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FORMULATION AND *IN-VITRO* EVALUATION OF TASTE MASKED ORALLY DISINTEGRATING TABLETS OF A BITTER BCS CLASS II DRUG

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Abstract:

The present study concerns to mask the bitter taste of Ibuprofen as an orally disintegrating tab-let using Eudragit EPO (Film former) as a taste masking agent. FT-IR spectrometries were used to investigate the compatibility of drug: resin complex. Six batches (F1, F2, F3, F4, F5, and F6) of orally disintegrating tablets were prepared by wet granulation method with super disintegrant like Crosscarmellose sodium, Crospovidone. The granules were evaluated for pre-compression parameters like angle of repose, bulk density, tapped density, compressibility index and Hausner's ratio. And post-compression parameters like weight variation, thickness, hardness, friability, and in-vitro disintegration and in-vitro dissolution tests. The results indicate that orally disintegrating tablets of Ibuprofen containing Eudragit EPO provides good taste and better option for quick disintegration and fast release and improved bioavailability. 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 min.

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INTRODUCTION:

1. 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. 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.[1,2]

The most common solid dosage forms in contemporary use are tablets, which may be defined as, unit forms of solid medicaments prepared by compaction. One of the major properties governing the patient compliance of the drug is its taste. Oral administration of the bitter drug with an acceptable degree of palatability is a key issue for health care providers. To achieve better compliance and therapeutic value for the patient and more business and profits for the company main practical problem that confronts a pharmacist is to mask the unpleasant taste of the drug. Major taste-masking efforts are required before acceptance of the drug for marketing. [3,4]

2. Fast-Dissolving Dosage Forms

For the past one decade, there has been an enhanced demand for more patient-friendly and compliant dosage forms. As a result, the demand for developing new technologies has been increasing annually. Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency, and the production of more cost-effective dosage forms**.** For most therapeutic agents used to produce systemic effects, the oral route still represents the preferred way of administration, owing to its several advantages and high patient compliance compared to many other routes.[5] Tablets and hard gelatin capsules constitute a major portion of drug delivery systems that are currently available. However, many patient groups such as the elderly, children, and patients who are mentally retarded, uncooperative, nauseated, or on reduced liquid-intake/diets have difficulties swallowing these dosage forms. Those who are traveling or have little access to water are similarly affected. Recent market studies indicate that more than half of the patient population prefers ODTs to other dosage forms and most consumers would ask their doctors for ODTs (70%), purchase ODTs (70%), or prefer ODTs to regular tablets or liquids (>80%).[6,7]

3. Ideal Properties of ODT's

The performance of ODTs depends on the technology used during their manufacture. The necessary property of such tablets is the ability to disintegrate rapidly and disperse or dissolve in saliva, thereby obviating the need for water.[8] Various technologies have been developed that enable ODT to perform this unique function. An ideal ODT should meet the following criteria:

- It does not require water for oral administration yet disintegrates and dissolves in oral cavity within a few seconds.[9]
- It has sufficient strength to withstand the rigors of the manufacturing process and post-manufacturing handling
- It allow high drug loading
- It has a pleasant mouth feel
- It is insensitive to environmental conditions such as humidity and temperature
- It is adaptable and amenable to existing processing and packaging machineries.
- It is cost-effective.[10,11]

Table 1: Drugs explored for orally disintegrating tablets.[12,13]

Category	Drug
NSAIDS	Ketoprofen, Piroxicam, Paracetomol, Rofecoxib, Nimesulide, Ibuprofen
Anti ulcer	Famotidine, Lansoprazole
Anti parkinsonism	Selegiline
Anti depressants	Mitraxepine, Fluoxetine
Anti migrane	Sumatriptan, Rizatriptan benzoate, Zolmitriptan
Anti histaminics	Loratadine, Diphenhydramine, Meclizine
Hypnotics and sedatives	Zolpidem, Clonazepam, Atenolol
Anti psychotics	Olanzepine, Pirenzepine, Risperidone
Anti emetics	Ramosetoron HCl, Ondansetron

Table 2: ODT patents. [14,15]

Technology	Basis	Patent owner
Zydis	Lyophilization	R.P.Scherer Inc.
Quicksolv	Lyophilization	Janseen Pharmaceutica
Lyoc	Lyophilization	Farmlyoc
Flashtab	Multiparticulate compressed Tablets	Ethypharm
Orasolv,Durasolv	Compressed Tablets	Cima Labs Inc.
RapiTab	Compressed Tablets	Schwarz Pharma
WOWTAB	Compressed molded tablets	Yamanouchi Pharma Technologies, Inc.
Fast melt	Molding	Élan Corp.
Ziplets	Molding	Eurand
FlashDose	Cotton-candy process	Fuisz Technology Ltd.

