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DEVELOPMENT OF TABLET CONTAINING NSAIDS DRUGS WITH EXCIPIENTS TREATED WITH CO – PROCESSED TREATMENT OF SPRAY TECHNOLOGY WITH DETAIL STUDY OF OPTIMIZATION AND EVALUATION

Dr. Santosh Kirtane[1] and Dr. Darshit Ram*[2]

[1]Principal, Dean, Faculty of Pharmacy, Noble University, Junagadh, Gujarat, India.
[2]Professor, HOD, Faculty of Pharmacy, Noble University, Junagadh, Gujarat, India.

***Corresponding Author: Dr. Darshit Ram**

Professor, HOD, Faculty of Pharmacy, Noble University, Junagadh, Gujarat, India.

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ABSTRACT

Objective: To optimize suitable processing parameters for the preparation of directly compressible co-excipient, develop suitable method for preparation of directly compressible co-excipient. To develop fast disintegrating directly compressible co-excipient. To develop time and cost saving methods for the development of Fast disintegrating tablet dosage form. To compare the release profile of developed formulation with marketed formulations. **Material and Methods:** UV and IR were carried out with Standard Calibration Curve. The drug-excipients interaction study was carried out by physical observation and also by using FTIR spectroscopy and DSC. From this spray dried diluents; diluent used for further preparation of co-excipients was selected on the basis of their evaluation like spray dried yield, moisture content in spray dried product, flow properties and post-compression characteristics. **Result and Discussion:** For the selection of suitable spray drying parameters, a general suspension containing selected diluent i.e. mannitol, along with disintegrant and binder was sprayed into spray dryer and optimization was done by Box-Behnken design. It was found that for fast disintegrating co-excipient, small quantities of disintegrating agent and binder were required. Therefore, the general suspension (20% w/v) containing diluent, along with disintegrant and binder was prepared by dispersing them in water and then continuous stirring and heating on magnetic stirrer which was then spray dried in Labultima-LU222 lab spray dryer and evaluated for response factors. so as to make the selection of suitable spray drying parameters. The general suspension was contained selected diluent (i.e. mannitol- 94%w/w), disintegrant (Kollidon- 4%w/w) and binder (HPMC-E15LV-2%w/w). quadratic effects of the process parameters of spray dryer on the % yield, moisture content and compressibility index of co-excipient. A 3-factor, 2-level design was used to explore the quadratic and linear response surfaces using Design Expert (Version 8.0.1, Stat- Ease Inc., Minneapolis, MN). **Conclusion:** Spray drying method is suitable for the preparation of directly compressible fast disintegrating co-processed excipient. This co-processed excipient showed improved flow properties, compressibility and less disintegration time with less friability when compressed in tablet form with model drugs. Many Fast disintegrating tablets are prone to friable as their aim is to achieve the less disintegration time; but this problem is successfully solved by using fast disintegrating co-excipient. This new technique saves the time and cost for the development of table dosage forms because of direct compression behavior and multifunctional of co-excipients. The co-processed excipient containing mannitol, HPMC-E15LV and Kollidon has provided less disintegration time with less friability and sufficient strength to the tablets. So it can be used for formulation of Fast Disintegration.

KEYWORD: Ibuprofen, SEM, HPMC, co-excipient, Box-Behnken design.

INTRODUCTION

Fast Disinterrating Tablets

Fast dissolving tablets are one such drug delivery technology that has become a popular dosage form, capturing a market value of $1.1 billion worldwide. Although many fast dissolving tablets technologies are currently available, only a few have reached the commercial market. A new dosage form allows a manufacturer to extend market exclusivity, while offering its patient population a more convenient dosage form or dosing regimen.[1] Oro-dispersible tablet formulations are ideal for either a line extension for existing drugs that the company already owns, or for drugs that no longer have patent protection. Formulating Oro-dispersible tablets of an existing fast dissolving tablet means that both formulations must be bioequivalent. Shorter disintegration times do not necessarily mean quicker absorption in case of some patients.[2-4] Typically, depending on the regulatory strategy, the pharmaceutical company wants to see drug

dissolution rates for an Oro-dispersible tablets that are similar to the immediate-release innovator, at least until an In Vivo In Vitro Correlation (IVIVC) can be made. Mouth feel is critical, and patients should receive a product that feels pleasant. Any large particles from the disintegrating tablet that are insoluble or slowly soluble in saliva would lead to an unpleasant gritty feeling. This can be overcome by keeping the majority of the particles below the detectable size limit. In some cases, certain flavours can imbibe an improved mouth feel perception, resulting in a product that is perceived as being less gritty, even if the only change is the flavour. Effervescence can be added to aid disintegration and improve mouth feel by reducing the "dryness" of a product.[5-8]

Techniques Used in Preparation of Oro-Dispersible Tablets

Basic approaches to developing Oro-dispersible tablets include maximizing the porous structure, incorporating the appropriate disintegrating agent, and using water-soluble excipients in the formulation. Various technologies used in the manufacturing of Orodispersible tablets include, Freeze drying, Molding, Cotton Candy Process, Melt granulation, Mass Extrusion, Phase transition process, Sublimation, Conventional methods-Wet granulation, Direct compression Conventional method includes use of superdisintegrants and highly water-soluble sugar based diluents in the formulation by direct compression or wet granulation.[9]

Another approach used in developing such tablets is maximizing pore structure of the tablets by freeze-drying and vacuum-drying techniques. Freeze-drying yields a fragile and hygroscopic product. It is likely that a porous hydrophilic matrix will easily pick up the disintegrating medium and break quickly. Lyophilization is useful for heat sensitive drugs i.e. thermo-labile substances.[10,11]

