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Research Article

FORMULATING TASTE-MASKED ORALLY DISINTEGRATING TABLETS OF A BITTER DRUG IBUPROFEN

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ABSTRACT
This study is aimed at formulating taste-masked orally disintegrating tablets of a bitter drug i.e., Ibuprofen. Taste masking was carried out by fluid bed coating of extruded and spheronized pellets comprising of Ibuprofen, microcrystalline cellulose and lactose. Two marketed taste-masking systems, namely Eudragit EPO and Opadry tm were evaluated. For the formulation of orally disintegrating tablets a range of excipients such as super disintegrants, diluents, sweeteners and flavours were evaluated and a prototype formulation was selected. This prototype formulation had Eudragit EPO coated taste masked pellets and selected excipients. Its disintegration time was found to be about 8 seconds. Tablets were evaluated for their taste, disintegration time, hardness, friability, water uptake and drug release profile. It was concluded from this study that water insoluble, water permeable polymer system like Eudragit EPO can effectively taste mask bitter drugs without unduly affecting their drug release profile. As per objective of the work, the formulation was found to have a disintegration time of less than 30 seconds (about 8 seconds), had good mouth feel and organoleptic properties. With Eudragit EPO the bitterness and burning sensation of drug was significantly masked at low coating levels (15 %) without affecting the Ibuprofen release.
Keywords: Ibuprofen, Eudragit, Taste masking, Bitter.

INTRODUCTION

Oral Drug Delivery

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance and convenience in administration.[1] Oral dosage form is the most popular route for drug therapy. Over 80 % of the drugs formulated to produce systemic effects in the United States are produced as oral dosage forms. Compared to other oral dosage forms, tablets are the manufacturer's dosage form of choice because of their relatively low cost of manufacture, package, and shipment.

Taste Masking of Oral Pharmaceuticals

Taste masking is of critical importance for active ingredients with an unpleasant bitter taste, due to the need for increased patient compliance. Taste masking technology involves the development of a system that prevents the active substance interacting with the taste buds, thereby eliminating or reducing the negative sensory response. There are three general tastes masking principles, the use of a physical barrier, chemical or solubility modification, and solid dispersions, each of them further subdivided into several methods. Additionally, unique platforms such as orally disintegrating and chewable tablets, applicable for taste masking have been extensively employed. Taste masking of drug may be achieved with preventing the exposure of drug to the tongue through processing or adding competing taste-masking agents. Exposure of solubilized drug to the oral cavity can be prevented by encapsulation in polymer systems or complexation[2].

MATERIALS AND METHODS

Pre Formulation – API Characterization

Bulk Density

It's a measurement to describe packing of particles. Bulk density/apparent density are used to determine the amount of drug that occupies the volume (g/ml).

$$\rho_b = m / V_b$$

Where ρ_b = bulk density, m = mass of the blend, V_b = untapped volume

Determination of Bulk density

Weighed quantity of Ibuprofen (25g) was transferred into 100 ml measuring cylinder without tapping during transfer. The volume occupied by the drug was measured. Bulk density was measured by using formula

$$\rho_b = m / V_b.$$

The values obtained are reported in the table.

Tapped density

25 g of Ibuprofen was taken in 100 ml measuring cylinder that was placed in Electro lab tapped density apparatus (method USP-I). Initial volume (V_0) of the cylinder was noted and then the cylinder was tapped 500 times and volume was measured. Then further an additional 750 tapings were repeated. No difference was noted between the volumes of the two tapings (500 and 750). The final volume (V) was considered after completion of 750 taps. Tapped density was measured by using formula

$$\rho_t = m / V_t.$$

The values obtained are reported in the Table[3,4].

