disintegrated tablet formulations (ODT1 to ODT9) were evaluated as shown in Table 3. All PIOH ODT tablet showed values for hardness in the range of 4.8 ± 0.11 to 5.2 ± 0.13 kg/cm<sup>2</sup>, and friability 0.11 ± 0.09 to 0.29 ± 0.11%. In addition, the manufactured tablet exhibited a uniform weight range of 99.1 ± 0.78 to 100.8 ± 0.45.

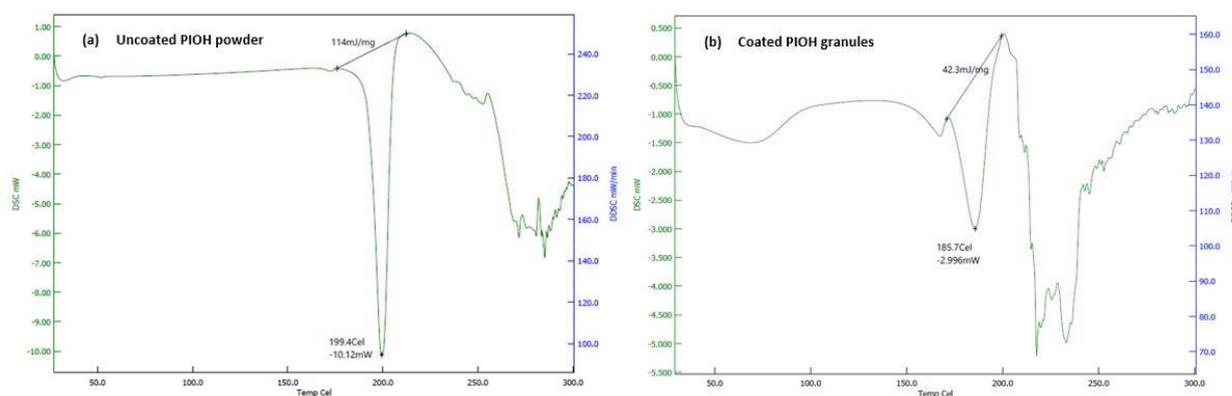
## 2.2. Confirmation studies to check the impact of processing conditions on drug properties

### 2.2.1 Differential scanning calorimetry analysis

Figure 2 shows endotherms for pure PIOH powder and an optimized batch of coated PIOH granules (formulation F3). It reveals a significant endothermic peak at 199.4°C for uncoated PIOH powder, which corresponds to the loss of water during crystallization and melting. The crystalline state/nature of PIOH is revealed by the height and sharpness of the endothermic peak. Similarly, the endothermic peak for coated PIOH granules with polymeric dispersion is 185.7°C. Due to the presence of coating material and uniformity of coating, the endotherms corresponding to the coated are somewhat reduced, i.e., by 14°C. This is further confirmed by the decline in enthalpy change from 114mJ/mg to 42.3mJ/mg. The crystalline state/nature of PIOH is inherent, and the polymorph after the coating is thermodynamically stable, as evident by the height and sharpness of the endothermic peak in coated API. The application of the polymeric coating does not effect on the properties of PIOH.

**Table 4.** Powder properties of PIOH ODT formulations

Formulation Code	The Angle of repose (deg)	Bulk density (gm/cc)	Tapped Density (gm/cc)	% Compressibility	Hausner's Ratio
ODT1	17.5 ± 0.12	0.52 ± 0.05	0.63 ± 0.06	17.46 ± 0.58	1.21 ± 0.06
ODT2	17.7 ± 0.15	0.57 ± 0.05	0.70 ± 0.04	18.57 ± 0.03	1.23 ± 0.04
ODT3	17.4 ± 0.34	0.50 ± 0.07	0.603 ± 0.05	17.12 ± 0.15	1.21 ± 0.09
ODT4	22.6 ± 0.20	0.47 ± 0.03	0.56 ± 0.04	16.07 ± 0.13	1.19 ± 0.08
ODT5	22.8 ± 0.40	0.45 ± 0.05	0.56 ± 0.01	19.64 ± 0.04	1.24 ± 0.06
ODT6	23.0 ± 0.57	0.48 ± 0.07	0.58 ± 0.01	17.24 ± 0.02	1.21 ± 0.06
ODT7	20.5 ± 0.61	0.49 ± 0.08	0.60 ± 0.04	18.33 ± 0.27	1.22 ± 0.07
ODT8	20.8 ± 0.90	0.50 ± 0.07	0.62 ± 0.04	19.35 ± 0.20	1.24 ± 0.06
ODT9	20.6 ± 0.51	0.48 ± 0.02	0.61 ± 0.03	21.31 ± 0.26	1.27 ± 0.06



**Figure 2.** (a) Differential scanning calorimetry curves of uncoated PIOH powder and (b) Differential scanning calorimetry curves of coated PIOH granules

### 2.2.2 Fourier-transform infrared spectroscopy (FTIR) analysis

Figure 3 shows the IR spectrum for uncoated PIOH powder and an optimized batch of coated PIOH granules (formulation F3). The observed absorbance bands in the IR spectrum indicate characteristic functional groups that match PIOH. Similar absorbance bands were also seen in the case of the spectrum obtained for coated PIOH granules. This suggests that the identity of the molecule is not changed during the manufacturing of the coating of PIOH. Of course, some bands are not seen in the case of coated formulation because of the presence of excipients (coating dispersion) in coated PIOH leading to low-intensity bands.

