© IJCIRAS | ISSN (O) - 2581-5334
April 2021 | Vol. 3 Issue. 11

TASTE MASKED ORALLY DISINTEGRATING GRANULES OF IBUPROFEN BY MELT GRANULATION TECHNIQUE: A COMPARATIVE STUDY

Dr. Mrs. Pradnya palekar – Shanbhag [1], Miss. Drushti Rane [2]

[1]HOD & Professor in Pharmaceutics Department of Pharmaceutics Oriental College of Pharmacy Sector No. 2, Plot No. 3, 4, 5 Sanpada West, Navi Mumbai

[2]Oriental College of Pharmacy Sector No. 2, Plot No. 3, 4, 5 Sanpada West, Navi Mumbai Pin Code 400 705 Affiliated to University of Mumbai

Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) used for treatment of pain and fever relief are generally bitter in taste. Ibuprofen is an NSAID, belonging to the class of propionic acid derivatives. Conventional solid dosage forms such as tablets and capsules with bitter taste are not palatable; also geriatric and pediatric patient population usually suffer from swallowing difficulties because of the size and weight of these dosage forms. The objective of the study was to formulate taste masked orally disintegrating granules of Ibuprofen with polymer and low melting waxes using melt granulation technique. Formulations using stearic acid with Eudragit EPO and combination of different types of waxes such as glyceryl monostearate, glyceryl behenate with stearic acid were prepared for effective taste masking of the drug. The ratio of Ibuprofen and stearic acid 1:1 was able to give optimal result in masking the bitter taste and obtained desired in vitro release. The granules were found to have excellent flow properties. The in vitro release of the granules was compared with marketed tablet. Optimized formulations of granules showed 90% release of Ibuprofen in 60 mins which is comparable to that of the marketed tablet.

Keyword: orally disintegrating granules; ibuprofen; melt granulation; taste masking; glyceryl monostearate; glyceryl behenate; stearic acid; Eudragit EP

1.INTRODUCTION

Naturally occurring bitter drugs create important challenges for formulation scientists and pharmaceutical industry. This is because it indirectly becomes the deciding factor in the compliance of the formulation, mainly by the paediatric and geriatric population thus affecting the pharmacotherapy. In order to accomplish desired palatability, addition of flavors and sweeteners is required but has its own limitations; also might not be efficient enough to effectively mask the taste buds. Therefore various technological processes are implemented in formulation development in the field of taste masking.[1]

Various methods are employed for effective taste masking such as use of flavours and sweeteners, microencapsulation, complexation with ion exchange resins, use of insoluble prodrug, formation of inclusion complexes, gelation, granulation and colloidal dispersions such as liposomes, multiple emulsions etc. Along with the objective to give better patient compliance, formulation scientists also aim at the process and formulation to be economical, rapid and easy, involving least number of equipment and processing steps with minimal use of excipients without adversely affecting the drug and its bioavailability.[2]

The demand for orally disintegrating dosage forms has enormously increased particularly for geriatric and paediatric patients who experience difficulty in swallowing tablets and capsules. Orally disintegrating dosage forms provide patients with more convenient means of taking their medication thus serving as an effective alternative for such patients.

The objective of the present study was to prepare taste masked orally disintegrating granules of a bitter tasting drug, Ibuprofen. Ibuprofen has very irritating throat catch, and therefore requires taste masking technique that is promising and cost effective.

