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FORMULATION AND EVALUATION CO-PROCESSED EXCIPIENT BASED SUSTAINED RELEASE TABLET

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ABSTRACT

Ibuprofen is widely used as a prescription and non-prescription medicine. The aim of study is to prepare Ibuprofen tablets (400mg) using direct compression technique which is now days considered a cost effective and simple method of manufacturing. Compression of solid particle directly into tablets is the method of choice for the preparation of tablets. This method has several advantage such as, cost effective as it has less number of unit operation than wet granulation, highly adaptive for products and APIs sensitive to moisture and heat. Tablets prepared by direct compression method exhibit comparatively faster dissolution. The method of direct compression require excipients with good flow ability and compressibility. Hence, this research work has been taken up with the purpose of developing a new, efficient and cost effective directly compressible vehicle for the preparation of tablets by direct compression method.

KEYWORDS – Tablet, co-process, Hpmc, ibuprofen.

1. INTRODUCTION

For many decades various pharmaceutical dosage forms such as tablets, capsules, suppositories, creams, ointments, liquids, aerosols, and injectable have been used for the delivery of drugs to the patients for the treatment of various diseases. The basic goal of drug therapy is to achieve a therapeutic effect. Almost 90% of all the drugs used to produce systemic effect are administered by oral route.

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms. The oral route is the most preferred method of administration the reasons that the oral route achieved such popularity may be in part due to its ease of administration as well as the traditional belief that by oral administration the drug is well absorbed along with the gastrointestinal tract along with food stuff.

1.1 Tablets

Tablets are defined as a "solid dosage forms containing medical substances with or without suitable excipients". The excipients may include diluents, disintegrants, binders, glidants, lubricants, flavoring agents and sweeteners to ensure the efficient tableting & elegance. The idea of forming a solid dosage form by powder compression is not new. In 1843, the first patent for a hand operated device used to form a tablet was granted. The use of tablets as a dosage form became an interest to the growing pharmaceutical industries but within pharmacies.

1.2 Introduction of co-processed excipients

Co-processing is another way that new excipients are coming to advertise without encountering the intensive prosperity testing of a new concoction. It could be portrayed as uniting at least two settled excipients by a fitting system. Co-processing of excipients could incite the improvement of excipients with preferable properties considered over the fundamental physical blends of their segments.

A co-processed excipient is a blend of at least two compendial or non-compendial excipients intended to genuinely adjust their properties in a way not feasible by basic physical blending, and without critical substance change. A wide range of co-preparing techniques might be utilized, including standard unit tasks, for example, granulation, shower drying, dissolve expulsion, processing, and so forth. The decision for a particular application will rely upon the materials utilized, their structure (for example regardless of whether dry powders or fluid), and the particular physical properties wanted. In like manner, the proportions of the parts may shift contingent upon the ideal execution.

Novel co-processed excipients can likewise be utilized in oral supported discharge measurement structure which conveys the medication for a longer period and aides in creating the remedial impact for 24 h for that medication which is having low plasma life.

1.2.1 Need for co-processed excipients

- Excipient are product of the food industry, which has helped maintain a good safety profile.
- Increasing regulatory pressure on purity, safety, and standardization of the excipient has catalyzed the formation of an international body IPECIPEC is a tripartite council with representation from United States, Europe and Japan and has made efforts to harmonize requirements for purity and functionality testing.
- The popularity of the direct compression process is increasing and in search of ideal filterbinder that can replace two or more excipient.
- It speeds up the work of tablet machines that need additives to ensure excellent compressibility and small weight changes, despite the short residence time.
- No excipient to meet the needs of a particular patient, For example: Diabetes, Hypertension, Lactose and Sorbitol sensitivity.
- The ability to control the solubility, permeability or stability of drug molecules.
- The proceeded with popularity of solid dosage forms, a slender pipeline of new chemical excipients, and an expanding inclination for the direct compression procedure makes an opportunity for the advancement of high-usefulness excipients. The improvement of new excipients to date has been business sector driven (i.e., excipients are created in light of business interest) as opposed to advertising driven (i.e., excipients are produced first and business interest is made through showcasing methodologies) and has not seen much movement as demonstrated by the way that, for the past numerous years, not a single new chemical excipient has been brought into the business. The essential explanation behind this absence of new chemical excipients is the generally high cost included in excipients revelation and improvement. On the other hand, with the expanding number of new medication moieties with changing physicochemical and stability properties, there is developing pressure on formulators to search down new excipients to accomplish the desired set of functionality.