FTIR spectra of PIOH API revealed the presence of peaks at  $3435.22\text{ cm}^{-1}$  (N-H stretching),  $3091.89\text{ cm}^{-1}$  (aromatic C-H stretching),  $1691.57\text{ cm}^{-1}$  (C=O stretching),  $1514.12\text{ cm}^{-1}$  (aromatic C=C stretching),  $1456.26\text{ cm}^{-1}$  (C-H bending),  $1240.23\text{ cm}^{-1}$  (C-O stretching),  $651.94\text{ cm}^{-1}$  (C-S stretching). Thus, the FTIR spectrum confirms the identity of the PIOH.

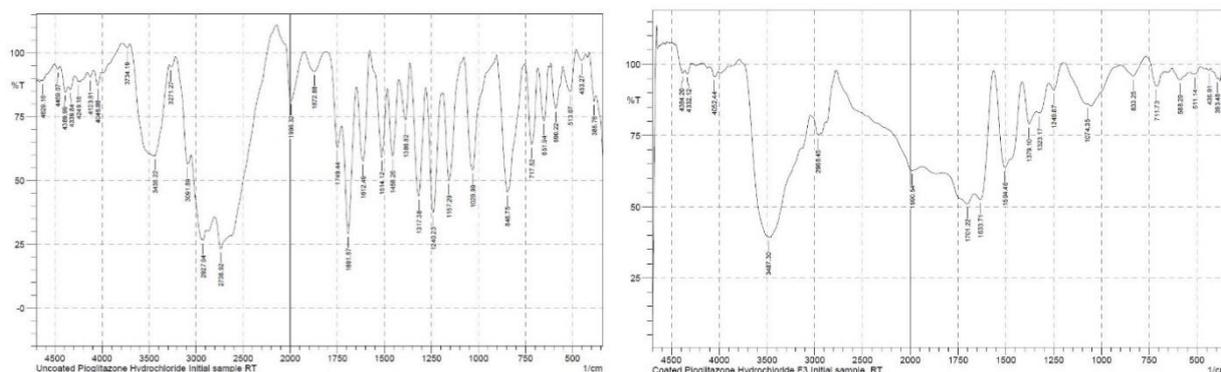


Figure 3. (a) FTIR spectra of uncoated PIOH powder and (b) FTIR spectra of coated PIOH granules

### 2.2.3 Powder X-ray diffraction analysis

Figure 4 shows the overlay of diffractograms for uncoated PIOH powder and coated PIOH granules (formulation F3). The uncoated PIOH powder showed several sharp peaks in the PXRD diffractogram, suggesting the crystalline nature of API. After coating PIOH with polymeric dispersion, the characteristic 2-Theta peaks are exactly overlaid with the pure API, which suggested that polymorphism is not changed after coating and the polymorph is thermodynamically stable.

### 2.2.4 Scanning electron microscopy

Uncoated PIOH powder had a particle size of 30 to 60 microns. However, the coating process resulted in significant particle growth or agglomeration as shown in Figure 5. Additionally, the image of a scanning electron microscope of coated PIOH granules (formulation F3) indicated the deposition of polymeric particles over the surface of agglomerates, resulting in a homogeneous polymeric covering to achieve the desired masking of the unpleasant taste of PIOH and achieving the desired retardation of drug release at initial time point followed by complete drug release.

Comparison of various evaluation criteria for uncoated PIOH powder and coated PIOH granules indicated that processing conditions did not have any significant impact on drug properties. On the contrary, powder properties of formulation F3 were improved significantly as compared to uncoated PIOH powder and drug content was also within the acceptable range. Application of polymeric dispersion by top spray also helped in the formation of a layer on PIOH particles, as indicated in SEM imaging analysis, resulting in the desired retardation of drug release at the initial time point of 1 minute and thereby masking unpleasant taste followed by complete drug release.