The lyophilisation and molding techniques produce Oro-dispersible tablets which disintegrate within about 30 seconds, but that have low physical resistance and high friability. On the other hand, tablets obtained by direct compression are less friable but disintegrate in a longer time. Molded tablets had less mechanical strength. Drug can be present as micro particles or discrete particles dispersed in the matrix. However, adding sucrose, acacia or polyvinyl pyrrolidone can increase mechanical strength. They possess highly porous structure which is supposed to increase their disintegration and dissolution rates.[12]

Directly Compressible Adjuvants

In direct compression, tablets are made from powder blends of active ingredient/s and suitable excipient which are directly compressed. Pre-treatment of the powder blends like wet or dry granulation is avoided.[13] The simplicity of the direct compression process is apparent from a comparison of the steps involved in the manufacture of tablets by wet granulation, roller compaction and direct compression techniques. About less than 20 percent of pharmaceutical materials can be compressed directly into tablets. The rest of the materials lack flow, cohesion or lubricating properties necessary for the production of tablets by direct compression. Although simple in terms of unit process involved, the direct compression process is highly influenced by powder characteristics such flowability, compressibility and dilution potential. No single material likely to exhibit all the ideal characteristics.[22]

Co-Processed Excipients[24]

The physico-mechanical properties of excipients that ensure a robust and successful process are good flowability, good compressibility, low or no moisture sensitivity, low lubricant sensitivity, and good machine-ability even in high speed tableting machines with reduced dwell times. Excipients with improved functionality can be obtained by developing new chemical excipients, new grades of existing materials and new combination of existing materials. New combinations of existing excipients are an interesting option for improving excipients functionality because all formulations contain multiple excipients.[14-18] Co-excipients prepared by incorporating one excipient into the particle structure of another excipient using processes such as co-drying. The concept of co-processing has been applied either to excipients or drug-excipient combinations. The major advantages of co-processed excipients are the elimination of wet granulation production stages, avoidance of keeping and handling various excipients, and the synergetic effect of having homogenous free flowing directly compressible formulation of the required excipients.[19]

Co-processing of excipients causes them to interact at the sub-particle level and lead to superior properties than simple physical mixtures of their components. Co-processing by spray drying is an established industrial process that involves onestep conversion of solution/ dispersion to fine, dustless, porous, agglomerated particles that are spherical and of narrow size range. The powders produced are amenable to processing by direct filling/ compression, thus significantly reducing the validation efforts. As direct compression process is directly influenced by the properties of the excipients.[20-22]

The actual process of developing a co-processed excipient involves the following steps:

- Identifying the group of excipients to be co-processed by carefully studying the material characteristics and functionality requirements
- Selecting the proportions of various excipients
- Assessing the particle size required for co-processing.
- This is especially important when one of the components is processed in a dispersed phase. Post-processing the particle size of the latter depends on its initial particle size.

- Selecting a suitable process of drying such as spray- or flash-drying

Properties of Co-excipients[24]

Absence of chemical change, Improved flow properties, Improved compressibility, Better dilution potential, Fill weight variation, Reduced lubricant sensitivity With the absence of a chemical change during processing, co-processed excipients can be considered generally regarded as safe (GRAS) if the parent excipients are also GRAS-certified by the regulatory agencies.

The present study was an attempt to develop co-processed directly compressible fast disintegrating excipient for fast disintegrating tablets. For this study Ibuprofen was selected as the model drug.

MATERIAL AND METHODS

The following materials was used for the experimental work

(1) Ibuprofen, USP grade Nishchem International Pvt. Ltd, INDIA, (2) Mannitol AR grade Pure chem. (3) HPMC-E15LV AR grade Loba (4) PVP-K30 AR grade Loba (5) Kollidon/Crospovidone AR grade Reseach Lab Fine Chem (6) Croscarmellose sodium AR grade Reseach Lab Fine Chem (7) Talc AR grade Loba (8) Magnesium Stearate AR grade Loba (9) Sodium chloride AR grade Loba (10) Disodium hydrogen phosphate AR grade Loba (11) Potassium dihydrogen phosphate AR grade Loba (12) Sodium hydroxide AR grade Loba (13) Methanol AR grade Merk (14) Hydrochloric acid GR Loba.

The following equipments and instruments have been used in the present research work.

Table 1: The following equipments and instruments have been used in the present research work.

Sr. no.	Model No.	Instruments
1	D455003609	Weighing balance
2	D-Compact	Ultrasonicator
3	LI-86-D	Hot Air Oven
4	Rimek Minipress 2D	Tablet compression machine
5	13-1	Hardness tester
6	EF 1W	Friabilator
7	ETD-1020	Tap density tester
8	2MLH	Mechanical stirrer
9	CL 180	Digital pH meter
10	TDT 08L	USP Dissolution apparatus
11	ED-2L	USP Disintegration test apparatus
12	V-630	UV-vis spectrophotometer
13	CHM-6S	Stability Chamber
14	DSC-60	DSC
15	LU-222 Advanced	Lab Spray dryer
16	DMWB-1	Digital microscope
17	JSM - 6390LV	SEM

Preformulation Identification of Drug Candidates

Identification of Ibuprofen

The sample of Ibuprofen obtained was subjected to identification by its melting point, UV, Differential Scanning Calorimetry thermogram determination.[23]

Melting Point

The melting point of drug was determining by Melting point apparatus using capillary method. The observed value was compare with the reported value.[24]

Ultraviolet Spectrum

UV spectrphotometric study of Ibuprofen was carried out to identify λmax of drug in distilled water. The prepared solution was scan from 200 to 400 nm in UV spectrophotometer and the spectrum was recorded as shown in figure.