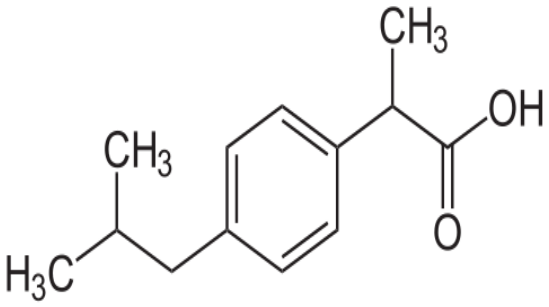

Figure 1: Chemical Structure of Ibuprofen.

Ibuprofen is a commonly used non-steroidal anti-inflammatory (NSAID) drug which is available both by prescription and over-the-counter. Ibuprofen is considered to be among the safest NSAIDs and is generally well tolerated but can, nevertheless, rarely cause clinically apparent and serious acute liver injury. IUPAC name is 2-[4-(2-methylpropyl) phenyl] propanoic acid. Ibuprofen is a non-selective COX inhibitor and hence, it inhibits the activity of both COX-1 and COX-2. The inhibition of COX-2 activity decreases the synthesis of prostaglandins involved in mediating inflammation, pain, fever, and swelling while the inhibition of COX-1 is thought to cause some of the side effects of ibuprofen including GI ulceration. The present study concerns to mask the bitter taste of Ibuprofen as an orally disintegrating tablets using Eudragit EPO as a taste masking agent.[16,17]

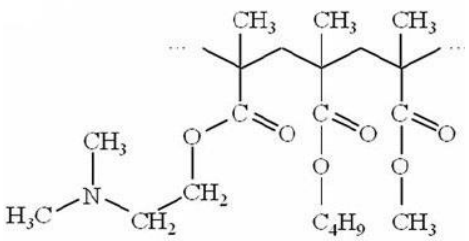

Figure 2: Chemical Structure of Eudragit EPO.

Eudragit EPO (Figure 2), a solid substance obtained from Eudragit E100 polymer was selected for the taste masking. It is a cationic copolymer based on dimethyl aminoethyl methacrylate, butylmethacrylate, and methyl methacrylate and chemically known as poly(butyl methacrylate-co-(2 dimethyl aminoethyl) methacrylate-co-methyl methacrylate. Eudragit EPO shows excellent taste-masking properties even at low film thickness. It can also be used to coat difficult dosage forms, such as multi-particulate fast disintegrating tablets. It is a polymer having low viscosity and high pigment binding capacity and also has good adhesion and low polymer weight gain. It is soluble in gastric pH up to 5.10–12 The oral bioavailability of Ibuprofen is found to be roughly 50% due to first-pass metabolism.8 To enhance its oral bioavailability many techniques were used to develop ODT's Ibuprofen. However, the major problem associated with this drug is its unpalatable taste. Therefore, in the present study, an attempt was made to mask the bitter taste of Ibuprofen by mass extrusion technique using Eudragit EPO in different drug-polymer ratios and later formulated it into more convenient and improved compliance ODTs tablet using different superdisintegrants.[18,19]

MATERIALS AND METHODS:

Ibuprofen and its reference standard were received from Simca Laboratories Pvt. Ltd., Byasi, Bhaktapur, Nepal, as a gift sample. Eudragit EPO was received from Evonik Industries Pvt Ltd as a gift sample. Excipients including MCCP 200, talc, magnesium stearate, sodium starch glycollate, croscarmellose sodium, crospovidone, orange flavor, and sucralose were received from Sigma Aldrich Laboratories Pvt. Ltd, Mumbai as a gift sample. All other chemicals used were of chemical grade.