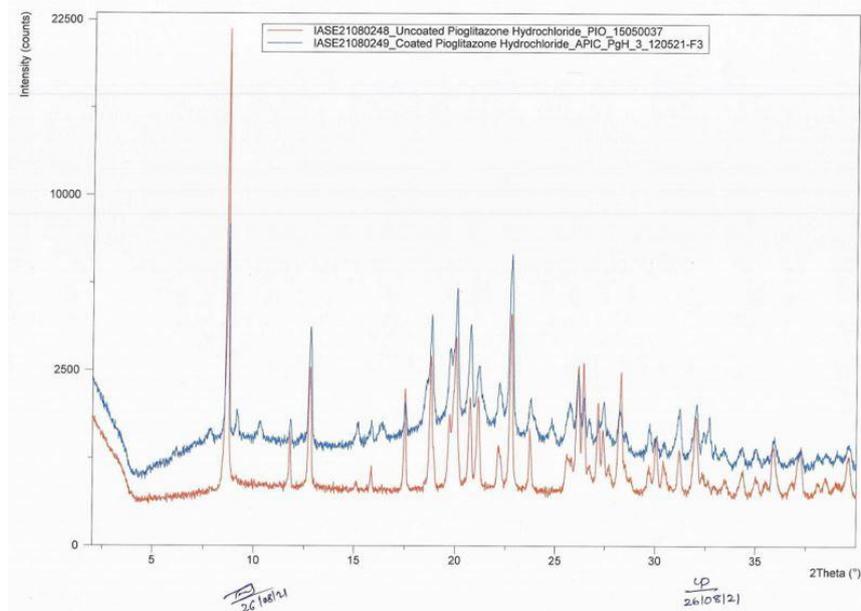


Figure 4. PXRD images of uncoated PIOH powder and coated PIOH granules

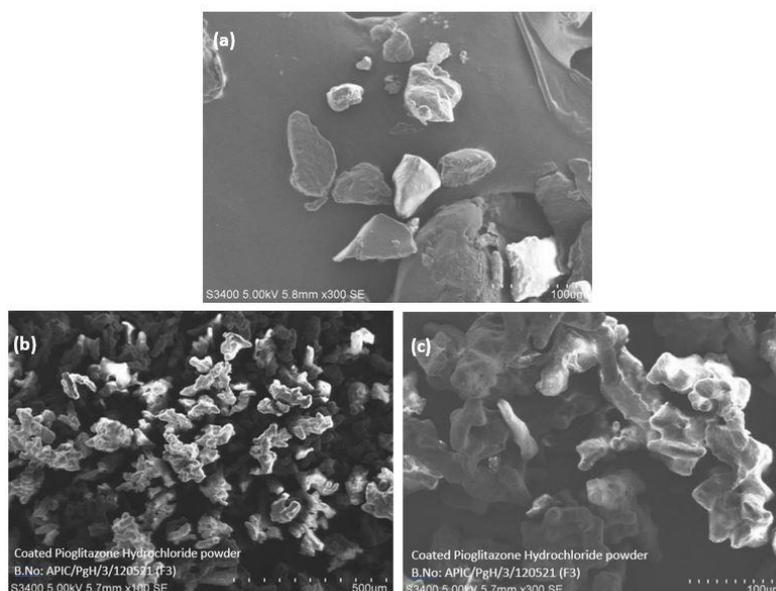


Figure 5. Scanning Electron Microscopic images of (a) uncoated PIOH powder and (b & c) coated PIOH granules

### 2.3. Drug-excipient compatibility studies

To understand the impact of processing conditions, Drug-Excipient compatibility was carried out by exposing the below set of samples at accelerated conditions (40 deg C/75% RH) for 15 days:

- Sample 1: Uncoated PIOH powder
- Sample 2: Coated PIOH powder
- Sample 3: Physical mixture (Powder) of PIOH ODT component and
- Sample 4: Physical mixture (Powder) of Placebo - PIOH ODT

These samples were evaluated for physical appearance, drug content, and FTIR analysis.

#### 2.3.1 Physical appearance

Exposure of all the samples in glass vials to 40°C / 75% relative humidity condition for 15 days did not make any significant difference except for a slight soggy possibly due to moisture pick-up.

### 2.3.2 Percent drug content

The percent drug content of all the samples, when exposed to 40 deg C / 75% RH for 15 days in glass vials, was within the acceptable limit. Details are given in Table 5.

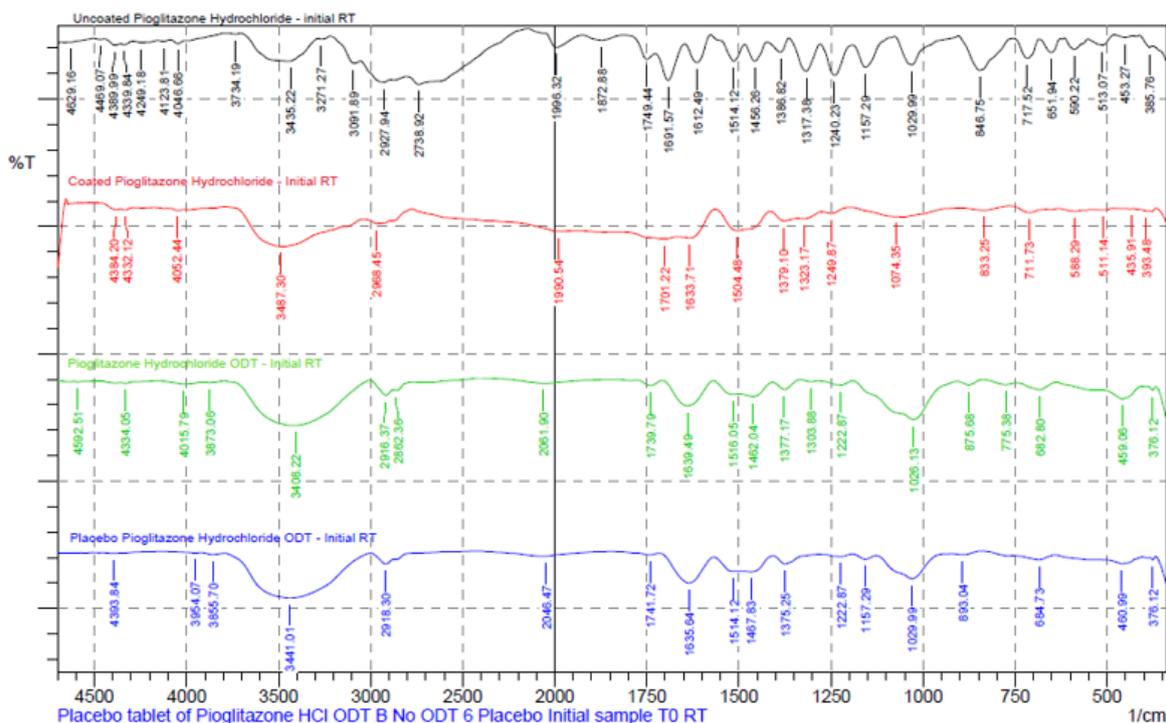
**Table 5.** Drug-Excipient compatibility studies of PIOH formulations – Drug content