Ibuprofen is administered 200mg dose once/ twice a day i.e. 200 - 400mg/per day for paediatrics; 200mg dose twice/ thrice a day i.e. 400 - 800mg/per day for adults and 200mg dose twice/ thrice a day i.e. 200 - 400mg/per day (in case of hepatic disorders) or else same as adults for geriatrics. It is prescribed in fever and pain conditions resulting from past injuries or surgeries, migraine, arthritis, abdominal, joint pain etc. As the major problem that occurs with this drug is bitterness and throat catch, taste masking can be achieved with various lipids, waxes or polymers. Different types of low melting point waxes such as glyceryl monostearate, glyceryl behenate, palmitic acid, myristic acid, etc. are used as they form a dense coating over the drug molecules.[2]

Melt granulation of bitter tasting drug with waxes, lipids or polymers along with sweeteners and diluents is one of the easiest and cost effective methods for taste masking. It is a rapid operation with easy scalability. Granulation lowers the effective surface area of the bitter drug that comes in contact with the tongue upon oral administration. Taste masked granules prepared from saliva insoluble polymers can be formulated into different types of oral dosage forms. Hence melt granulation was selected for the taste masking of Ibuprofen.

Concept of orally disintegrating taste masked granules:[3,4]

- Unit dosage form in a sachet
- No requirement for any special measurement
- Placed on the tongue or in the oral cavity
- Self administration is easy
- No requirement of water during administration
- Rapid hydration by saliva to release the medicament
- No fear of chocking
- No special packaging
- Suitable for paediatric and geriatric population, bedridden and dysphagic patients who have difficulty in swallowing.

Thus it was decided to carry out taste masking of Ibuprofen and formulate it as oral disintegrating granules that can be easily administered to patients.

2. MATERIALS AND METHODS

The ingredients were obtained as gift samples. Ibuprofen (Gansons Ltd.); Eudragit EPO (Evonik India); sucralose (Gangwal Chemicals Pvt. Ltd.); glyceryl monostearate and glyceryl behenate (Gattefosse); orange flavour (Asian Flavours And Fragrances); pearlitol and xylitol (Signet Chemical Corporation Pvt. Ltd.). All other chemicals were purchased from Thomas Baker Chemicals Pvt. Ltd.

Development of Taste masked orally disintegrating granules of Ibuprofen

Optimization studies were performed to determine compatibility between the waxes such as glyceryl monostearate, glyceryl behenate and stearic acid and also with polymer such as Eudragit EPO in different trial batches. The aim to perform these trials was to select wax suitable for taste masking and also compatible with Eudragit EPO since the dose of the drug was high. The formulations were prepared using combination of waxes and/ or the polymer as shown in Table 1 and 2. The required quantity of wax(es) was melted and/ or Eudragit EPO was added to the molten mixture. Ibuprofen was added to this molten mass in aliquots with continuous stirring. The homogenous molten mass was poured over the diluent blend and mixed well till the molten mass was completely absorbed by the diluents. The obtained granulated mass was passed through #40 sieve. The extra-granular sweeteners and flavors were blended with the granules for 10 minutes.

Table 1: Composition of trial batches using waxes glyceryl monostearate, glyceryl behenate and stearic acid

Formulation Ingredients	F1	F2	F3	F4	F5	F6
	mg					
Ibuprofen	200	200	200	200	200	200
Glyceryl monostearate	35.7	40.0	35.7	45.7	35.7	35.7
Glyceryl behenate	35.7	40.0	35.7	45.7	35.7	35.7
Stearic acid	-	-	20.0	15	20	14.3
Dextrose Monohydrate	495.5	595.5	-	528.1	-	497.0
Sucrose	-	-	577.9	-	-	-
Microcrystalline Cellulose	94	-	-	-	500.0	94
Sucralose	3.6	3.6	-	3.6	3.6	4.0
Orange Flavour	11.4	11.4	11.4	11.4	11.4	15
Citric Acid	8.9	8.9	8.9	8.0	8.9	8.0
Sodium Chloride	4.6	4.6	7.1	7.0	7.1	4.7
Colloidal Silicon Dioxide	4.5	4.5	5.4	5.5	5.4	5.4
Xylitol	107.1	92	107.06	130.0	-	-
Pearlitol	-	-	-	-	175.0	87.0