Compressibility Index

Weighed amount of Ibuprofen (25g) was transferred to 100 ml-graduated cylinder and subjected to 500,750 and1250 taps in tap density tester (Electro lab). The difference between two taps should be less than 2 %. The % of compressibility index calculated using formula

$$\text{Compressibility Index} = 100 * (\rho_{tapped} - \rho_{bulk}) / \rho_{tapped}$$

Hausner's ratio
It is measurement of frictional resistance of the drug .the ideal range should be 1.2 –1.5.it is the determined by the ratio of tapped density and bulk density.

$$\text{Hausners ratio} = \rho_{tapped} / \rho_{bulk}$$

Angle of repose
It is defined as the maximum angle that can be obtained between the free standing of powder heap and horizontal plane, which is given by the equation:

$$\theta = \tan^{-1} h / r$$

Where θ = Angle of repose, h = Height of the pile, r = Radius of the base of the conical pile

Procedure
Weighed quantity of the drug was passed through a funnel kept at a height 2 cm from the base. The powder is passed till it forms a heap and touches the tip of the funnel. The radius was measured and angle of repose was calculated by using the above formula[5,6].
From the results in Table 1, it is evident that the drug has very poor flow properties, as the compressibility index, Hausner's ratio and Angle of repose values are high.

Particle size distribution
Ibuprofen was analyzed for particle size distribution by means of mechanical sieve shaker (Retsch) Table 2.

Construction of calibration curve of Ibuprofen
Standard curve of Ibuprofen was prepared in pH 7.2 phosphate buffer and in 0.1 N HCl.

Procedure for construction of calibration curve of Ibuprofen in pH 7.2 phosphate buffer
Preparation of stock solution
100 mg of the drug is accurately weighed and transferred into a 100 ml volumetric flask. 7.2 pH phosphate buffer was added to it so as to dissolve the drug and finally diluted up to the mark to give 1000 µg/ml.

Preparation of dilutions
Different dilutions were made using the stock solution prepared. 0.5, 1, 1.5, 2, 2.5 ml of stock solution was taken and diluted to 100 ml of pH 7.2 phosphate buffer to get the concentrations of 5, 10, 15, 20 and 25 µg/ml. The absorbance of above solutions was measured in UV-spectrophotometer at 221 nm wavelength. Plot the graph between the concentration (µg/ml) on x-axis and absorbance (nm) on y-axis as shown in Figure 1. (Table 3)

Formulation Development
Selection of formulation method
Orally disintegrating tablets of Ibuprofen were formulated using direct compression method.

Direct Compression
Procedure
- API, disintegrant, diluent, and lubricant was sifted through ASTM #40 separately.
- Glidant, flavour, sweetener were sifted through ASTM #60.
- All ingredients were weighed accurately.
- Ingredients of Step 1 were blended in a poly bag for 10 minutes.
- Ingredients of Step 2 were added to the blended material and mixed for 5 minutes.
- Compressed the material of step 5 materials into biconvex, round shaped tablets using 11 mm punch at 3.0 ± 0.5 kp (Table 4).

Selection of disintegrant in the formulation
Procedure
- API, disintegrant(s), diluent, and lubricant were sifted through ASTM #40 separately.
- Glidant, flavour and sweetener were sifted through ASTM #60.
- All ingredients were weighed accurately.
- Ingredients of Step 1 except lubricant were blended in a poly bag for 10 minutes.
- Ingredients of Step 2 and lubricant were added to the blended material and mixed for 5 minutes.
- Compressed the material of step 5 materials into biconvex, round shaped tablets using 11 mm punch at 3.0 ± 0.5 kp (Table 5 & 6).

Taste Masking Methods
Taste is one of the most important parameters governing patient compliance. Undesirable taste is one of the several important formulation problems that encounters with certain drugs. So, any pharmaceutical formulation with a pleasing taste would definitely be preferred over a competitor's product that would translate into better patient compliance and therapeutic value for the patient and more business and profits for the company. In the present scenario, bitterness of the Ibuprofen was observed in the formulated ODT tablets. So the challenge was to achieve a taste masked fast-disintegrating dosage form for the drug[7,8]. Following strategies were used to mask bitterness of Ibuprofen.

Organoleptic Modification
Shown in Table 7-9

Evaluation of Tablets
Physical properties
The surface of the formulated tablets was evaluated to ensure that there was no capping, lamination, sticking or other defects during compression. The tablet surface should be smooth, and color should be white since no color is used in formulation and all ingredients were white in color. If color and odor of the tablet changes, it may be the indication of any chemical reaction that may effect the properties of formulation.

Weight variation
Weight variation test was performed according to USP. Average weight of twenty tablets was calculated and individual weight of each tablet was taken. % deviation was calculated with respect to average weight. The maximum % deviation allowed is 5 % as the tablet weight is more than 324 mg. the tablets meet the USP test if no more than two tablets are outside the % limit and if no tablet differs by more than two times the % limit.