Exposure time	Sample 1	Sample 2	Sample 3	Sample 4
Initial Assay value	98.8 ± 0.99%	98.1 ± 0.78%	97.9 ± 0.92%	N/A
Assay value after 15 days of exposure	98.3 ± 1.13%	97.4 ± 0.99%	97.2 ± 1.21%	N/A

### 2.3.3 FTIR analysis

The identification of PIOH is elucidated using FTIR spectroscopy. The characteristic functional groups as shown in Figures 6 and 7 are matching both – uncoated PIOH as well as coated PIOH, even the sample of formulation shows the characteristics peaks after exposure studies.

This suggests that the identity of the molecule is not changing during the process of formulation manufacturing and even after exposure to 40 deg C / 75% RH. Some bands are seen with low intensity in the sample of formulation which is because of the presence of excipients at relatively higher concentrations in tablet formulation resulting in low intensities bands of API.



**Figure 6.** FTIR spectra overlay of PIOH ODT samples before exposure to 40°C / 75% relative humidity

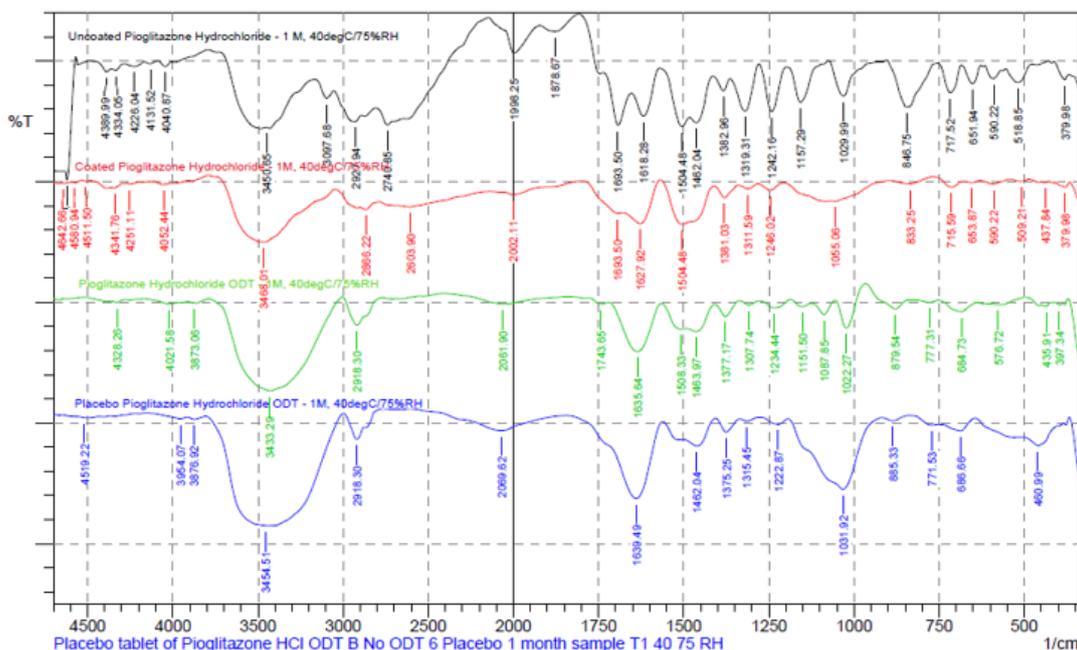


Figure 7. FTIR spectra Overlay of PIOH ODT samples after exposure to 40°C / 75% relative humidity

## 2.4 Stability studies

The optimized formulation of PIOH ODT (Formulation ODT6) was packed in two different packaging conditions and exposed to accelerated stability conditions at 40° C / 75% RH for 1, 3, and 6 months. These formulations were evaluated for Disintegration time, Drug content, and Cumulative percent drug release, details are given in Table 6.