Differential Scanning Calorimetry

The thermal behavior of Ibuprofen was examined by DSC, using instrument. Accurately weighed sample of Ibuprofen (5 mg) was run at the scanning rate of 10°C/min over a temperature range of 150 to 300°C. The DSC thermogram was recorded and reported in figure.[25]

Calibration curve of Ibuprofen in Phosphate buffer pH 6.8

Preparation of Standard Stock Solution

An accurately weighed amount (10mg) of drug was dissolved in 25ml of phosphate buffer (pH 6.8) in 100ml volumetric flask and sonicated for 10 minutes and then volume was make upto the mark with same buffer solution which gives 100 µg/ml solution. This was subsequently dilute with phosphate buffer to obtain solutions with concentration of 2-20 µg/ml. The absorbance of these solutions was measured at 266 nm (λmax) using phosphate buffer as blank. The observations was record in table 8.3 and the calibration curve was prepare by plotting absorbance versus concentration of Ibuprofen as shown in figure 7.3.

CHARACTERIZATION OF EXCIPIENTS[26-30]

All the excipients was characterize for its odour, appearance, nature and for solubility determination and results was recorded in table

Appearance and Nature

Appearance and nature of the excipient was observing by visual observation.

Solubility

The pre-weighed sample of excipients was take and study for solubility behaviour in aqueous and some organic solvents.

Development of spray dried co-processed directly compressible fast disintegrating excipient

Formulation of spray dried co-excipient was make in 3 stages, which includes,

1. Selection of diluent which used for further preparation of spray dried co- excipient.
2. Optimization of spray drying conditions so as to make the selection of suitable spray drying parameters.
3. Preparation of fast disintegrating co-excipient by using optimized spray drying parameters.

Spray drying operations was performing on Labultima LU 222 advanced lab spray dryer. From literature and preliminary trials, it was found that, it is necessary to use optimized operating spray drying conditions along with selection of proper excipients in their proper concentration so as to get the desired characteristics of co-excipient which is formed.

Selection of diluent

In this study, 20% w/v suspensions/solutions of individual diluent (lactose, MCC and mannitol) was prepared by dispersing them in distilled water and then continuous stirring and heating on magnetic stirrer which was then spray dried in Labultima-LU222 lab spray dryer.[31-33]

Table 2: Process conditions of spray dryer.

Sr. no.	Process parameters	settings
1	Inlet drying air temperature	120°c
2	Outlet drying air temperature	80°c
3	Feed rate	5 rpm
4	Atomisation pressure	2 bar
5	Aspiration speed	80

After characterisation of the flow properties of spray dried diluents, they was compress by using rotary tablet compression machine (Karnavati, 8 station, 8.6 mm circular, concave faced). These tablets was then evaluate for hardness, disintegration and friability tests to determine the strength of spray dried diluent in terms of its tablet hardness, along with disintegration and friability.[34]

Table 3: Diluents for spray drying.

Sr. No.	Diluent	Suspension/solution	Evaluation of spray dried diluent
1	Lactose	20%w/v Solution	Spray dried yield, moisture content in spray dried product, Flow properties, Post-compression properties.
2	Mannitol	20%w/v Suspension	
3	MCC	20%w/v Suspension	

From this spray dried diluents; diluent used for further preparation of co-excipients was selected on the basis of their evaluation like spray dried yield, moisture content in spray dried product, flow properties and post-compression characteristics.

Optimization of spray drying conditions[35-37]

For the selection of suitable spray drying parameters, a general suspension containing selected diluent i.e. mannitol, along with disintegrant and binder was spray into spray dryer and optimization was done by Box-Behnken design.

Preliminary trials was carried out to evaluate necessity of disintegrant and binder and it was found that for fast disintegrating co-excipient, small quantities of disintegrating agent and binder was required. As selected diluent alone produces hard tablets and more disintegration time, hence it was necessary to use disintegrant to decrease the disintegration time, but use of disintegrating agent increases friability and decreases binding strength of tablets, hence binder was requiring. herefore, the general suspension (20% w/v) containing diluent, along with disintegrant and binder was preparing by dispersing them in water and then continuous stirring and heating on magnetic stirrer which was then spray dried in Labultima-LU222 lab spray dryer and evaluated for response factors (dependent variables) so as to make the selection of suitable spray drying parameters. The general suspension was containing selected diluent (i.e. mannitol-94%w/w), disintegrant (Kollidon- 3%w/w) and binder (HPMC-E15LV-3%w/w).[38]

Preparation of fast disintegrating co-excipients

From the stage-1 study it was found that the spray dried mannitol is a better diluent and therefore can be used for further preparation of co-excipients. Also from stage-2 study, i.e. experimental design of spray dryer, it was found that the processing parameters of spray dryer such as inlet temperature 100°c, atomization pressure 2 bar and feed rate 5 rpm was suitable parameters for co-processing of excipient by spray drying method. Hence it was confirmed that these processing parameters of spray dryer was be used in stage-3 study.[39]

In this stage-3 study, feed suspensions of diluent along with binder and disintegrant was prepared by using 32 factorial designs as per shown in table 6.6. In this design, levels of binder (HPMC-E15LV, PVP-K30) and disintegrant (i.e. Kollidon, Croscarmellose) has made and remaining weight for co-excipient preparation was adjusted by diluent i.e. mannitol. The feed suspensions was spray dried using optimised spray drying process parameter After characterisation of the flow properties of co-excipients, they was compress by using rotary tablet compression machine (Karnavati, 8 station, 8.6 mm circular, concave faced). These tablets was then evaluate for hardness, disintegration and friability.[40]

Table 4: Preparation of co-excipients C1 to C9.