Table 2: Composition of trial batches with stearic Acid and Eudragit EPO

Formulation Ingredients	F7	F8	F9	F10	F11	F12
	mg					
Ibuprofen	200	200	200	200	200	200
Eudragit EPO	50	12.5	100.0	20.0	22.0	22.0
Stearic acid	-	-	150.0	200.0	175.0	200
Dextrose monohydrate	307.1	550.0	350.0	375.0	375.0	375.0
Microcrystalline cellulose	300	100	90.0	90.0	80.0	70.0
Sucralose	5.0	5.0	7.0	10.0	5.0	5.2
Orange flavour	35	45	45	50.0	60.0	42
Citric acid	9.0	9.0	5.0	5.0	5.0	5.0
Sodium chloride	4.6	4.0	4.0	4.0	4.0	4.0
Colloidal silicon dioxide	8.0	5.0	9.0	6.0	8.0	8.0
Pearlitol	83.0	70.0	40.0	40.0	66.0	70.0

Characterization Parameters

Determination of Bitterness Threshold Concentration for Ibuprofen: [5-7]

The bitterness threshold concentration for Ibuprofen examines the level of drug bitterness. For this, eight volunteers in the age group of 21-26 years were taken into consideration. The aqueous solution of Ibuprofen with different concentrations (5, 10, 20, 30, 40, 50 μg/ml) were prepared. About 1ml of the solution of each concentration was placed on the volunteer's tongue for a period of 30 seconds, and was spat out later. The same process was repeated with all the volunteers. A gap of 30 minutes was kept in between as tasting intervals with the solutions of different concentrations. The threshold

value was selected on the basis of the lowest concentration that gave bitter taste.

In vivo Taste Evaluation of orally disintegrating granules: Each batch of orally disintegrating granules was subjected to taste evaluation. A panel of ten volunteers in the age group of 21-26 years was used to determine acceptability and palatability of the granules. For taste evaluation, each of the volunteers was given quantity of granules equivalent to a single dose and their responses were recorded according to a standard format. The taste evaluation of the batches was conducted as per score-card for taste evaluation of granules [2,5] as shown in Table 3.

Table 3: Score-card for taste evaluation of granules

Score	Parameters					
	Throat Catch	**Bitter Taste**	**Sweet Taste**	**Flavor**	**Grittiness**	**Overall mouth feel**
1	Extreme throat catch	Extremely Bitter	No sweetener	No flavored	Very high grittiness	Unpalatable
2	Allowable throat catch	Bitter	Less sweetener	Less flavored	High grittiness	Not acceptable
3	Less throat Catch	Less bitter	Acceptable sweetener	Acceptable flavor	Low grittiness	Just acceptable
4	Very less throat catch	Slightly bitter	More than acceptable sweetener	More than acceptable flavored	Low grittiness	Acceptable
5	Slight throat catch	No Bitterness	More than acceptable sweetener	More than acceptable flavored	Very low grittiness	Acceptable
6	Throat catch Absent	No Bitterness	Perfect sweetener	Perfectly flavored	No grittiness	Pleasant mouth feel

Differential Scanning Calorimetry:

It was performed on drug-carrier complex prepared by melt granulation technique to examine molecular interaction between the drug and the carriers. 2-4mg of drug-carrier complex to be analyzed was placed into an aluminium pan of DSC device and covered with aluminium lid. The pan was kept in the oven along with a blank. The sample and blank were unceasingly purged with nitrogen gas and the thermograms were recorded over a temperature range of (0-400˚C) with programmed heating rate of 10°C/min. Temperature calibration was made with an indium standard.