Table 6. Stability studies of PIOH formulations - Disintegration time, drug content, and cumulative % drug release in 30 minutes

Stability study at 40°C and 75 % RH (FOR OPTIMIZED FORMULATION ODT6)						
Time points (Months)	Disintegration time (Sec.)		% Drug Content		Cumulative % drug release after 30 min.	
	Package: Aluminum pouch	Package: HDPE container	Package: Aluminum pouch	Package: HDPE container	Package: Aluminum pouch	Package: HDPE container
0	2 ± 1	2 ± 1	98.95 ± 0.93	98.95 ± 0.93	98.89 ± 0.87	98.89 ± 0.87
1	4 ± 1	5 ± 1	97.20 ± 1.04	97.45 ± 0.87	97.77 ± 0.92	97.02 ± 0.65
3	8 ± 2	9 ± 1	97.05 ± 1.23	96.86 ± 1.01	96.32 ± 1.23	95.67 ± 0.93
6	10 ± 2	12 ± 2	95.89 ± 1.32	95.56 ± 1.10	97.12 ± 1.34	96.45 ± 1.23

### 3. DISCUSSION

Retardation of drug release at the initial time point (1 min) followed by complete drug release at later time points from polymeric coated PIOH granules in aqueous media is an essential criterion that determines the product's quality. The need of controlling drug release up to the first time point of 1 minute is very crucial to achieve desired taste masking of bitter tasting drug while still retaining the immediate release criteria of drug release specifications. Taste masking by film coating technique adopted for masking the bitterness of PIOH comprises of pH independent polymeric dispersion "Surelease E-7-19040" an aqueous dispersion of Ethyl cellulose and "Opadry YS-1-19025-A" an Hypromellose based polymeric system as a water-soluble pore former. The drug release mechanism from such coated particles is supposed to be by "Molecular Hindered Diffusion" as well as "Convection". The mechanism of drug release from such coated particles is governed by Fick's first law of diffusion, the higher the extent of a polymeric material deposited on the particle, the higher the diffusional path length and slower would be the drug release. The presence of water-soluble pore former in a continuous water insoluble polymeric phase would facilitate drug release or diffusion of relatively insoluble drugs. At the lowest concentration of pore former (10%), all the formulations resulted in relatively slower drug release at the first time point of 1 minute ranging from 39.4%, 44.3%, and 67.33%, and at the highest level of pore former (20%), all the formulations resulted in relatively faster drug release. This data is very well correlated with *in-vivo* Taste evaluation ratings given by human volunteers. Formulation with 10% pore former concentration, resulted in a higher overall score by human volunteers, ranging from 4.43 to 7.50, indicating better acceptability. However, formulation with 20% pore former concentration resulted in the lowest overall score by human volunteers, ranging from 3.10 to 4.20, indicating the least acceptability.

### 4. CONCLUSION

In comparison to traditional oral dosage forms, ODT's have higher patient acceptability and compliance and may have better biopharmaceutical characteristics, effectiveness, and safety. To fulfill the demand of patients and healthcare professionals, novel, simple, and desired PIOH ODT was formulated to release the drug in the buccal cavity. When exposed to accelerated condition in two different packaging, this formulation exhibited desired formulation characteristics such as disintegration time, drug content and cumulative % drug release in 30 min and no significant differences reported in two packaging conditions evaluated. In addition, this formulation of PIOH (formulation ODT6) also provided a desirable taste and mouth feel within the buccal cavity and hence could be considered an appropriate ODT formulation for PIOH. The technique and the concept presented in this study for masking the unpleasant taste of the drug and using that taste masked API to prepare fast dissolving solid oral dosage form such as ODT can be very well explored for various other bitter tasting drugs.

### 5. MATERIALS AND METHODS

#### 5.1. Materials

PIOH was obtained from Wockhardt, Aurangabad, India; Surelease E-7-19040 and Opadry YS-1-19025-A Clear were provided by Colorcon Asia Pvt Ltd, Goa, India; Avicel pH 102 was obtained from DuPont, Mumbai, India; Pearlitol 25C was provided by Roquette, Mumbai, India; Pharmatose 200M was obtained from DFE Pharma, Bangalore, India; Kollidone CL was obtained from BASF, Mumbai, India; Citric acid, Talc, and Magnesium stearate were obtained from Colorcon Asia Pvt Ltd., Goa, India; Aspartame and Peppermint flavor were obtained from Cipla Ltd, Mumbai, India; All other ingredients and reagents used in the study were of analytical grade.

#### 5.2. Methods

##### 5.2.1 Preparation of polymeric dispersion for taste masking

To improve the palatability of PIOH, a combination of pH-independent water-insoluble and water-soluble polymeric dispersion was used. pH-independent, water-insoluble part of the polymeric dispersion i.e., Surelease E-7-19040 served as a continuous phase of ethylcellulose polymer whereas pH-independent, water-soluble part of the polymeric dispersion i.e. HPMC based Opadry YS-1-19025-A Clear ready-to-coat film coating system served as a pore former[16]. To evaluate taste masking efficiency, two formulation variables were studied i.e., polymer to pore ratio (90:10, 85:15, and 80:20) and percent weight gain upon

coating (20%, 35%, and 50%). Opadry YS-1-19025-A Clear was added to water under stirring and stirring was continued for 45 minutes to form a clear solution. This solution was then added to the dispersion of Surelease E-7-19040 and stirred for 20 minutes[17].