Sr. No.	Excipient	Trial no.								
		C1	C2	C3	C4	C5	C6	C7	C8	C9
1	Mannitol (%w/w)	97	95	93	96	94	92	95	93	91
2	Kollidon (%w/w)	3	3	3	4	4	4	5	5	5
3	Croscarmellose (%w/w)	-	-	-	-	-	-	-	-	-
4	HPMC-E15LV (%w/w)	0	2	4	0	2	4	0	2	4
5	PVP-K30 (%w/w)	-	-	-	-	-	-	-	-	-

Table 5: Preparation of co-excipients C10 to C18.

Sr. No.	Excipient	Trial no.								
		C10	C11	C12	C13	C14	C15	C16	C17	C18
1	Mannitol (%w/w)	97	95	93	96	94	92	95	93	91
2	Kollidon (%w/w)	3	3	3	4	4	4	5	5	5
3	Croscarmellose (%w/w)	-	-	-	-	-	-	-	-	-
4	HPMC-E15LV (%w/w)	-	-	-	-	-	-	-	-	-
5	PVP-K30 (%w/w)	0	2	4	0	2	4	0	2	4

Table 6: Preparation of co-excipients C19 to C27

Sr. No.	Excipient	Trial no.								
		C19	C20	C21	C22	C23	C24	C25	C26	C27
1	Mannitol (%w/w)	97	95	93	96	94	92	95	93	91
2	Kollidon (%w/w)	-	-	-	-	-	-	-	-	-
3	Croscarmellose (%w/w)	3	3	3	4	4	4	5	5	5
4	HPMC-E15LV (%w/w)	0	2	4	0	2	4	0	2	4
5	PVP-K30 (%w/w)	-	-	-	-	-	-	-	-	-

Table 7: Preparation of co-excipients C28 to C36.

Sr. No.	Excipient	Trial no.								
		C28	C29	C30	C31	C32	C33	C34	C35	C36
1	Mannitol (%w/w)	97	95	93	96	94	92	95	93	91
2	Kollidon (%w/w)	-	-	-	-	-	-	-	-	-
3	Croscarmellose (%w/w)	3	3	3	4	4	4	5	5	5
4	HPMC-E15LV (%w/w)	-	-	-	-	-	-	-	-	-
5	PVP-K30 (%w/w)	0	2	4	0	2	4	0	2	4

Formulation of NS Fast Disintegrating Tablets

Formulation Development

It is necessary to understand the theoretical formulation and target processing parameters as well as the ranges for each excipients and processing parameter. Conventional oral tablets usually contain the same classes of components in addition to the active pharmaceutical ingredients which are one or more agents functioning as a diluent, a binder, a flow promoter, a disintegrant and a lubricant. Other more optional components include colorants, and infast disintegrating and chewable tablets, flavours and sweeteners. Oro-dispersible tablet according to the present investigation comprised of a model drug, co-excipient (which functions as diluent, disintegrant as well as binder) and optionally other pharmaceutical excipients like flow promoters. After determining drug loading capacity of selected co-excipient, it has been decided that tablet formulation had to be formed as per stated in table.[41]

Table: 8 Formulation design of Ibuprofen sodium Oro-dispersible tablets.

Sr. No.	Materials (% Amount per tablet)	Amount in mg
		Naproxen Sodium
1.	Model drug dose (X)	250
2	Co-excipient C5 (98.5-X)	196.25
3.	Glidant- talc (0.5)	1.25
4.	Lubricant- Mg. stearate	2.5
5	Weight of tablet	450

Process Development

ODT of Ibuprofen was formulated by direct compression method because of use of directly compressible spray dried co-excipient. Direct compression is regarded as a relatively quick process was the powdered materials are compressed directly without changing the physical and chemical properties of the drug. The use of direct compression reduced number of manufacturing steps like

granulation, drying and performed by use of conventional equipment.[42]

Drug Content for Ibuprofen tablets

Twenty tablets was weigh and powdered. The blend equivalent to 50 mg of Ibuprofen was weighed and dissolved in 60 ml of methanol in a 200-ml volumetric flask and dilute to volume with methanol. Dilute 5.0 ml of this solution to 100.0 ml with methanol and measure the absorbance of the resulting solution at the maximum at about 285 nm, using a UV-Visible double beam spectrophotometer.[43]

Content Uniformity of Ibuprofen tablets[44]

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch. Due to increased awareness of physiological availability, the content uniformity test has been included in the monographs of all coated and uncoated tablets intended for oral administration was the range of size of the dosage form available includes 50 mg or smaller sizes. The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch. For content uniformity test, 10 tablets was assay individually. At least 9 must assay within ± 15% of the declared potency and none may exceed ± 25%.[61]

In vitro Disintegration Time

The disintegration time offast disintegrating tablets was determining in disintegration test apparatus in accordance with the official European Pharmacopoeia monograph 'Oro-dispersible tablets' stating a maximum disintegration time of 3 min.[6] Disintegration or more specifically dispersion times was measure in 900 ml purified water according to the I.P. method without using disc at room temperature (25°C ± 2°C).[44-46]

In vitro Dissolution Study

A direct relationship between in vitro dissolution rate of many drugs and their bioavailability has been demonstrated and is generally referred to as in vitro-in vivo correlation, IVIVC. Dissolution conditions for drugs listed in a pharmacopoeia monograph, is a start with for a bioequivalent study of ODT. Other media such as 0.1N HCl and buffers (pH - 4.5 and 6.8) should be evaluated for ODT. The USP 2 Paddle apparatus is the most suitable and common choice for orally-disintegrating tablets, with a paddle speed of 50 rpm commonly used. Typically, the dissolution offast disintegrating tablet is very fast when using USP monograph conditions; hence slower paddle speeds may be utilized to obtain a profile. The USP 1 Basket apparatus may have certain applications but sometimes tablet fragments or disintegrated tablet masses may become trapped on the inside top of the basket at the spindle was little or no effective stirring occurs, yielding irreproducible dissolution profiles.[47,48]

RESULTS AND DISCUSSION

Identification of Ibuprofen

Melting point

Melting point was found at 153-158 ° C which matches with the reported value.