Thickness
The thickness in millimeters (mm) was measured individually for 10 pre weighed tablets by using a Mitutoyo

portable dial hand micrometer. The average weight, standard deviation and relative standard variation were reported.

Hardness

This test gives the indication for the tablets ability to with stand its integrity of drug with the drug release can be optimized. It was determined by placing the tablet between the anvils only one of which is movable, driven by electricity. It presses the tablet at constant load till the tablet breaks. It was recorded in KP (1kP = 1 kg). Hardness of 10 tablets determined and average hardness and range was calculated.

Friability

Friability is related to tablets ability to withstand both shocks and abrasion without crumbling during manufacturing, packing, transportation and consumer handling. Friability can be evaluated by means of friability test apparatus. Compressed tablets that loose less than 0.5 % to 1.0 % in weight are generally considered acceptable. Friability of the formulated tablets was determined in Roche friabilator. Ten tablets were weighed accurately and then initial weight was note down. There are introduced in the apparatus and subjected to 100 revolutions at a speed of 25 rpm for 4 minutes. When the drum stopped, tablets were taken and dedusted and final weight was taken. % Friability was calculated by the formula

$$\% \text{ Friability} = \frac{\text{Initial weight (g)} - \text{Final weight (g)}}{\text{Initial weight (g)}} \times 100$$

Acceptance criteria: the friability value should be less than 1.0 %

Taste Evaluation

The taste characteristic of taste masked ODT Formulations was compared in healthy human volunteers, from whom informed consent was first obtained. The subjects were informed of the purpose and protocol of the study. As per the protocol all volunteers were asked to rinse their mouth with distilled water prior to the test. The formulated Opadry tm and Eudragit EPO drug coated ODT Tablets were given to 10 healthy volunteers and were compared with the uncoated ODT Tablets. Samples equivalent to 100 mg drug were given to the 10 volunteers. Bitterness was recorded immediately according to the bitterness intensity scale from 0 to 3; 3 being strongest, 2 being moderate, 1 being slight, and 0 for no bitterness taste. The volunteers were asked to rank accordingly based on the evaluation of the given samples.

Wetting Time

Five circular tissue papers were placed in a petridish of 10 cm diameter. Ten millimeters of water was added to the petridish. A tablet was carefully placed on the surface of the tissue paper in the petridish at 25^0C. The time required for water to reach the upper surface of the tablets and to completely wet them was noted as the wetting time. These measurements were carried out in replicates of six. Wetting time was recorded using a stopwatch.

Water absorption Ratio (R)

The weight of the tablet prior to placement in the petridish was noted (W_b) using a Shimadzu digital balance. The wetted tablet was removed and reweighed (W_a). Water absorption ratio, R, was then determined according to the following equation[9-11].

$$R = 100 * (W_a - W_b) / W_b$$

Where W_b and W_a were tablet weights before and after water absorption, respectively

***In vitro* Disintegration test**

This test provides determination for compliance with the limits on disintegration. The purpose of the test, disintegration does not comply complete solution of the unit or even of its active constituents. Complete disintegration is defined as that state in which any residue of the unit, remaining on the screen of the test apparatus is a soft mass having no palpability firm core. Electro lab disintegration apparatus was used where one tablet was placed in each of the 6 tubes of the basket. Operated the apparatus using water as media at 37° ± 0.5°C as the immersion liquid[12]. The time of disintegration was noted.

***In-vitro* release study**

Dissolution

Dissolution was done for each batch of Taste masked orally disintegrating tablets of Ibuprofen in pH 7.2 Phosphate buffer for 1 h.

Dissolution conditions

Dissolution media – pH 7.2 Phosphate buffer
Apparatus – USP II (Paddle)
Volume – 900 ml
rpm – 100
Temp. – 37 + 0.5^o C
Sampling points – 5, 10, 15, 20, 30, 45, 60 minutes.

Preparation of sample dilutions

3.0 ml of sample which is filtered through 0.45 µm filters was taken and diluted to 20 ml using pH 7.2 Phosphate buffer to give the concentration of 15 µg/ ml.