### 5.2.2 Preparation of taste masked PIOH granules

To achieve taste masking of PIOH, all the nine formulations as shown in Table no 7 were processed using top spray granulation technique in ACG's fluid bed granulator MiniQuest-F which is designed with a cylindrical container having a conical top portion and a fine mesh retention screen at the base to retain powder material on the screen while allowing air to pass through. The container top features six bag filters to avoid particle elutriation[18]. A blower produces the fluidization air, which is then fed via a heater, fine mesh retention screen, and into the product container. Before entering the bed, the flow rate, humidity, and temperature are all monitored. The nozzle must be positioned vertically within the column at a specified height i.e. 5-6 cm above the powder bed while the polymer dispersion is sprayed so that each particle of powder is evenly moistened through with the polymer dispersion[19]. The polymeric dispersion is drawn into the nozzle by a peristaltic pump and atomized by compressed air. It's also vital to keep track of compressed air flow. Two thermocouples, one beneath the distributor plate and one in the bed, are used to check the temperature of the inlet air and the temperature of the product bed. To eliminate the initial moisture contained in the powder, the bed was filled with 50 grams of powder and fluidized with hot air at a velocity of 0.8 to 1.0 cubic feet per minute (cfm)[20]. Polymeric dispersion was injected via spray nozzle at a rate of 0.5 to 1.2 g/minute after the required product bed temperature was reached. When powder particles collided with one another during spray application, liquid bridges formed between the particles, resulting in the development of granules, a process known as agglomeration[21]. Surface tension at the interface and hydrostatic suction both contributed to the creation of a liquid bridge between the particles, which resulted in particle bonding[22]. These liquid bridges become solid bridges when the water evaporates, eventually forming a larger agglomeration.

Once the required amount of polymeric dispersion was applied, a peristaltic pump was turned off, and the fluidization rate was slowed to enable particles to dry until the correct moisture level was reached. The bed temperature and pressure decrease were also measured throughout the granulation process. Coated PIOH granules were manually sieved through 20 mesh diameters since sieving was less labor demanding and reduced attrition.

**Table 7.** Composition of PIOH granules

Exp no:	F1	F2	F3	F4	F5	F6	F7	F8	F9
PIOH (g)	50	50	50	50	50	50	50	50	50
Surelease (g)	9	15.75	22.5	8.5	14.87	21.25	8	14	20
Opadry (g)	1	1.75	2.5	1.5	2.63	3.75	2	3.5	5
Total load (g)	60	67.5	75	60	67.5	75	60	67.5	75

### 5.2.3 Preparation of PIOH ODT

The coated PIOH granules from the optimized batch were employed in the direct compression process to develop an ODT formulation. PIOH granules were combined with other ingredients such as microcrystalline cellulose, mannitol, lactose monohydrate, crospovidone, citric acid aspartame, peppermint flavor, magnesium stearate, and talc in the formulation and compressed into ODT's, the composition of all the nine PIOH ODT formulations is provided in Table 8 . Tablets were compressed using 5.5 mm round, standard concave tooling in an 8 station Tablet press (Remik) with an 85 mg core weight[23].

**Table 8.** Composition of PIOH ODT formulations

Ingredients	Composition (mg)								
	ODT1	ODT2	ODT3	ODT4	ODT5	ODT6	ODT7	ODT8	ODT9
Drug: Polymer complex	22.52	22.52	22.52	22.52	22.52	22.52	22.52	22.52	22.52
MCC (Avicel pH102)	56.06	54.36	52.66	-	-	-	-	-	-
Mannitol	-	-	-	56.06	54.36	52.66	-	-	-
Lactose (Supertab 11SE)	-	-	-	-	-	-	56.06	54.36	52.66
Crospovidone	1.70	3.40	5.10	1.70	3.40	5.10	1.70	3.40	5.10
Citric acid	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.04
Aspartame	2.55	2.55	2.55	2.55	2.55	2.55	2.55	2.55	2.55
Peppermint Flavour	0.85	0.85	0.85	0.85	0.85	0.85	0.85	0.85	0.85
Magnesium Stearate	0.64	0.64	0.64	0.64	0.64	0.64	0.64	0.64	0.64
Talc	0.64	0.64	0.64	0.64	0.64	0.64	0.64	0.64	0.64
Core weight	85	85	85	85	85	85	85	85	85

### 5.3 Evaluation parameters of uncoated PIOH powder, coated PIOH granules and PIOH ODT

#### 5.3.1 Flow properties

The following methods were used to determine the flow properties of coated PIOH granules obtained from all the nine formulations F1 to F9 as well as the lubricated blend of all the nine ODT formulations ODT1 to ODT9 that were prepared using an optimized batch of coated PIOH granules[24]

#### Bulk Density and Tapped Density:

To determine the density, a measuring cylinder was filled with the sample. The weight of a sample per unit volume is measured by weight-to-volume density. The bulk density was calculated per the following formula.

$$\text{Bulk density: } \frac{\text{Weight of blend}(M)}{\text{Bulk Volume}(V)} \quad (2)$$