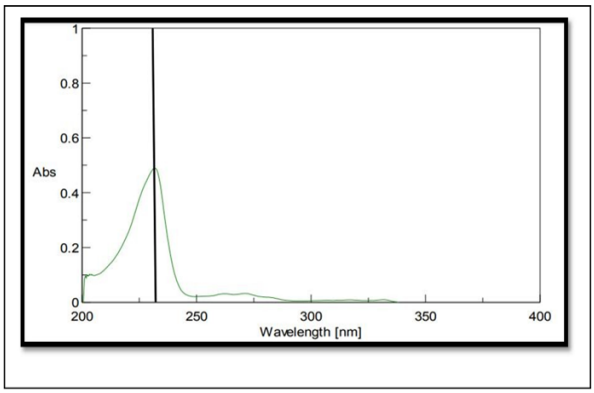

Fig 1: UV spectra of Ibuprofen in phosphate buffer (pH 6.8).

Differential Scanning Calorimetry

Differential scanning thermogram showed endotherm at 289.32° C which was ascribed to drugs melting.

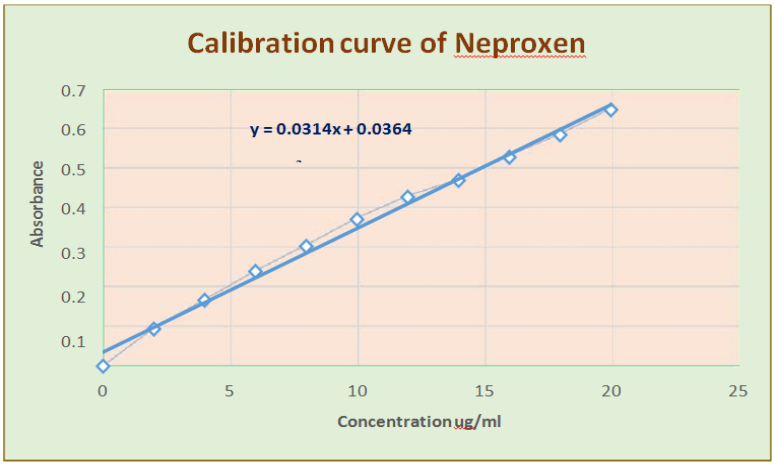

Fig 2: Calibration curve of Ibuprofen in Phosphate buffer pH 6.8.

Fourier-Transform Infrared Spectroscopy

Drug-polymer interactions were studied by FTIR spectroscopy. The spectra were recorded for pure drug, polymer and various ratios drug and polymer. All the prominent peaks of the drug and polymer were retained.

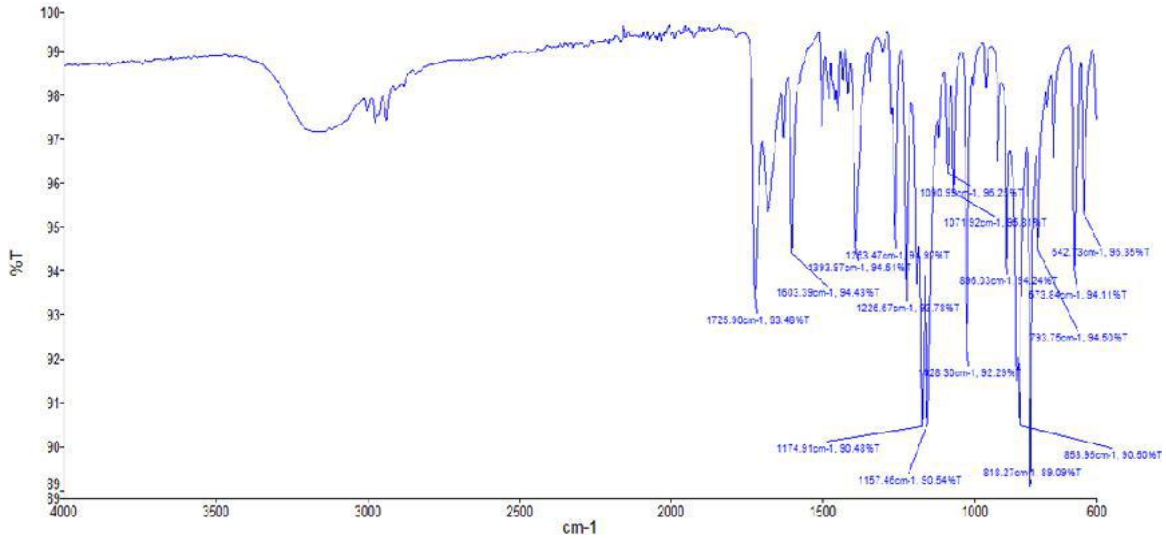

Fig 3: FTIR spectra of M1 (Pure drug – Ibuprofen).