Flow Properties:

The orally disintegrating granules were evaluated for following standard flow properties:

a. Angle of Repose: Fixed funnel method was used to determine angle of repose of the granules.

b. Bulk Density and Tapped Density: To determine the density, the granules were filled in a 100ml capacity measuring cylinder at least till 3/4th the height. Bulk density is calculated as the ratio of weight to the volume of the sample. Tapped density is calculated as the ratio of weight of the sample to the volume after tapping a measuring cylinder for 100 times.

c. Hausner Ratio: Hausner ratio was calculated using the following formula:

$$\text{Hausner Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

In Vitro Dissolution Study of orally disintegrating granules: [8,9]

The dissolution study of optimized formulations was carried out using USP II Apparatus at 50rpm in 900ml of phosphate buffer pH 7.2 at 37±0.5 0C. Aliquots were withdrawn at different time intervals. The withdrawn aliquots were filtered and the filtrate was used to determine the absorbance using UV spectrometer at λ264nm. Dissolution study on marketed tablet (Brufen Film Coated Tablet, 200mg) was also carried using similar conditions.

Drug Content:

A quantity of granules equivalent to 200mg of Ibuprofen was powdered and placed into 100ml volumetric flask. 50ml of ethanol was added to this powder and shaken for 20 mins. The mixture was made to 100 ml with ethanol and after uniform mixing it was filtered using Whatman filter paper. 0.1ml of the filtrate was diluted to 10ml with phosphate buffer pH 7.2 to obtain a concentration of 1000µg/ml. Absorbance of the resultant solution was determined using UV spectrophotometer at λ 264nm to obtain the drug content.

3. RESULT AND DISCUSSION

The bitterness threshold concentration for Ibuprofen was found to be 30µg/ml as shown in Table 4.

Table 4: Bitterness Threshold Concentration for Ibuprofen

Concentration (µg/ml)	Human Volunteers							
	1	2	3	4	5	6	7	8
5	N	N	N	N	N	N	N	N
10	N	N	N	N	N	N	N	N
20	N	N	N	N	N	N	N	N
30	N	N	Y	N	Y	Y	N	N
40	Y	N	Y	N	Y	Y	Y	Y
50	Y	Y	Y	Y	Y	Y	Y	Y

The excipients used in the formulations of orally disintegrating granules were selected based on the result of preformulation study. The low melting point waxes used in the formulation form a dense coat around the drug particles and mask bitter taste of the drug. Eudragit EPO used as a functional polymer for taste masking is insoluble in the mouth and in water therefore prevents release of Ibuprofen in the mouth. Furthermore, Eudragit EPO does not delay the drug release and once the dosage form reaches the stomach, the coating immediately dissolves and releases the drug. Formulation F6 prepared using three lipid waxes glyceryl monostearate, glyceryl behenate and stearic acid could mask the bitter taste of Ibuprofen but left slight throat catch and very low gritty mouth feel and therefore had a Score 5. In comparison, Formulation F12 prepared using stearic acid and Eudragit EPO was satisfactorily taste masked and gave excellent mouth feel with no throat catch and was given a Score 6. Use of stearic acid in the

formulations reduced the throat catch persistent with Ibuprofen. Standard excipients such as sweeteners and flavours enhanced the overall palatability and patient acceptability of the formulations.

Hence formulations F6 and F12 were taken ahead for further evaluation such as flow properties, drug content and in vitro drug release.

From the DSC thermographs it is clearly seen that Ibuprofen has been efficiently coated with stearic acid and Eudragit EPO. Ibuprofen-stearic acid-Eudragit EPO complex is amorphous, seen from the DSC thermograph Figure 4. This indicates formation of a new solid phase, essentially the drug– polymer complex.