The tapped density was obtained by tapping a measuring cylinder from a height of 1.5 inches 500 times and tapped density was as per the following formula:

$$\text{Tapped density: } \frac{\text{Weight of blend}(M)}{\text{Volume occupied in the cylinder}(Vt)} \quad (3)$$

#### 5.3.2 Carr's index and Hausner's ratio

A Carr's index is calculated as per the following formula:

$$\text{Carr's index: } \frac{(\text{Tapped density} - \text{Bulk density}) \times 100}{\text{Tapped density}} \quad (4)$$

Using the following equation, the Hausner's ratio was calculated:

$$\text{Hausner's Ratio: } \frac{\text{Tapped density}}{\text{Bulk density}} \quad (5)$$

### 5.3.3 Angle of repose

The angle of repose was determined for the lubricated blend of all the nine PIOH ODT formulations (ODT1 to ODT9) using a funnel or sample holder which is stationary. The sample was poured through this funnel which was raised vertically until a maximum cone height (h) was obtained. The radius of the heap (r) and the angle of repose ( $\Theta$ ) were calculated using the formula

$$\Theta = \tan^{-1} (h/r) \quad (6)$$

### 5.3.4 Thickness and weight variation

For evaluation of tablet thickness, Digital Vernier Calliper was used. 20 tablets were randomly selected from nine formulations of PIOH ODT (ODT1 to ODT9) and average thickness values were estimated[25].

For estimation of weight variation, the weighing scale from Shimadzu corp. Japan Type AX200 was used. Again, 20 tablets were randomly selected from nine formulations and weight variation was estimated.

### 5.3.5 Hardness

For evaluation of hardness, Erweka GmbH hardness tester was used. 10 tablets were selected randomly from nine formulations of PIOH ODT (ODT1 to ODT9) and the average value of hardness was estimated[25].

### 5.3.6 Friability

The friability test was performed on 10 randomly selected tablets from nine formulations of PIOHODT (ODT1 to ODT9) by Roche friabilator, and the average friability was determined. Pre-weighed tablets (10 in numbers) were placed in friability apparatus that rotates at a speed of 25 RPM  $\pm$ 1 for about 100 revolutions resulting in a tumbling action causing attrition to the tablets by lifting them to the height of six inches and then dropping them. The standard Roche operates at a specified speed of 25 RPM  $\pm$ 1. Loss of weight and friability are calculated as per equation 6. The acceptance criteria for uncoated tablets is not more than 1% [25].

$$\text{Friability: } \frac{(\text{Initial weight} - \text{final weight})}{\text{Initial weight}} \times 100 \quad (7)$$

### 5.3.7 In-vitro disintegration time

Disintegration time for PIOH ODT was estimated according to the pharmacopoeial criteria of USP 30-NF 25 for immediate release ODT's. Six tablets were randomly selected from nine formulations of PIOH ODT (ODT1 to ODT9) and disintegration time was studied using Electro Lab, ED-21 disintegration test apparatus. One tablet was introduced in each basket carrying water maintained at 37°C  $\pm$  1°C. Disintegration time and standard deviation were recorded when all the particles slipped through the screen[26].

### 5.3.8 In-vitro dissolution studies in pH 6.8 phosphate buffer

The following procedures were used to assess the drug release of coated PIOH granules produced from formulations F1 to F9 and PIOH ODT produced from formulations ODT1 to ODT9:

*In-vitro* release tests of coated PIOH granules (equal to 30 mg PIOH) were carried out in 900ml 6.8 Phosphate Buffer at 37  $\pm$  0.5°C using a USP XXII dissolution apparatus with a basket rotation speed of 50 rpm. Each drug solution was tested for PIOH content using a spectrophotometer at 268 nm. An aliquot sample (5 ml) was removed at 1-, 3-, 5-, 10-, and 15-minutes intervals with the replacement of fresh medium, and each drug solution was assessed for PIOH content using a spectrophotometer at 268 nm.

USP dissolution test apparatus type 2 (paddle) was used to carry out the dissolution study of PIOH ODT. In the covered vessel pH 6.8 phosphate buffer of 900ml was taken which is maintained at a temperature of 37  $\pm$

0.5°C with paddle speed at 75rpm. An aliquot sample of 5ml was withdrawn at 2, 4, 6, 8, 10, 15, 20, 25 & 30 minutes. For each sample, 5 ml of the dissolution medium was withdrawn and replaced with the same quantity of dissolution media warmed to 37°C. The absorbance of the withdrawn sample was analyzed using a spectrophotometer at 268 nm and the percentage absorbance was calculated. To calculate percent cumulative drug release, a standard calibration curve of PIOH developed in a pH 6.8 medium was utilized.

#### 5.3.9 Determination of drug content

The following procedures were used to assess the drug content of coated PIOH granules obtained from formulations F1 to F9 and PIOH ODT from formulations ODT1 to ODT9:

To synthesize the standard stock solution, methanol was used. To prepare the stock solution, 1.00 mg mL<sup>-1</sup> of PIOH was mixed with methanol. The typical stock solution was maintained in the dark and kept at 2–8°C. For PIOH, test solutions were produced by diluting the aforementioned stock solution in the mobile phase to reach a range of concentrations of 1–10g mL<sup>-1</sup>. It was possible to get the UV spectrum of a pharmacological ingredient at a concentration of 10 g mL<sup>-1</sup>. The maximum absorbance of PIOH was found to be 268 nm. The drug content was calculated using the standard curve equation.