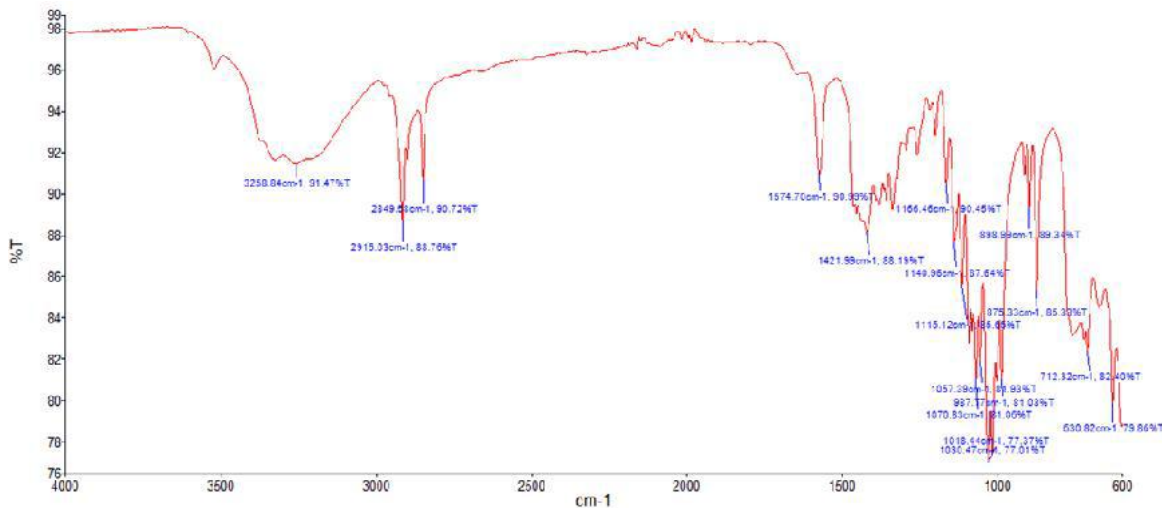

Fig 4: FTIR spectra (Polymer- HPMC E15).

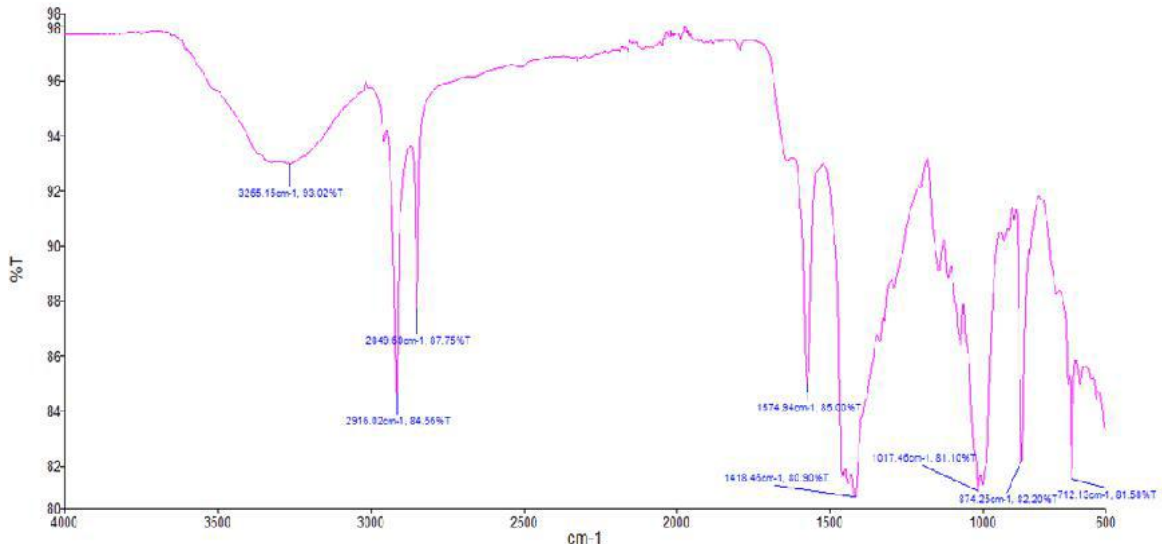

Fig 5: FTIR spectra of M3 (Ibuprofen+ Mannitol+ Kollidon+HPMC.

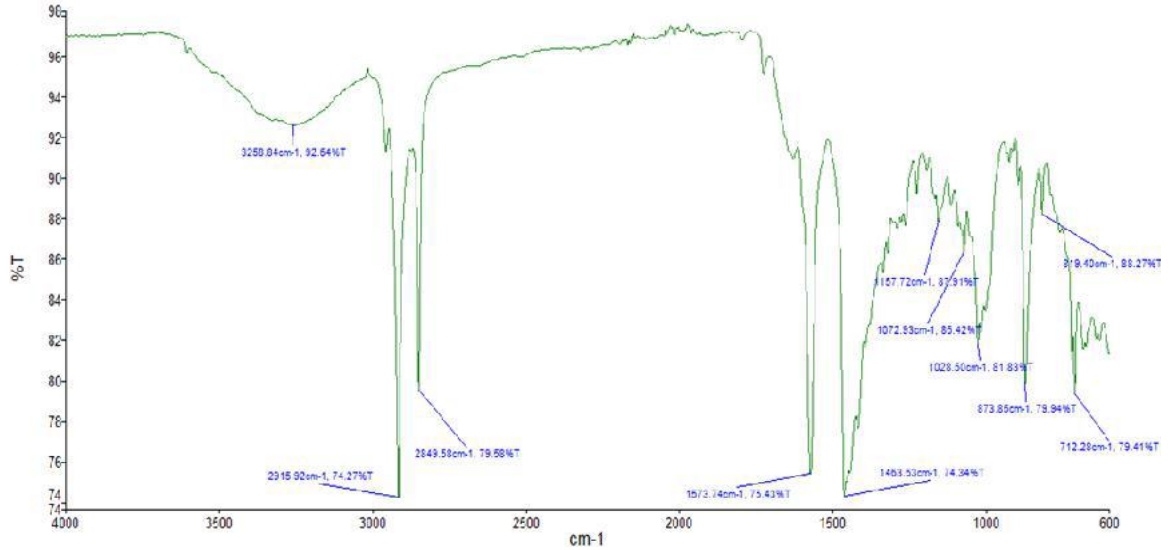

Fig 6: FTIR spectra (Ibuprofen +Mannitol +Kollidon+ PVP K30)

Characterization Of Spray Dried Diluents

In this study, diluents was spray dried and from this spray dried diluents; diluent used for further preparation of co-excipients was selected on the basis of their evaluation characteristics. Spray drying of diluents was done by using processing parameters of spray dryer as shown in table. In this stage, diluent for preparation of co-excipient was selected among lactose, MCC and mannitol. Here, spray dried diluents were prepared and evaluated for flow properties, moisture content, percentage yield and for postcompression characteristics. The results obtained from this evaluation were recorded in table.