Preparation of standard solution

55 mg of drug was dissolved in 100 ml of pH 7.2 Phosphate buffer and from this solution 3 ml was taken and diluted to 100 ml. Analysis of samples was done by using UV Spectrophotometer at 221 nm wavelength.

$$\text{Cumulative percentage drug release} = \frac{\text{Absorbance}_{test} \times \text{Dilution}_{std} \times \text{Drug purity}}{\text{Absorbance}_{std} \times \text{Dilution}_{test} \times \text{label claim}} \times 100$$

Corrected cumulative percentage drug release = Cumulative percentage drug release + Correction factor

$$\text{Correction Factor} = \frac{\text{Vol of sample taken} \times \% \text{ drug released at previous time point}}{\text{Percentage drug release at that time point}} \times 100$$

Different dissolution profiles were compared to establish the effect of formulation or process variables on the drug release.

***In-vivo* Disintegration Time**

The formulated Opadry tm and Eudragit EPO Ibuprofen coated tablets were given to 10 healthy volunteers and were compared with the uncoated pellets. The subjects were informed of the purpose and protocol of the study. As per the

protocol all volunteers were asked to rinse their mouth with distilled water prior to the test. Tablets were placed on the tongue and a stopwatch was started immediately. Volunteers were allowed to move the tablet against the upper palate of the mouth with their tongue and cause a gentle tumbling action on the tablet without chewing it. Time taken for the volunteer to feel that the last noticeable granule had disintegrated in the oral cavity was considered as the *in vivo* DT. This experiment was conducted in all 10 subjects and the mean ± SD were calculated for each[13].

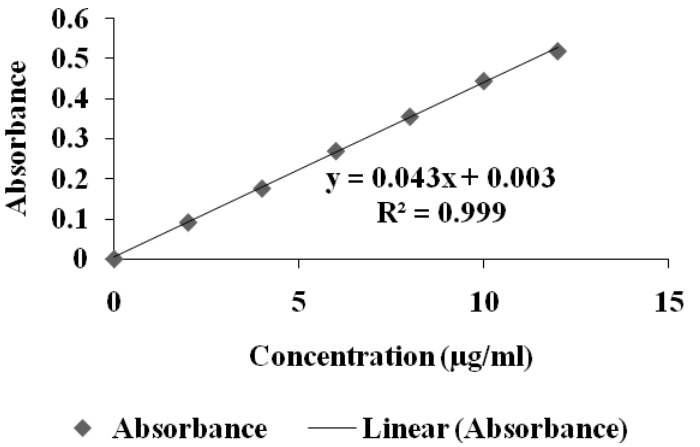

Figure 1: Calibration curve of Ibuprofen in pH 7.2 phosphate buffer (λmax = 221 nm)

Table 1: Flow properties of Ibuprofen

Parameters	
Bulk density	0.378 g/cc
Tap density	0. 609 g/cc
Compressibility / Carr's index (%)	38 %
Hausner's ratio	1.61
Angle of repose	49.57

Table 2: Particle size distribution

Sieve No.	Sieve size (micron)	Initial Wt. (g)	Final Wt. (g)	% Retained
#80	180	269.5	269.5	0
#100	150	247.5	248.0	2
#140	106	268.5	279.0	42
#200	75	238.0	250.5	50
#230	63	239.0	240.5	6
Collector		343.5	343.5	0
		Total		**100**

Table 3: Calibration data of Ibuprofen in pH 7.2 Phosphate buffer

Concentration (µg/ml)	Absorbance
0	0.0
2	0.0914
4	0.1763
6	0.2699
8	0.3559
10	0.4451
12	0.5198

Table 4: Formulation of drug by direct compression

Ingredients	F001
	Quantity (mg / Tab)
Ibuprofen (20 %)	100.0
Pearlitol SD 200 (73.75 %)	358.75
Ac – Di – Sol (5 %)	25.0
Sodium stearyl fumarate (0.5 %)	2.5
Aerosil (0.25 %)	1.25
Orange flavor (0.5 %)	2.5
Acesulfame potassium (2 %)	10.0
Total	500.0