2. MATERIAL & METHOD

2.1 Materials

All the material used in this study were of analytical grade and procured from following source as shown in table below.

Table 3: List of Materials.

Sr. No.	Name of Chemical & Polymers	Role	Manufacture/ Supplier	
1	Ibuprofen	Model Drug NSAID	Research Chem. Mumbai	Lab. Fine Industries,
2	Eudragit RSPO	Release retardant Polymer	Research Chem. Mumbai	Lab. Fine Industries,
3	Hydroxy propyl Methyl cellulose (HPMC)	Polymer	Research Chem. Mumbai	Lab. Fine Industries,
4	Ethyl Cellulose	Hydrophobic polymer (insoluble matrix)	Research Chem. Mumbai	Lab. Fine Industries,
5	Xanthan Gum	Hydrophilic polymer (Natural gum) Polymer	Research Chem. Mumbai	Lab. Fine Industries,
6	Lactose	Diluent	Ozone India	International
7	Microcrystalline Cellulose (MCC)	Filler Disintegrant	Thermosil Fine Chem. Industries Charholi, Tq. Khed Dist. Pune	
8	Magnesium Stearate	Lubricant	New Modern Chemical Corporation, Mumbai	
9	Starch	Binder	Mercury lab. Pvt. Ltd Unit No. 2, Halol Baroda Road Jarod, Dist. Baroda	
10	Talc	Glident	Thermosil Fine Chem. Industries Charholi, Tq. Khed Dist. Pune	

Table 4: List of Equipment.

Sr. No.	Name	Company
1	Analytical Weighing Balance	Arkeys scientific instrument
2	Hot air oven	Bio-technology lab
3	Magnetic Stirrer	HJ Laboratories
4	pH meter	Avi scientific (India)
5	Tablet punching machine	Cemach Ahmedabad
6	Bulk Density Apparatus	Tamilnadu engineering instrument
7	Heating Mental	U- tech laboratories
8	Hardness tester	
	• Monsanto tester	Ambala Harayana
	• Pfizer tester	Ambala Harayana
9	Friability apparatus	Roach friabilitor
10	Thickness tester	
	• Vernier caliper	Bharat scientific world
11	Dissolution apparatus	Electrolab
13	Sonicator	Ambala Harayana
14	UV Spectrophotometer	Shimadzu 1800
15	FTIR	Agilent technology (Cary 630)

2.2 Preformulation Study for Ibuprofen

- The preformulation studies include the physicochemical characterization of the drug and Excipients which are useful in formulation the dosage form.
- The main motto of preformulation studies is to get adequate information useful in developing the stable formulation and should satisfy the criteria.

2.2.1 Drug identification – Model Drug: Ibuprofen

2.2.2 Organoleptic characteristics of pure drug

Organoleptic characters like color, odor and taste and powder nature of the drug were observed using visual inspection and general methods.

2.2.3 Solubility

The solubility of the drug was performed by adding excess quantity of drug to different solvents.

2.2.4 Pre-compression characteristics of pure drug

The flow property and compression characteristics of the pure drug were observed by determining the results for Bulk Density, Tapped Density, Carr's Index, Hausner's Ratio and Angle of Repose.

2.2.5 Melting point determination

Melting point of the drug sample was determined by open capillary tube method.

Method- The capillary tube was closed at one end by fusion and was filled with the drug on the other end by repeated tapings. The capillary tube was placed in the digital melting point apparatus. The instrument was set to automatically increase the temperature of heating bath at a rate of 1^0C per minute. The melting process was viewed through the magnifying lens. The temperature at which the drug started melting is recorded. This was performed thrice and their average was taken as a result.

2.2.6 Analytical Method Development

Before any product development, it is very important to develop an appropriate analytical method that provides accuracy and precision which will be used throughout the development process for the determination of assay and in-*vitro* dissolution process.