Table 9: Characterization of spray dried diluents.

Diluent	EVALUATION PARAMETERS*						
	Spraydried yield (%)	Moisture content	Carr's Index(%)	Flow	Hardness (Kg/cm^2)	Friability (%)	Disintegration Time (sec)
Lactose	14.32	2.41	17.39 ± 0.019	Poor	4.5±0.015	0.212 ±0.014	121±0.231
Mannitol	19.71	1.83	24.96 ± 0.091	Fairto pass	4.2±0.015	0.324 ±0.045	84±0.117
MCC	8.07	4.67	33.06 ± 0.017	Verypoor	5.1±0.015	0.127 ±0.031	247±0.421

Optimization of Spray Drying Conditions

From literature and from preliminary study, it was found that it is necessary to use optimized operating spray drying conditions along with selection of proper excipients in their proper concentration so as to get the desired characteristics. From preliminary study, it was found that fast disintegrating co-excipient was required diluent, along with small quantities of disintegrating agent and binder. As selected diluent alone produces hard tablets and more disintegration time, hence it was necessary to use disintegrant to decrease the disintegration time.

Table 10: Analysis of variance for response Y1 (spray dried yield).

Source	Sum of Squares	Df	Mean Square	F Value	p-value Prob > F	Significance
Model	60.73	9	6.75	35.06	<0.0001	S
X1-inlet temp.	39.03	1	39.03	202.78	<0.0001	S
X2-Atom.pres.	10.58	1	10.58	54.97	0.0001	S
X3- feed rate	2.99	1	2.99	15.53	0.0056	S
X1X2	1.06	1	1.06	5.51	0.0513	NS
X1X3	0.06	1	0.06	0.31	0.5939	NS
X2X3	0.21	1	0.21	1.09	0.3292	NS
$X1^2$	5.74	1	5.74	29.83	0.0009	S
$X2^2$	0.54	1	0.54	2.83	0.1363	NS

$X3^2$	0.84	1	0.84	4.37	0.0748	NS
Residual	1.34	7	0.19	-	-	-
Lack of fit	1.19	3	0.39	10.31	0.0236	S
Pure error	0.15	4	0.038	-	-	-
Cor total	62.08	16		-	-	-

*S indicates significant #NS indicates non-significant

The Model F-value of 35.06 implies the model is significant. There is only a 0.01% chance that a "Model F-Value" this large could occur due to noise. Values of "Prob > F" less than 0.0500 indicate model terms are significant. In the table p values for response Y1 (spray dried yield) represent

Validation of Optimum Parameters

A numerical optimization technique by the desirability approach was used to generate the optimum settings for the spray dryer. The process was optimized for the dependent (response) variables Y1, Y2 and Y3. The optimum batch was selected based on the criteria of attaining the maximum value of percent spray dried yield, minimum value of percent moisture content and minimum compressibility index. This illustrates the comparison between the observed and predicted values of the responses Y1, Y2 and Y3 for the entire batch presented. It can be seen that in all cases there was a reasonable agreement between the predicted and the experimental values, as prediction error was found to be minimum. For this reason, it can be concluded that the equations describe adequately the influence of the selected independent variables on the responses under study.

Evaluation of Prepared Oro-Dispersible Tablets And Their Comparison With Marketed Products

Table 11: Evaluation of prepared Oro-dispersible tablets and their comparison with marketed products.

Evaluation Parameters*	Ibuprofen ODT	
	Prepared	Marketed
Appearance	450 mg, off-white, 8.7 mm, round concave faced.	500 mg, white, triangular flat faced
Weight Variation (± %)	0.714±2.756	0.732±2.193
Hardness (Kg/cm2)	3.91±0.047	5.05±0.117
Thickness (mm)	4.55±0.097	3.9±0.443
Friability (%)	0.7818±0.08	0.3399±0.05
Drug Content (%)	101.58±1.5	100.75±0.85
Content Uniformity (%)**	101.90±1.2	100.9±1.02
Water Absorption Ratio (%)	70.73±0.24	79.34±0.843
Wetting Time (Sec)	42.21±0.31	48.70±0.791
***In vitro* DT (Sec)**	65.41±0.12	85.37±0.655
DP60 (%)	15.3±0.173	12.91±0.341

In vitro Disintegration Time

Disintegration, the first important step for a drug absorption from a solid dosage form after oral administration was preliminarily focused. It was reported that tablet disintegration was affected by the particle size, the degree of substitution, and extent of cross-linkage. An important factor affecting the disintegration is the tablet hardness and/or the compaction force used in making the tablet hardness. The hardness of the tablet has an influence on the disintegration time as it affects the porosity of the matrix and, accordingly, the ability of water to penetrate through the matrix. Tablets containing Kollidon seemed to swell immediately despite the limited swelling capacity and also exhibit a high capacity to retain deformation during post-compression.