1. Physical barrier – Fluidized Bed Coating:

Organoleptic modification failed because of the burning sensation observed in the throat. So, taste masking by using fluidized bed processor was chosen, as it is the simplest and most feasible method. Other taste masking techniques like usage of β - Cyclodextrins, ion exchange resins increases the cost of the final dosage form and time for formulating respectively, which is not required, as Ibuprofen is for an OTC market only. Hence other methods for taste masking were not chosen for Ibuprofen used in the present scenario.

Coating method was chosen as it acts as a physical barrier to the drug particles, thereby minimizing interaction between the drug and taste buds. Coating of fast disintegrating tablets, chewable tablets provides excellent taste masking while still providing acceptable bioavailability. [20]

A) Coating of Ibuprofen with Opadry tm coating solution:[21]

Procedure:

1. Drug was accurately weighed and passed through ASTM # 40.
2. Opadry tm film coating material was accurately weighed and passed through ASTM # 40.
3. Isopropyl alcohol was accurately weighed and transferred into a beaker. The Opadry tm coating system was added to isopropyl alcohol under stirring and stirring was continued for about 45min to make a 16% w/w solution.
4. Ibuprofen was loaded in the product cone of the fluid bed processor with the cone in inclined position to avoid dust generation and powder blocking the spray gun.
5. Bottom spray gun was fixed to the fluid bed processor and the process parameters of fluid bed processor were set as given in the table below.

Table 3: 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 4: Coating of Ibuprofen using Opadry tm.

S.No.	Ingredients	Batch Quantity (gm)
1	Ibuprofen	300
2	Opadry tm	16
3	Isopropyl alcohol	84

B) Granulation of Ibuprofen with Povidone K–30 binder in planetary mixer and coating of the granules with Opadry tm:[22, 23]

Procedure:

1. Ibuprofen, Povidone K - 30 were accurately weighed and passed through ASTM # 40 separately.
2. Purified water was accurately weighed and transferred into a beaker.
3. Weighed amount of PVP K-30 binder was added into the water under stirring and stirring was continued for about 20min.
4. The drug was loaded in a planetary mixer and binder solution was gradually added into the dry mix. Mixing was done until granules were achieved.
5. The granules were dried in a retsch rapid dryer for about 30 – 45 min and were checked for their loss of drying.
6. The dried granules were taken and processed for further coating.
7. A 16% w/w solution of opadry tm coating system was prepared by adding weighed amount of opadry coating system into isopropyl alcohol under stirring for about 45min.
8. Top spray gun was fixed to the fluid bed processor.
9. The process parameters of fluid bed processor were set as given in the table below.
10. The granules were loaded in the glatt 1.1 fluid bed processor and coated with the marketed opadry tm solution.
11. The product was dried after completion of the granulation.

Table 5: 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 6: Granulation of Ibuprofen using PVP K - 30 as binder

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

C) Extrusion – Spheronization of Ibuprofen and MCC with PVP K – 30 and coating of pellets with Opadry tm coating solution:[24, 25]

Procedure:

1. Ibuprofen, MCC PH 101, Povidone K – 30, Opadry tm were passed through ASTM # 40 separately and weighed accurately.
2. Drug and MCC were blended in a poly bag for 5 – 10 min.
3. Purified water was accurately weighed and transferred into a beaker.
4. Weighed quantity of PVP K-30 was added slowly into purified water under stirring. Stirring was continued for about 20min.
5. The drug, MCC blend was loaded in a planetary mixer and dry mixing was done up to 5 min.
6. Then the Povidone binder solution was gradually added into the dry mix. Purified water was added until the wet mix showed extrusion property.
7. The wet mass was loaded into an extruder that has a 0.5mm (500μ) extrusion screen to get the cylindrical extrudates that were then passed through an spheronizer to get spherical pellets of 0.5mm.
8. The pellets obtained were then dried in a rapid dryer until they get the dry blend LOD.
9. The dried pellets were then sifted through #35 (500μ), #40, #60 sieves. The pellets retained on #40 were taken for further processing.
10. Opadry tm coating solution was prepared by adding the sifted opadry coating material in a weighed quantity of isopropyl alcohol under stirring. Stirring was done for 45 min to get a 16%w/w solution.
11. Bottom spray gun was fixed to the fluid bed processor and the process parameters were set as given in the table below.
12. The dried pellets were loaded in the product cone with the cone in inclined position to avoid dust generation and pellet blocking the spray gun.
13. Stirring was continued throughout the process to avoid settling of the talc and titanium dioxide in the prepared Opadry tm dispersion.
14. The pellets were dried after completion of the coating process.