Table 5: Selection of disintegrants and selected disintegrant concentration

Ingredients	Quantity (mg / Tab)					
	Disintegrant selection				Disintegrant concentration selection	
	F001	F002	F003	F004	F005	F006
Ibuprofen (20 %)	100	100	100	100	100	100
Pearlitol SD 200	358.75	358.75	358.75	358.75	368.75	348.75
Super disintegrant	25.0	25.0	25.0	25.0	15.0	35.0
Sodium stearyl fumarate (0.5 %)	2.5	2.5	2.5	2.5	2.5	2.5
Aerosil (0.25 %)	1.25	1.25	1.25	1.25	1.25	1.25
Orange flavor (0.5 %)	2.5	2.5	2.5	2.5	2.5	2.5
Acesulfame potassium (2 %)	10.0	10.0	10.0	10.0	10.0	10.0
Total	500	500	500	500	500	500

F001 – 5 % Ac-Di-Sol, F002 – 5 % Polyplasdone XL, F003 – 5 % Sodium starch glycolate, F004 – 5 % L-Hydroxy propyl cellulose
F005 – 3 % Polyplasdone XL, F006 – 7 % Polyplasdone XL

Table 6: Selection of diluents

Ingredients	F002	F007
	Quantity (mg / tab)	
Ibuprofen (20 %)	100.0	100.0
Pearlitol SD 200 (73.75 %)	358.75	358.75
Ac – Di – Sol (5 %)	25.0	25.0
Sodium stearyl fumarate (0.5 %)	2.5	2.5
Aerosil (0.25 %)	1.25	1.25
Orange flavor (0.5 %)	2.5	2.5
Acesulfame potassium (2 %)	10.0	10.0
Total	500.0	500.0

F002 – Pearlitol® SD 200 (Insoluble), F007 – Lactose monohydrate [Tablettose 80] (Soluble)

Table 7: Selection of flavours and sweeteners

Ingredients	Quantity (mg / Tab)				
	Flavour selection				Sweetener selection
	F008	F009	F010	F011	F012
Ibuprofen (20 %)	100	100	100	100	100
Pearlitol SD 200	311.25	336.25	328.75	338.25	330.25
Superdisintegrant (5 %)	25.0	25.0	25.0	25.0	25.0
Sodium stearyl fumarate (0.5 %)	2.5	2.5	2.5	2.5	2.5
Aerosil (0.25 %)	1.25	1.25	1.25	1.25	1.25
Orange flavor (6 %)	30	-	-	-	-
Peppermint flavor (1 %)	-	5	-	-	5
Grape flavor (2.5 %)	-	-	12.5	-	-
Lemon flavor (0.6 %)	-	-	-	3	-
Acesulfame potassium (6 %)	30.0	30.0	30.0	30.0	-
Aspartame (7.2 %)	-	-	-	-	36.0
Total	500	500	500	500	500

F008 – Orange flavor and Acesulfame potassium sweetener, F009 – Peppermint flavor and Acesulfame potassium sweetener, F010 – Grape flavor and Acesulfame potassium sweetener, F011 – Lemon flavor and Acesulfame potassium sweetener, F012 – Peppermint flavor and Aspartame sweetener

Table 8: Process parameters

S. No	Parameters	Limits
1	Spray gun	Pam Glatt Top spray gun
2	Blower drive speed (%)	45 – 55
3	Inlet air temperature (°C)	30 – 35
4	Product temperature (°C)	35 – 40
5	Atomization air pressure (bar)	1.5
6	Spray pump speed (rpm)	1.0
7	Filter shaking mode	Asynchronous
8	Filter shaking interval (sec)	8
9	Filter shaking pause (sec)	60

Table 9: Granulation of Ibuprofen using PVP K - 30 as binder

S. No.	Ingredients	Quantity (g)
1	Ibuprofen (95.23 %)	300
2	Povidone K – 30 (4.77 %)	15
3	Purified water	q.s

Table 10: Physical evaluation of tablets

	F001
Colour	White
Surface	Smooth
Thickness (mm)	4.48 ± 0.2
Hardness (kP)	3.0 ± 0.5
Weight (mg)	500 ± 1.0
Assay (%w/w)	99.98
D.T. (sec)	27.5 ± 1.45
Friability (%)	1.19 ± 0.37