In vitro Dissolution Study

Disintegration usually reflects the effect of formulation and manufacturing process variables, whereas the dissolution from drug particles mainly reflects the effect of solubility and particle size, which are largely properties of the drug raw material, but can also be influenced significantly by processing and formulation. Like disintegration testing, dissolution tests do not prove conclusively that the dosage form will release the drug in vivo in a specific manner, but dissolution does come one step closer, in that it helps establish whether the drug can become available for absorption in terms of being in solution at the sites of absorption. Differences in the particle size generated in the disintegrated tablets could affect drug dissolution since breaking tablets into finer fragments may promote drug dissolution by providing larger total surface areas for drug dissolution to take place. Dissolution and release and absorption be heavier is varying from drug to drug and it depends on nature, characteristics and BCS class of the system. In present investigation Ibuprofen as model drug was utilized. Therefore, their dissolution conditions were different.

Comparison of dissolution profiles of prepared and marketed tablets

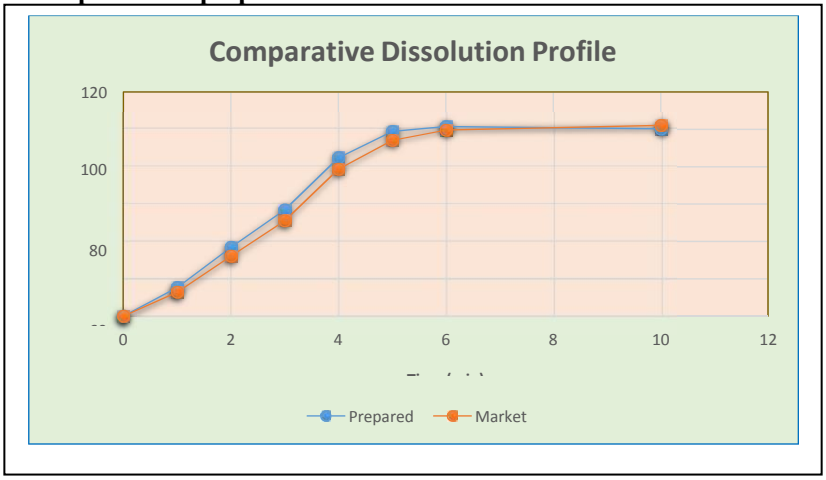

Fig.7: Comparative dissolution profile for prepared and marketed Ibuprofen tablets.

Stability Study

Three stability batches of optimized formulation C5 was prepared and subjected for stability studies as per ICH guideline for 30 days. The pellets were evaluated for physical appearance, assay, in-vitro dissolution studies.

Table 12: Stability Study of an Optimized Formulation.

Stability (400C±20C,75 ±5%RH)	Hardness (Kg/cm2) *	Friability (%)*	Drug content (%)*	%CDR *
0 Days	3.91 ± 0.047	0.7818 ± 0.08	101.58 ± 0.15	100.21 ± 0.112
10 Days	3.89 ± 0.55	0.7796 ± 0.12	99.24 ± 0.78	99.33 ± 0.72
20 Days	4.12 ± 0.39	0.7279 ± 0.08	98.72 ± 0.39	101.63 ± 0.75
30 Days	3.98 ± 0.21	0.6989 ± 0.11	97.92 ± 0.55	98.92 ± 0.46

DISCUSSION

In the present dissertation work, development of directly compressible fast disintegrating co-processed excipient for Oro-dispersible tablets was done by spray drying method. First, general setting of spray dryer was done to select the suitability of one diluent from three diluents which was used for the preparation of co-excipient. The selected diluent mannitol (94%w/w) which was then mixed with disintegrant (kollidon-3%w/w) and binder (HPMC-E15LV-3%w/w) to form 20%w/v suspension which was then spray dried using Box-Behnken experimental design for optimization of processing parameters of spray dryer. The results of experimental design showed that the processing parameters of spray dryer such as Inlet temperature 100°C, atomization pressure 2 bar and feed rate 5 rpm produced the good quality spray dried product, therefore these parameters were selected for further study.

The next step of this work was to develop the directly compressible fast disintegrating co-processed excipient for Oro-dispersible tablet. In this stage, 36 coexcipients were prepared containing mannitol, Kollidon, Croscarmellose, PVP-K30 and HPMC-E15LV at various concentration using optimized processing parameters of spray dryer. All the batches of co-processed excipient were evaluated for flow properties and for post-compression properties. From this evaluation, co-excipient C5 (containing mannitol-94%w/w, kollidon-4%w/w, and HPMC-E15LV-2%w/w) was selected because of its good flow properties and post-compression properties

The next stage of this work was to prepare the oro-dispersible tablets containing model drugs using co-excipient C5. Aceclofenac and was selected as model drugs and tablets were made by direct compression technique. These tablets were evaluated for its quality parameters and dissolution study. All tablets passed the quality control test as well as complete drug was released within 15 min. Finally, all tablets were compared with marketed fast disintegrating tablets and found that drug release of all prepared tablets were comparable to marketed tablets. This indicates that the prepared co-excipient was good for formulation of disintegrating tablets.

CONCLUSION

Hence, it was concluded that the spray drying method is suitable for the preparation of directly compressible fast disintegrating co-processed excipient. This co-processed excipient showed improved flow properties, compressibility and less disintegration time with less friability when compressed in tablet form with model drugs. Many Oro dispersible tablets are prone to friable as their aim is to achieve the less disintegration time; but this problem is successfully solved by using fast disintegrating co-excipient. This new technique saves the

time and cost for the development of tablet dosage forms because of direct compression behavior and multifunctional of co-excipients. The coprocessed excipient containing mannitol, HPMC-E15LV and Kollidon has provided less disintegration time with less friability and sufficient strength to the tablets. So it can be used for formulation of fast Disintigration tablets.

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