RESULTS AND DISCUSSION:

Table 7: Physical evaluation of tablets

	F002	F003	F004	F005	F006
Color	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

1. 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 sweetener was used. The results of the formulations were given in table below.

Table 8: Physical evaluation of tablets

	F008	F009	F010	F011	F012
Color	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 & Acesulfame potassium sweetener
F009 – Peppermint flavor & Acesulfame potassium sweetener
F010 – Grape flavor & Acesulfame potassium sweetener
F011 – Lemon flavor & Acesulfame potassium sweetener
F012 – Peppermint flavor & Aspartame sweetener

2. Physical barrier – Fluidized Bed Coating:

The drug being a propionic acid derivative gives bitter or burning acid taste of the free acid. An attempt was made to mask the disagreeable acid taste of the drug by coating process.

A) Coating of Ibuprofen with Opadry tm coating solution:

The drug has poor flow property, so the drug did not get fluidized in the fluidized bed processor. Agglomerates were formed during the process. So, drug coating with Opadry tm coating solution was not successful.

B) Granulation of Ibuprofen with Povidone K-30 as binder in planetary mixer and coating with Opadry tm in Fluid Bed Processor:

Granules were prepared in a planetary mixer and were dried. The dried granules were sifted through #20 and were further used for coating in FBP using Opadry tm coating solution. The fluidization was better in this trial but even on 20% coating the taste masking was not attained due to irregular shape of the granules. As the objective of the work was to attain good coating efficiency (i.e., good taste masking for minimum coating) the process was stopped at 20% coating level keeping in mind of the weight build up in the formulation. The weight of an ODT should not be more than 500mg as per US FDA guidelines to the industry. So, the weight also played an important role in the formulation. By considering an increase in weight on further coating of the process this trial was stopped.

C) Extrusion – Spheronization of Ibuprofen and MCC with PVP K – 30 and coating of pellets with Opadry tm coating solution:

Uniform coating on granules was not possible as they have improper size and shape and further an increased coating level will be required when compared to that of pellets. As pellets will have uniform shape and size coating will be uniform for each and every pellet. So Extrusion Spheronization process was used for the production of pellets by using an extruder screen of 0.5mm. An attempt was made to formulate Ibuprofen pellets with microcrystalline cellulose and PVP K-30 solution as binder. Microcrystalline cellulose (Avicel PH 101) was used as a spheronization aid in the pellet production. A 0.5mm (500µ) extruder screen was used to get pellets of 0. 5mm.The pellets formulated were further dried and sifted through #35(500µ), #40(425µ) and #60(250µ) sieves. The pellets retained on #40 were taken for coating in FBP. Fluidization of pellets was good when compared to that of granules and taste masking was achieved at 20% coating level.

***In – vitro* evaluation:**

Table 9: Physical evaluation of tablets

	Uncoated tablet	F013
Color	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 10: % Cumulative drug release of Opadry coated tablet

Time (min)	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

% Cumulative drug release of Opadry tm coated tablet is shown in figure 3.

A) Extrusion – Spheronization of Ibuprofen and MCC with PVP K – 30 and coating of pellets with Eudragit EPO spray suspension:

A trial with an water insoluble polymer was carried out. Eudragit EPO is a micronized grade of Eudragit® E 100 solution. In combination with stearic acid and SLS it forms a colloidal solution in water that appears slightly turbid (Tyndall effect). The basic Eudragit® EPO coating suspension contains 10% SLS as a wetting and dispersing agent and 15% stearic acid which forms a soluble salt with the polymer. Though Stearic acid is commercially available in different grades it is highly recommended to use a powder grade quality in order to get optimal processing. Addition of Stearic acid before Eudragit® EPO addition in the preparation of spray suspension helps the polymer to dissolve faster. Aqueous Eudragit® EPO spray suspension was coated onto the Ibuprofen pellets. Prominent taste masking effect was not observed with 5% coating level. At 10% coating, burning taste was slightly masked. At 12% coating level the taste masking was better. At 15% coating level total taste masking was observed.