F001 – 5 % Ac-Di-Sol

Table 11: Physical evaluation of tablets

	F002	F003	F004	F005	F006
Colour	White	White	White	White	White
Surface	Smooth	Smooth	Smooth	Smooth	Smooth
Thickness(mm)	4.45 ± 0.3	4.43 ± 0.3	4.42 ± 0.3	4.48 ± 0.3	4.43 ± 0.3
Hardness (kP)	3.0 ± 0.5	3.0 ± 0.5	3.0 ± 0.5	3.0 ± 0.5	3.0 ± 0.5
Weight (mg)	500 ± 1.2	500 ± 1.3	500 ± 1.6	500 ± 1.0	500 ± 1.5
Assay (%w/w)	101.6 ± 1.1	98.86 ± 0.9	99.76 ± 2.0	98.5 ± 1.3	100.2 ± 1.7
D.T. (sec)	12.1 ± 1.1	42.2 ± 2.3*	35.8 ± 1.66*	13 ± 0.9	15 ± 1.7
Friability (%)	1.15 ± 0.2	1.31 ± 0.5	1.25 ± 0.21	1.19 ± 0.5	1.09 ± 0.9

*Since D.T does not meet intended time of 30 sec, it fails.
F002 – 5 % Polyplasdone XL, F003 – 5 % Sodium starch glycolate, F004 – 5 % L-Hydroxy propyl cellulose, F005 – 3 % Polyplasdone XL, F006 – 7 % Polyplasdone XL

Table 12: Physical evaluation of tablets

	F002	F007
Colour	White	White
Surface	Smooth	Smooth
Thickness (mm)	4.45 ± 0.3	4.43 ± 0.3
Hardness (kP)	3.0 ± 0.5	3.0 ± 0.5
Weight (mg)	500 ± 1.2	500 ± 1.8
Assay (%w/w)	101.6 ± 1.1	99.75 ± 1.3
D.T. (sec)	12.1 ± 1.1	11.8 ± 0.7
Friability (%)	1.15 ± 0.2	1.22 ± 1.4

F002 – Pearlitol® SD 200 (Insoluble), F007 – Lactose monohydrate [Tablettose 80] (Soluble)

Table 13: Physical evaluation of tablets

	F008	F009	F010	F011	F012
Colour	White	White	White	White	White
Surface	Smooth	Smooth	Smooth	Smooth	Smooth
Thickness(mm)	4.44 ± 0.3	4.45 ± 0.3	4.43 ± 0.3	4.44 ± 0.3	4.45 ± 0.3
Hardness (kP)	3.0 ± 0.5	3.0 ± 0.5	3.0 ± 0.5	3.0 ± 0.5	3.0 ± 0.5
Weight (mg)	500 ± 1.2	500 ± 1.8	500 ± 1.6	500 ± 2.0	500 ± 1.0
Assay (%w/w)	100.1 ± 1.4	99.33 ± 0.5	100.7 ± 0.9	99.8 ± 1.7	101.3 ± 2.0
D.T. (sec)	12.8 ± 1.9	12.3 ± 1.2	12.5 ± 1.6	12.2 ± 1.5	12.6 ± 1.7
Friability (%)	1.19 ± 0.9	1.33 ± 1.6	1.26 ± 1.9	1.11 ± 0.6	1.23 ± 1.4

F008 – Orange flavor and Acesulfame potassium sweetener, F009 – Peppermint flavor and Acesulfame potassium sweetener, F010 – Grape flavor and Acesulfame potassium sweetener, F011 – Lemon flavor and Acesulfame potassium sweetener, F012 – Peppermint flavor and Aspartame sweetener

Table 14: Selection of orally disinterating tablets containing different flavors

Volunteer	Flavours											
	Orange			Peppermint			Grape			Lemon		
	A	B	G	A	B	G	A	B	G	A	B	G
1	√				√		√				√	
2		√			√		√			√		
3	√				√		√			√		
4		√				√		√			√	
5	√				√		√			√		
6	√			√				√			√	
7		√			√		√				√	
8	√			√			√			√		
9		√			√			√		√		
10		√		√				√		√		

A – Average, B – Better and G – Good

Table 15: Selection of orally disintegrating tablets with different sweeteners

Volunteer	Sweeteners					
	Acesulfame Potassium			Aspartame		
	A	B	G	A	B	G
1			√			√
2		√	√			√
3			√			√
4		√				√
5			√			√
6			√		√	
7			√			√
8		√				√
9			√		√	
10			√			√

