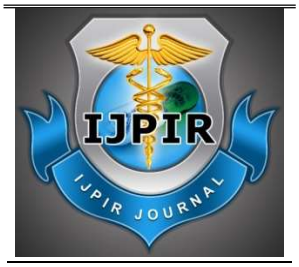
Research Article



ISSN Print 2231 – 3648
Online 2231 – 3656

Available Online at: www.ijpir.com

International Journal of Pharmacy and Industrial Research

Formulation and evaluation of orally disintegrating tablets of ibuprofen with improved oral palatability

Mohamed Rizwan Kareem*; Chandra S; Kavibharathi S; Suresh R; Sangeetha; Dhivya Bharathi P

Department of Pharmaceutics, JKKMMRF Annai JKK Sampoorani Ammal College of Pharmacy, Komarapalayam 638183.

ABSTRACT

The aim of this study was to formulate and evaluate the oral tablet formulations of Ibuprofen fast oral disintegration and increasing the oral palatability by masking the bitter taste of the drug component. As the drug imparts a bitter taste it is optimised in aspect of sweeteners and flavours also obtained by coating a different polymer. The plan of work comprises of characterisation of API with pre formulation studies such as Angle of Repose, Bulk Density, Tapped Density, Compressibility Index, Hausner's Ratio, Particle Size Distribution, Drug excipient comparability study, Solubility study. This is followed by taste masking achieved by addition of sweeteners and flavours and coating with hydrophobic additives. The drug component then processed with the developmental parameters such as Direct compression, Dry granulation and Wet granulation. This part of the formulation is further scaled to identification and optimization of the disintegrants in the formulation. Once the stability parameters of the formulation are accessed, it is then proceeded with analytical process conducted in order to select and evaluate the best formulation among them.

Keywords: Pre-formulation parameters, Taste masking of tablets, Ibuprofen, Hydrophobic polymers, Oral dispersion.

INTRODUCTION

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects, it is the most popular route for drug therapy. 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. The most common solid dosage forms in contemporary use are tablets, which may be defined as, unit forms of solid medicaments prepared by compaction.[5] For the past one decade, there has been an enhanced demand for more patient-friendly and compliant dosage forms.[8]

Recent market studies indicate that more than half of the patient population prefers ODTs to other dosage forms [3]and most consumers would ask their doctors for ODTs (70%), purchase ODTs (70%), or prefer ODTs to regular tablets or liquids

Author for Correspondence:
Mohamed Rizwan Kareem
Department of Pharmaceutics, JKKMMRF Annai JKK Sampoorani Ammal College of Pharmacy, Komarapalayam 638183, India.

(>80%).[1] 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. An ideal ODT should meet the following criteria such as does not require water for oral administration yet disintegrates, sufficient strength, allow high drug loading with a pleasant mouth feel and adaptable and amenable to existing processing and packaging machineries.[7] Various contemporary processes employed in formulating ODTs includes Lyophilization, Molding, Cotton candy process, Spray drying, Mass extrusion, Melt granulation, Phase transition process, Sublimation.

Taste masking is of critical importance for active ingredients with an unpleasant bitter taste, due to the need for increased patient compliance. There are three general taste 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.[4]

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] The approaches are as follows Layer/Coat Process, Granulation, Spray Drying, Complexation, Psychological Modulation of Bitterness, Coacervation, Extrusion Spheronization.[6]

MATERIALS AND METHODS

Materials

Ibuprofen (API - Primary drug, NSAID), Polymethacrylates (Film former, Tablet binder and diluent), Crospovidone (Excipient – Tablet disintegrant) Mannitol (Excipient – Sweetener, diluent and vehicle). Other components such as Sodium lauryl sulphate (NF), Stearic acid, Eudragit EPO, Talc USP, Titanium dioxide USP, Aspartame USP Sodium starch fumarate, Colloidal silicon dioxide.

Methods

In order to formulate a fast-dissolving tablet the choice of super disintegrant and optimisation of the concentration of super disintegrant plays an major role. The main principles for fast dissolving tablets are to disintegrate rapidly in the oral cavity within 15-60 seconds, without the need of water and should have pleasant mouth feel. Here the pre-formulation studies on the drug ibuprofen (API) were carried out as follows.

The pre-formulation studies performed on the drug Ibuprofen include the Bulk density (0.378 gm/cc), Tapped density (0.609 gm/cc), Compressibility (38%), Hausner's ratio (1.61) followed by Particle size distribution and calibration curve of the drug Ibuprofen with pH 7.2 phosphate buffer and 0.1 N Hcl. Adding to it the drug excipient compatibility study was also performed and the drug possesses an intense, well-defined infrared band at 1719.29 cm^{-1} attributed to the stretching of the carbonyl C=O group. This is followed by Formulation development and Evaluation of the tablets.