Figure 1: DSC thermograph of Ibuprofen

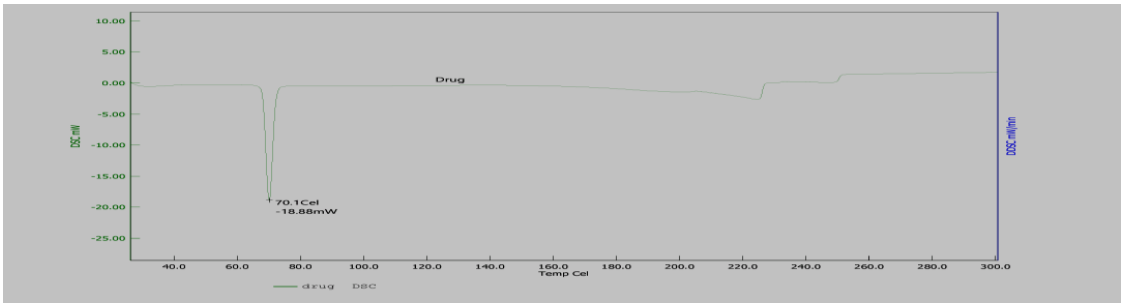


Figure 2: DSC thermograph of Stearic acid

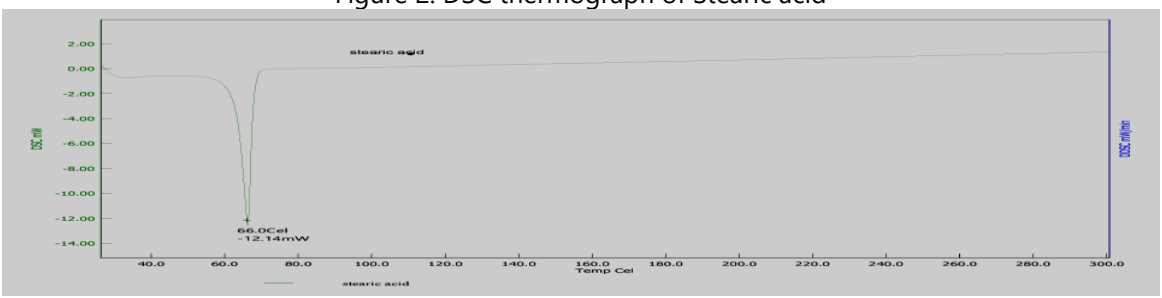


Figure 3: DSC thermograph of Eudragit EPO

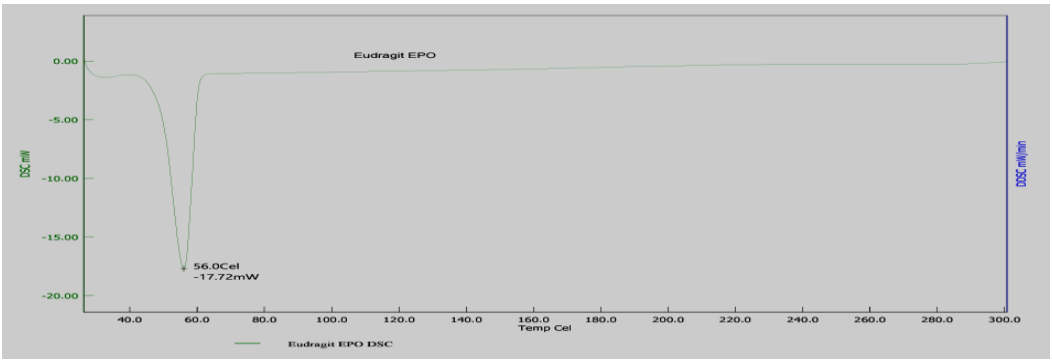
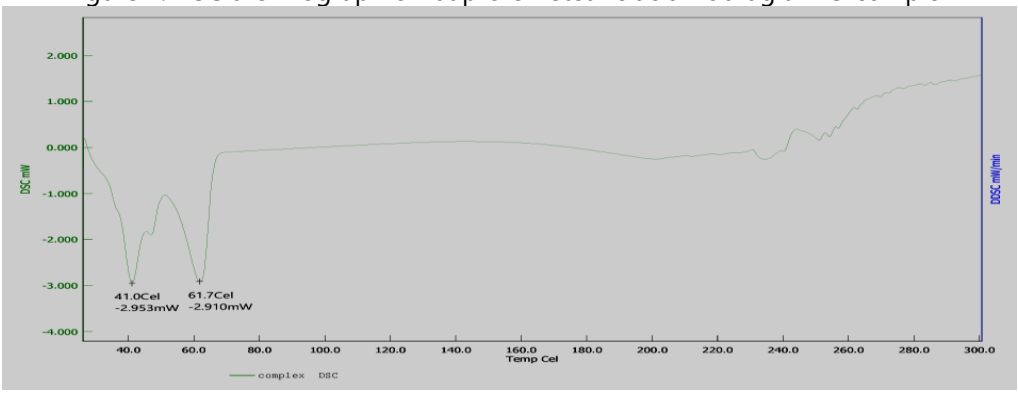