***In-vitro* evaluation:**

Table 11: Physical evaluation of tablets

	Uncoated tablet	F014
Color	Off white	Off white
Surface	Smooth	Smooth
Thickness (mm)	4.45 ± 0.3	4.48 ± 0.3
Hardness (kP)	3.0 ± 0.5	3.0 ± 0.5
Weight (mg)	500 ± 1.0	500 ± 1.4
Assay (%w/w)	100.16 ± 1.1	100.33 ± 1.9
D.T. (sec)	8.5 ± 1.5	8.3 ± 1.14
Friaibility (%)	1.38 ± 0.5	1.31 ± 1.29
Wetting time	15.7 ± 0.8	15.7 ± 0.4
Water absorption ratio	55.36	58.14

F014 – Eudragit EPO coated Ibuprofen MCC tablet

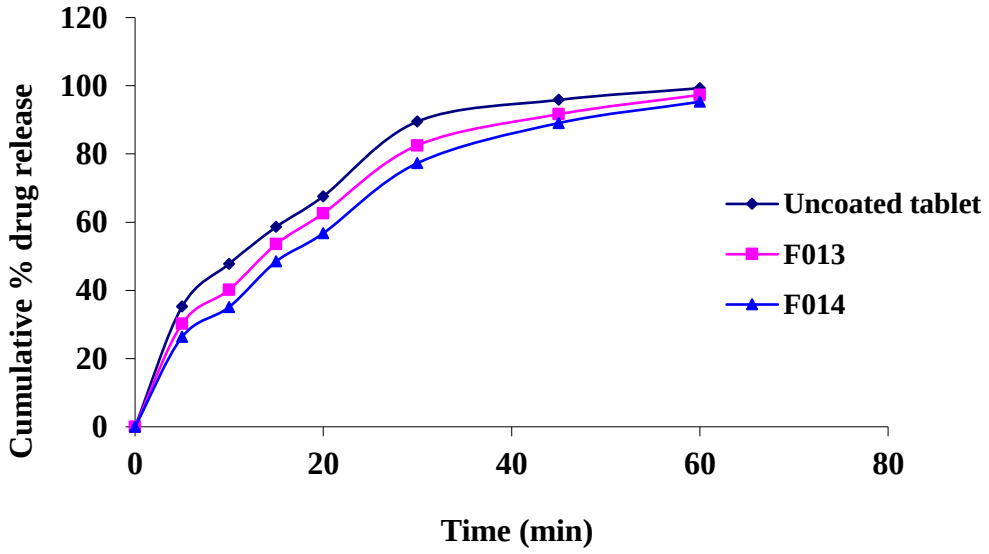

Figure 3: % Cumulative drug release of Opadry and Eudragit EPO coated tablets (Plotted values are average values, n=3, S.D < 2)

B) Extrusion – Spheronization of Ibuprofen, MCC and Lactose Monohydrate with PVP K-30 and coating of pellets with Eudragit EPO spray suspension:

Although microcrystalline cellulose exhibits good binding properties and provides the necessary plasticity for the wet mass to ensure both successful extrusion and spheronization, the MCC-based pellets do not disintegrate faster and drug release occurs via diffusion through an insoluble inert matrix. Lack of disintegration of MCC-based pellets becomes very critical if an active component has poor solubility in water, since the drug release will be prolonged. This might be the reason for the drug to get released slowly in the previous trial (F013 and F014). So, in this trail Lactose and MCC were taken in 1:1 ratio for the preparation of Ibuprofen pellets as the drug release occurs by both diffusion and dissolution. A ratio of Ibuprofen: MCC: Lactose taken in this trial is 1: 0.5: 0.5 i.e., Ibuprofen and excipients were taken in 1: 1 ratio. The pellets obtained by this combination were coated with Aqueous Eudragit® EPO spray suspension at 5%, 10% and 15% coating levels.

CONCLUSION:

From the present study, it can be concluded that the unpalatable taste of Ibuprofen can be masked using Eudragit EPO polymer by mass extrusion technique. It was concluded from this study that water insoluble, water permeable polymer system like Eudragit EPO can effectively taste mask bitter drugs without unduly effecting 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. As per objective of the work, the formulation was found to have a disintegration time of less than 30sec (about 8sec), 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 effecting 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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