Formulation Development

The Oral Disintegrating Tablets of Ibuprofen was achieved by direct compression method which incorporates super disintegrants, diluents, flavours, sweeteners and suitable methods employed for taste masking by Fluidised Bed Dryer with various coating preferences. The ibuprofen 100mg, Cross carmallose sodium (Ac-Di-sol), Mannitol, Sodium stearyl fumarate were mixed in glass mortar using a paste later passed through sieve no. 40. The glidant, flavouring and sweetening agent were mixed and sifter on sieve no. 60. Both the mixture were blended in a polybag for 10-15 mins and finally compressed into biconvex, round tablets in 11mm punch at 3.0 ± 0.55 kp.

The Disintegrants were selected from various formulation such asF001 – 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 by comparing the disintegration time (30 sec ideal).

The Diluents were selected from similar other formulation such asF002 – Pearlitol® SD 200 (Insoluble); F007 – Lactose monohydrate [Tablettose 80] (Soluble) the effect of filler was optimized by using these formulations.

Taste masking method were given by organoleptic modification of various flavors and sweeteners carried out by the following combination of formulations such as 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. Since these failed as they produce a burning sensation in

throat the taste masking is achieved by Physical barrier – Fluidized Bed Coating.

Taste masking by coating solution

The Physical barrier by FBD was performed with various coating solutions and the results were compared in order to select the best possible formulation. Initially the coating is performed with Opadry tm coating solution by adding the drug and Opadry tm passed in ASTM #40 with isopropyl alcohol in a beaker and stirring continues for 45min to make 16% w/w solution. Ibuprofen was loaded in the product cone of the FBD with all process parameters set and allowed to dry. Later the same is performed using Ibuprofen with PVP K-30 binder in a planetary mixture and coating of granules with Opadry tm.

Furthermore three formulations were attempted and their cumulative results were compared. **F013** - Extrusion – Spheronization of Ibuprofen and MCC with PVP K – 30 and coating of pellets with Opadry tm coating solution, **F014** - Extrusion – Spheronization of Ibuprofen and MCC with PVP K – 30 and coating of pellets with Eudragit EPO coating solution, **F015**- Extrusion – Spheronization of Ibuprofen, MCC and Lactose Monohydrate with PVP K – 30 and coating of pellets with Eudragit EPO coating solution.

They share similar procedures as the one for F015 is given by the drug, Lactose, MCC PH 101 and PVP K 30 - weighed and passed on ASTM #40 and then PVP K 30 binder added to water and stirred for 20min. The drug, Lactose and MCC were blended in a for 5min.Then the Povidone binder solution and the purified water was added until the wet mix showed extrusion property, which is later loaded onto an extruder that has a 0.5mm screen resulting in spherical pellets of 0.5mm after passing the spheronizer. This is dried in rapid dryer and checked for LOD.

The pellets sifted of #40 is processed using Eudragit® EPO Colloidal solution was prepared by adding SLS, Stearic acid and Eudragit® EPO successively into part of water under stirring, the formation of a clear colloidal solution indicates the end of the process.Talc and titanium dioxide homogenized in water to get a suspension, the colloidal solution formed earlier is mixed with this suspension while stirring homogenizer to get 16% w/w solution which is passed through 0.5mm sieve and processed with coating with bottom spray gun in FBD.

Evaluation of the Tablets

The preliminary evaluation process were carried out such as Physical properties (colour odour), Weight variation, Thickness (Mitutoyo micrometre), Hardness, Friability (Roche Friablator), Taste Evaluation (Healthy volunteers), Wetting Time, Water Absorption Ratio (R), in Vitro Disintegrating test, In Vitro release study etc.

RESULTS AND DISCUSSIONS

As pre-formulation studies showed ideal results as mentioned earlier the interpretation of the other parameters are followed.

Selection of Diluents and Disintegrants

The selection of disintegrants is based on the various formulations F001, F002, F003 and F004. Out of which Polyplasdone XL showed lesser D.T. Different concentrations of Polyplasdone XL (3, 5, 7%) were evaluated from which F002 -5% Polyplasdone XL was selected as it showed lesser D.T. of 12.1 sec when compared to other formulations (Table 1).

The effect of filler was optimized by using Pearlitol® SD 200 (Insoluble – F002) and Lactose monohydrate – Tablettose 80 (Soluble – F007). Pearlitol® SD 200 (F002) was selected for further trials due to better DT of 11.8 sec and good mouth feel taking In Vivo (Table 2).