A – Average, B – Better and G – Good

Table 16: Physical evaluation of tablets

	Uncoated tablet	F013
Colour	Off white	Off white
Surface	Smooth	Smooth
Thickness (mm)	4.45 ± 0.3	4.49 ± 0.3
Hardness (kP)	3.0 ± 0.5	3.0 ± 0.5
Weight (mg)	500 ± 1.0	500 ± 1.0
Assay (% w/w)	100.16 ± 1.1	98.79 ± 2.1
D.T. (sec)	8.5 ± 1.5	8.6 ± 1.67
Friaibility (%)	1.38 ± 0.5	1.39 ± 1.4
Wetting time	15.7 ± 0.8	15.3 ± 0.8
Water absorption ratio	55.36	55.85

F013 – Opadry tm coated Ibuprofen MCC tablet

Table 17: % Cumulative drug release of Opadry coated tablet

Time (minute)	Uncoated tablet	F013
5	35.26	30.23
10	47.80	40.19
15	58.63	53.56
20	67.60	62.60
30	89.53	82.53
45	95.86	91.66
60	99.30	97.33

F013 – Opadry tm coated Ibuprofen MCC tablet

Table 18: Physical evaluation of tablets

	Uncoated tablet	F015
Colour	Off white	Off white
Surface	Smooth	Smooth
Thickness (mm)	4.47 ± 0.3	4.48 ± 0.3
Hardness (kP)	3.0 ± 0.5	3.0 ± 0.5
Weight (mg)	500 ± 1.0	500 ± 1.5
Assay (%w/w)	99.51 ± 0.5	100.61 ± 1.7
D.T. (sec)	8.4 ± 1.9	8.3 ± 1.92
Friaibility (%)	1.45 ± 0.45	1.35 ± 0.8
Wetting time	15.2 ± 0.9	15.8 ± 1.2
Water absorption ratio	55.03	55.83

F015 – Eudragit EPO coated Ibuprofen MCC lactose tablet

Table 19: % Cumulative drug release of Eudragit EPO coated tablet and Marketed product

Time (minute)	Uncoated tablet	F015	Marketed product
5	49.03	34.43	88.32
10	66.23	51.46	90.91
15	78.66	63.03	91.29
20	84.90	76.60	91.68
30	96.36	89.26	91.81
45	98.33	94.60	91.94
60	99.06	98.43	95.18

Table 20: Dissolution parameters

Formulation	Dissolution parameters				
	DP_{30min}	$\%DE_{60min}$	$T_{50\%}$	$t_{75\%}$	$t_{90\%}$
F013	82.53	69.33	14	27	41
F014	77.32	65.72	16	28	47
F015	89.26	75.92	9	20	31
Market	91.81	84.49	2	3	13

DP – Percent drug released at particular time, % DE – Percent dissolution efficiency at particular time, $t_{50\%}$ – Time taken to release 50% Ibuprofen, $t_{75\%}$ – Time taken to release 75 % Ibuprofen, $t_{90\%}$ – Time taken to release 90% Ibuprofen, F013 – Opadry tm coated Ibuprofen MCC tablet, F014 – Eudragit EPO coated Ibuprofen MCC tablet, F015 – Eudragit EPO coated Ibuprofen MCC lactose tablet

Table 21: Taste panel study

Formulation	Degree of bitterness after time			
	10 seconds	1 minutes	5 minutes	10 minutes
Uncoated tablet	2	3	3	3
F013	1	1	1	1
F015	0	0	0	0

RESULTS AND DISCUSSION

Selection of formulation method

ODT tablets of Ibuprofen were formulated using Ac – Di – Sol as disintegrant by direct compression method (F001). The D.T. observed for this formulation was 27.5 seconds. To decrease the D.T. of the formulation further, a study was performed using different disintegrants. (Table 10-11)

Selection of diluents in the formulation

The effect of filler was optimized by using Pearlitol® SD 200 (Insoluble – F002) and Lactose monohydrate – Tablettose 80 (Soluble – F007). (Table 12)

Lactose monohydrate showed a lesser disintegration time of 11.8 seconds when compared to that of Pearlitol® SD 200. But when taken *in vivo* the mouth feel of Pearlitol® SD 200 was better than that of Lactose monohydrate as it exhibits negative heat of solution. So, Pearlitol® SD 200 (F002) was selected for further trials. More over the Ibuprofen showed bitter taste. Hence, trials for reduction of bitterness were further carried out.