#### 5.3.10 In-vivo taste evaluation

*In-vivo* Taste evaluation of coated PIOH granules obtained for formulations F1 to F9 and PIOH ODT formulation ODT1 to ODT9 were determined as described in the procedure. The taste evaluation format for coated PIOH granules and PIOH ODT was the same. Institutional Ethics Committee had approved the protocol, entitled IEC / NU / 19 / IP / 01, for in-vivo taste evaluation.

#### Procedure:

The study was divided into 3 phases with 3 hours gap between each phase. Three formulations along with one control sample were given to individual volunteers for tasting purposes with a minimum 20-minute gap between each formulation tasting. The sample was placed at the rear end of the tongue for about 30 seconds. After 30 seconds, the sample was spitted and gargled with plain water, if needed; volunteers were allowed to consume additional water. To neutralize taste buds, salty biscuits and salty peanuts were consumed by volunteers. Half a glass of water was given to individual volunteers who were asked to wait for 20 minutes before proceeding to the next sample evaluation. The bitterness of the sample was evaluated on a scale of 0 to 10 (0 being the highly bitter). A minimum 3 hours gap was maintained after completion of each Phase and before starting the next phase.

#### 5.3.11 Differential scanning calorimetry (DSC)

Differential Scanning Calorimetry was carried out on uncoated PIOH powder and coated PIOH granules derived from optimized formulation F3[27].

Optimized formulation (F3) was submitted to DSC tests to investigate the influence of processing conditions on the change in melting point, crystallization behavior, and chemical reaction of PIOH as a function of temperature or time. A differential scanning calorimeter (DSC 823 Mettler Toledo) was used to record the DSC thermograms of uncoated PIOH powder and coated PIOH granules. On the metal pans, samples were properly weighed and then packed with aluminum lids. Thermograms were taken at a frequency of 10°C/min in a liquid nitrogen environment at temperatures ranging from 30 to 250° C.

#### 5.3.12 Fourier transform infrared absorption spectra (FTIR)

The following procedures were used to determine the infrared absorption of uncoated PIOH powder, coated PIOH granules derived from optimal formulations F3, and PIOH ODT formulation ODT6.

Optimized formulation was submitted to FTIR tests to investigate the influence of processing conditions on the change in PIOH powder at the molecular level. The FTIR spectrophotometer (FT/IR 4100 Jasco) was used for analysis. The uncoated and coated PIOH granules were mixed with KBr respectively and turned into pellets at 100 kg pressure using a hydraulic press. The recorded spectra ranged from 4000 to 400 cm<sup>-1</sup>.

#### 5.3.13 Powder X-ray diffraction analysis (P-XRD)

Uncoated PIOH powder and coated PIOH granules derived from optimized formulations F3 were subjected to powder X-Ray Diffraction analysis as follows:

Optimized formulation was submitted to P-XRD tests to investigate the influence of processing conditions on the change in PIOH powder at the molecular level. Phillips-X'Pert MPD System, Netherland, was used to analyze P-XRD of both uncoated and coated PIOH granules. At a speed of scanning of 0.3 deg/s, P-XRD was observed from 2° to 60°. The X-ray supply was PW3123/00 curved Ni-filtered Cu-K (=1.54056) radiation.

#### 5.3.14 Scanning electron microscopy (SEM):

SEM analysis of uncoated PIOH powder and coated PIOH granules derived from optimal formulations F3 was carried out using SEM (Philips XL 30 SEM). Both the samples were previously gold-sputter-coated.

### 5.4 Accelerated Stability Testing Protocol of PIOH ODT

Optimized formulation of PIOH ODT formulation ODT6 was packed in two different packs "Aluminum pouch" and "HDPE container" and exposed to accelerated stability conditions. Details of the study protocol is given in the section below.

#### 5.4.1 Packaging condition

Optimized formulation of PIOH ODT formulation ODT6 was packed in two different packs before exposing to stability conditions. Aluminum pouch manually filled with 45 tablets and sealed with sealing machine and HDPE container manually filled with 45 tablets and one silica bag which was then sealed with aluminum seal. Both these packs were subjected to stability testing as per the protocol.

#### 5.4.2 Stability condition

Both the packs of optimized formulation of PIOH ODT formulation ODT6, one pack per time interval, were subjected to 40 deg C / 75% RH as well as 25 deg C / 60% RH for 6 months with intermittent testing at 1<sup>st</sup> month, 3<sup>rd</sup> month and 6<sup>th</sup> month. Formulations exposed to 25 deg C / 60% RH were treated as a back-up samples, just in case if failure is reported at 40 deg C / 75% RH.

#### 5.4.3 Evaluation criteria for stability study

Samples of packed PIOH ODT formulation ODT6 after completion of exposure period were evaluated for disintegration time, drug content and cumulative % drug release after 30 minutes.

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