Table – 1: Physical evaluation of tablets

Parameters	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

Table – 2: Physical evaluation of tablets

Parameters	F002	F007
Color	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

Physical Barrier – Fluidized Bed Coating

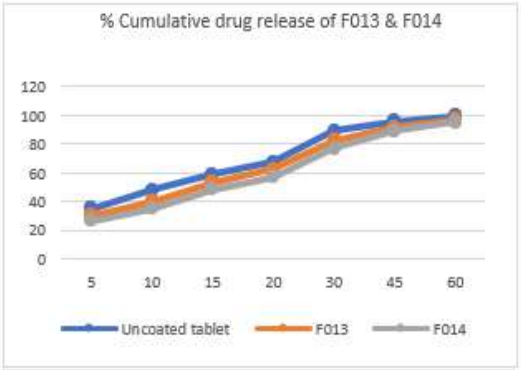
The coating of ibuprofen with Opadry tm coating solution failed due to poor flow property and agglomerates formation. Similarly, granulation of Ibuprofen with Povidone K-30 as binder in planetary mixer and coating with Opadry tm in fluid bed processor was failed to mask taste event with 20% coating.

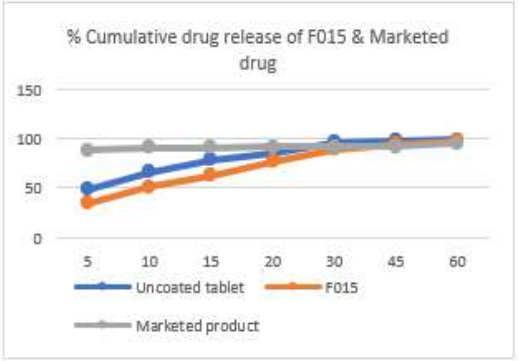
On attempt of Spheronization of drug and MCC with PVP K–30 and coating of pellets with Opadry tm coating solution(**F013**) we found that fluidization of pellets was good when compared to that of granules and taste masking was achieved at 20% coating level.

On attempt of Extrusion – Spheronization of Ibuprofen and MCCwith PVP K – 30 and coating of pellets with Eudragit EPO spray suspension (**F014**) we found that at 12% coating level the taste masking was better. At 15% coating level total taste masking was observed and results are compared. Table 3.

Table –3: Physical evaluation of Tablets

	Uncoated tablet	F013	F014
Colour	Off white	Off white	Off white
Surface	Smooth	Smooth	Smooth
Thickness (mm)	4.45 ± 0.3	4.49 ± 0.3	4.48 ± 0.3
Hardness (kP)	3.0 ± 0.5	3.0 ± 0.5	3.0 ± 0.5
Weight (mg)	500 ± 1.0	500 ± 1.0	500 ± 1.4
Assay (% w/w)	100.16 ± 1.1	98.79 ± 2.1	100.33 ± 1.9
D.T. (sec)	8.5 ± 1.5	8.6 ± 1.67	8.3 ± 1.14
Friability (%)	1.38 ± 0.5	1.39 ± 1.4	1.31 ± 1.29
Wetting time	15.7 ± 0.8	15.3 ± 0.8	15.7 ± 0.4
Water absorption ratio	55.36	55.85	58.14





On attempt of Extrusion – Spheronization of Ibuprofen, MCC and lactose monohydrate with PVP K-30 and coating of pellets with Eudragit EPO spray suspension (**F015**) we found that here we added Lactose in order to prevent the prolonged release of MCC based pellets especially when the API has poor water solubility. The % cumulative drug release of each formulation and physical evaluation were compared. Table 4.

Parameters	Uncoated Tablet	F015
Color	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

Dissolution parameters

The dissolution parameter of the final formulations compared with the marketed product. Table 5

Table –5: Dissolution parameters

Formulation	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

Taste panel studies

The experiment carried out by 10 volunteers and time taken to feel that the last noticeable granule has disintegrated in the oral cavity was considered as the in vivo DT. The resulting mean ±SD were calculated for each. Table 6.

Table –6: Taste study – degree of bitterness

Formulation	10 sec	1 min	5 min	10 min
Uncoated Tablet	2	3	3	3
F013	1	1	1	1
F015	0	0	0	0

Stability studies

The stability studies for the formulation F015 conducted over 3 months of time and the results were found acceptable.

SUMMARY AND CONCLUSION

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. Coating of Ibuprofen loaded MCC-Lactose pellets with Eudragit EPO masked the taste and increased the drug release profile by 12% in 30 min.Thus the final formulation F015 offered the anticipated results and with this the work is concluded.

Acknowledgement

The author would like to thank the Management, HOD and all the staffs of JKKMMRF for their support in this work.

Conflict of Interest

Nil

Source of Funding

None.

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