Taste Masking Strategies

Burning sensation of the Ibuprofen in throat was observed in the formulated ODT tablets (F002). So to mask the unacceptable taste of Ibuprofen a taste masked fast-disintegrating dosage form must be formulated. Taste masking of the drug was carried out by two simpler techniques viz., organoleptic modification and fluidized bed coating (physical barrier). Although many other techniques were popular for taste masking like, usage of β - cyclodextrins, Ion-exchange resins (complexation), solid dispersions like melt extrusion, spray congealing etc. these two methodologies were chosen because the final dosage form that is to be formulated is for an OTC drug and hence it must be cost – effective. Usage of β - cyclodextrins in the formulation increases the cost of final dosage form. Usage of ion exchange resins might increase the contact time between the drug species and the ion exchange resin and more over it also depends on the degree of crosslinking. So taste masking by organoleptic modification and fluidized bed coating were selected as these two methods are simpler and feasible.

Organoleptic Modification – Flavors, Sweeteners

The drug used in the formulation is a bitter / unpleasant tasting pharmaceutical agent. An attempt was made to suppress the bad taste using different flavors and sweeteners. Flavors for taste masking of bitter drugs such as orange, peppermint, lemon, grape flavors were used. Aspartame and Acesulfame potassium sweeteners were used. The results of the formulations were given in Table 13.

10 healthy human volunteers were selected to give ranking for the taste masking effect produced in the ODTs containing different flavors i.e., orange, peppermint, grape and lemon flavors. (Table 14)

5 volunteers ranked better for orange flavor. 6 volunteers ranked better and 1 volunteer ranked good for peppermint flavor. 4 volunteers ranked better for grape and lemon flavors. So, peppermint flavor was selected and incorporated in further formulations. Slight taste masking was observed with Peppermint flavor when compared to other flavors. So, a trial was taken by changing the sweetener (Aspartame) in the formulation. (Table 15)

7 volunteers ranked good for Acesulfame potassium. 8 volunteers ranked good for Aspartame. So, Aspartame was selected and incorporated in further formulations. Rankings given by the human volunteers showed that Aspartame was better than Acesulfame potassium but significant taste masking was not observed even with Aspartame sweetener. As taste masking by organoleptic modification did not work out, drug-coating trials were further carried out.

***In – vitro* evaluation**

% Cumulative drug release of Opadry tm coated tablet is shown in Table 16-17.

***In – vitro* evaluation**

Table 18-21

Results are the mean of 10 volunteers observations. 3 – Strongly bitter, 2 – moderate bitterness, 1 – slight bitterness, and 0 – no bitter taste.

CONCLUSION

This study is aimed at formulating taste-masked orally disintegrating tablets of a bitter drug i.e., Ibuprofen. Taste masking was carried out by fluid bed coating of extruded and spheronized pellets comprising of Ibuprofen, microcrystalline cellulose and lactose. Two marketed taste-masking systems, namely Eudragit EPO and Opadry tm were evaluated. For the formulation of orally disintegrating tablets a range of excipients such as super disintegrants, diluents, sweeteners and flavours were evaluated and a prototype formulation was selected. This prototype formulation had Eudragit EPO coated taste masked pellets and selected excipients. Its disintegration time was found to be about 8 seconds. Tablets were evaluated for their taste, disintegration time, hardness, friability, water uptake and drug release profile. It was concluded from this study that water insoluble, water permeable polymer system like Eudragit EPO can effectively taste mask bitter drugs without unduly affecting their drug release profile. Coating of Ibuprofen loaded MCC pellets with Eudragit EPO had masked the taste but to increase the *in vitro* drug release the pellet composition was changed. Ibuprofen release from MCC pellets involves mechanism of erosion and diffusion which is a slower process than dissolution and diffusion. Therefore to ensure faster drug release, a water soluble excipient, lactose was added to the pellets. Coating of Ibuprofen loaded MCC-Lactose pellets with Eudragit EPO masked the taste and increased the drug release profile by 12 % in 30 minutes. As per objective of the work, the formulation was found to have a disintegration time of less than 30 seconds (about 8 seconds), had good mouth feel and organoleptic properties. With Eudragit EPO the bitterness and burning sensation of drug was significantly masked at low coating levels (15 %) without affecting the Ibuprofen release. Also this method of fluidized bed coating for taste masking and formulation of orally disintegrating tablets by conventional tablet methods could be industrially scalable with further optimization studies.

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