Figure 4: DSC thermograph of Ibuprofen-stearic acid-Eudragit EPO complex



Formulations F6 and F12 exhibited excellent flow properties as shown in Table 5.

Table 5: Results of evaluation of flow properties

Flow Parameters	F6	F12
Angle of Repose (^{0})	28.3 ± 0.095	26.0 ± 0.133
Bulk density (g/cm^3)	0.5203 ± 0.024	0.5175 ± 0.045
Tapped density (g/cm^3)	0.5513 ± 0.038	0.5777 ± 0.033
Hausner ratio	1.18 ± 0.012	1.159 ± 0.034

Formulation F12 showed better drug release compared to the marketed tablet as seen in Table 6. Similarly, the drug release of formulation F6 was comparable with that of the marketed tablet. The drug release results are depicted in Table 7. The faster release in formulation F12 may be attributed to the solubility of Eudragit EPO. The slight delay in drug release from formulation F6 as compared to formulation F12 may be because of solubility of waxes i.e., waxes do not dissolve as rapidly as Eudragit EPO. Formulation F12 showed 91.20 ± 0.521% release, marketed tablet depicted 89.14 ± 0.241% release and formulation F6 gave 87.30 ± 0.545% release in 60 mins.

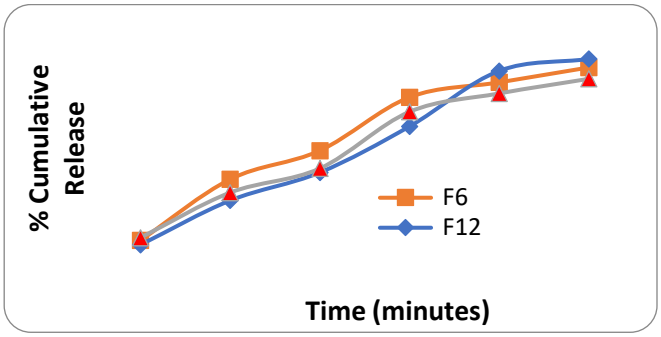
Table 6: In vitro drug release values t25%, t50% and t90% for F6, F12 and Marketed Tablet

***In vitro* drug release values**	**F6**	**F12**	**Marketed Tablet (Brufen Film coated tablet)**
$t_{25\%}$ (mins)	8.45 ± 0.012	6.59 ± 0.020	8.99 ± 0.042
$t_{50\%}$ (mins)	22.86 ± 0.0322	15.86 ± 0.0352	26.02 ± 0.0128
$t_{90\%}$ (mins)	63.5 ± 0.0431	60.07 ± 0.003	61.03 ± 0.058

Table 7: Percent cumulative drug release of F6, F12 and Marketed Tablet in phosphate buffer pH 7.2 and respective drug content

Time (mins)	F6	F12	Marketed Tablet (Brufen Film coated tablet)
5	7.51 ± 0.456	5.44 ± 0.326	8.74 ± 0.342
10	35.69 ± 0.234	38. 89 ± 0.435	29.54 ± 0.477
15	48.91 ± 0.591	52. 81 ± 0.522	40. 68 ± 0.572
30	73.56 ± 0.486	60.08 ± 0.452	66. 83 ± 0.491
45	80.41 ± 0.348	85.72 ± 0.382	75.31 ± 0.352
60	87.30 ± 0.545	91.20 ± 0.521	89.14 ± 0.241
Drug Content (%)	97.87 ± 0.274	102.2 ± 0.285	98.99 ± 0.292

Figure 5: Dissolution Profile of F6, F12 and Marketed Tablet



4. CONCLUSION

Oral administration of bitter drugs of high dose with effective palatability and acceptability especially in the case of paediatric patients is a crucial issue for formulators. Taste masking of oral medicaments has become an essential option to enhance patient compliance. There are several techniques that are adopted for masking bitter taste of various oral medicaments. Orally disintegrating dosage forms such as ODTs, fast disintegrating granules etc. have developed to provide better and convenient means of taking medications for the patients; particularly for geriatric and paediatric patients who experience difficulty in swallowing tablets and capsules. From the present study it was concluded that melt granulation of bitter tasting drug Ibuprofen with lipid waxes and polymer along with standard excipients is one of the simplest and cost effective techniques for taste masking.

5. CONFLICT OF INTEREST

There is no conflict of interest.

6. ACKNOWLEDGEMENT

The authors thank Management of Oriental College of Pharmacy for extending their support and co-operation throughout the research work. We also thank Gansons Ltd. for providing gift sample of Ibuprofen; Evonik India for providing gift sample of Eudragit EPO; Gattefosse for providing gift samples of glyceryl monostearate and glyceryl behenate; Gangwal Chemicals Pvt. Ltd. for providing gift sample of sucralose; Asian Flavours And Fragrances for providing gift sample of orange flavour; Signet Chemical Corporation Pvt. Ltd. providing gift sample of pearlitol and xylitol.

REFERENCES

[1] Ahire S, Gaikwad P, et al. Taste Masking of Metoclopramide Hydrochloride by Novel Melt Granulation. International Journal of Drug Delivery. 2012; 4, 89–94.

[2] Pawar H, Joshi P. Development and Evaluation of Taste Masked Granular Formulation of Satranidazole by Melt Granulation Technique. Journal of Pharmaceutics. 2014, 1–7.

[3] Palekar-Shanbhag P, Sahane C, Belatikar S. Development and Evaluation of Taste Masked Fast Dissolving Oral Strips of Montelukast Sodium and Levocetrizine Dihydrochloride as Combination Therapy. The Pharma Review. 2017;138-144.

[4] Amr H, Sherien K, et al. Preparation, Characterization and In-Vitro/Vivo Evaluation of Indion-Based Chewable Tablets of Paracetamol and Ibuprofen for Pediatric Use. Journal of American Science. 2011;7(12), 831-844.

[5] Albertini B, Cavallari C, Passerini N, et al. Characterization and Taste Masking Evaluation of Acetaminophen Granules: Comparison Between Different Preparation Methods In A High-Shear Mixer. European Journal of Pharmaceutical Sciences. 2004; 21(2-3),295–303.

[6] Chang W, Chung J, et al. The Relationship Between Phenylthiocarbamide (PTC) and 6-Npropylthiouracil (PROP) Taster Status and Taste Thresholds for Sucroseandquinine. Archives of Oral Biology. 2006; 51(5),427–432.

[7] Gao Y, Cui F, Guan Y. Preparation of Roxithromycin-Polymic Microspheres by The Emulsion Solvent Diffusion Method for Taste Masking. International Journal of Pharmaceutics.2006;318(1-2),62–69.

[8] Bora D, Borude P, K. Bhise K. Taste Masking by Spray Drying Technique. AAPS Pharm Sci Tech. 2008;9(4),1159– 1164.

[9] Yajima T, Ishii K, Umeki N, et al. Taste Masking Pharmaceutical Composition. United States Patent US005707646A. 1998.

[10] Shaik M, Arunachalam A, et al. Invention and In Vitro Evaluation of Floating Tablets of Metformin Hydrochloride Using Hydrophilic Polymer as Release Retardant. International Journal of Biological and Pharmaceutical Research. 2012; 3(3),339– 346.