2.2.7 UV-Spectrum

The 10µg/ml drug solution was prepared in ethanol and a spectrum was taken in the Ultra – Violet region (200nm to 400nm) in UV visible Spectrophotometer 1800, Shimadzu (Japan). The drug peak with the highest absorbance was obtained at 225nm. The observed wavelength was compared with the standard reported value.

2.2.8 FTIR Spectrum

Fourier Transform IR Spectroscopy was performed with the help of Agilent technology (Cary 630) FT-IR Spectrophotometer. The observed peaks of functional groups were compared with the peak values of the standard.

2.2.9 Preparation of calibration curve

Standard Drug Solution

Standard solution containing 1mg/ml was prepared using 0.001 mg Ibuprofen dissolved in 100ml ethanol in volumetric flask.

2.2.9.1 Preparation of standard solution of Ibuprofen

1. Weight accurately 0.001 gm. of Ibuprofen (pure drug) and dissolve in 100 mL Ethanol 1000ug/mL).
2. Take 10 ml and volume make up to 100 mL of Ethanol (100ug/mL)
3. Take 1ml and make up to 100 mL (10ug/mL)

4. UV Visible Spectrophotometer (Shimadzu) by scanning in UV range 200-400 nm

2.2.9.2 Absorption maxima (λ max) of the drug sample

0.001 mg of the drug was dissolved in 100 ml of phosphate buffer saline pH 6.8 and was denoted as stock solution, from this 1 ml was taken and diluted to 10 ml to get 1^{o} stock solution and from this 1 ml of sample is taken and diluted to 10 ml in volumetric flask to get 10 µg/ml. 10 µg/ml concentration sample was taken and were analyzed by using UV Visible Spectrophotometer (Shimadzu) by scanning in UV range 200-400 nm using phosphate buffer pH 6.8.

2.2.9.3 Preparation of the Calibration curve

0.001mg of the drug was dissolved in 100 ml of phosphate buffer saline pH 6.8 and was denoted as stock solution. From this 1 ml was taken and diluted to 100 ml to get 1^{O} stock solution and from this aliquots of 1, 2, 3, 4, 5 ml is transferred to 10 ml volumetric flask and diluted up to the mark to get the concentration of 1, 2, 3, 4, 5 µg /ml respectively. The absorbance of known samples was measured by using UV-Visible Spectrophotometry at 225 nm by using PBS pH 6.8 as blank. The graph was plotted taking concentrations on x-axis and respective absorbance on y-axis. The regression coefficient (R2) & straight line equation (Y= mx + c) were calculated with the application of Microsoft EXCEL statistical function program.

2.2.10 Compatibility Studies

2.2.10.1 Fourier transform infrared spectroscopy

The FTIR study of drug was carried out to identify the functional group. The spectra for the pure drug was recorded on Agilent CE-FTIR attached to an attenuated total reflectance (ATR) accessory. ATR was fitted with a single bounce diamond at 45°C internally reflected incident light providing a sampling area of 1mm in diameter with a sampling depth of several microns. A small amount of the sample was directly placed on the diamond disc and solid sample placed in solid sample holder. Sample was scanned for absorbance over the range from 4000 to 400 numbers (cm^{-1}) at a resolution of $1cm^{-1}$.

2.2.10.2 Drug excipient compatibility study

Tablet blend was thoroughly passed through the sieve no. #40 and finally Placebo (without API) was subjected for Attenuated total reflectance (ATR) studies. The blend was filled in glass vials and closed with gray rubber stoppers and sealed with aluminum seal and charged at 60ºC for 30 days in a stability chamber. ATR spectra was compared with the initial spectra and reported for any variations.

2.3 Method of preparation

2.3.1 Formulation of Tablets by Wet Granulation

Tablet of the selected drug Ibuprofen were formulated by wet granulation technology as per the composition given table 5.

Drug (Ibuprofen), Eudragit RSPO, HPMC and Lactose were blended thoroughly in dry mortar and granulated with starch paste (q.s). Starch paste was added and mixed thoroughly to form dough mass. The mass was passed through mess no. 12 to obtain wet granules. The wet granules were dried 60^{0}C for 2 h. The dried granules were passed through mess no. 16 to break the aggregates. Talc and Magnesium stearate (Crosspovidone and the Lubricant) were passed through mess no. 100 on to dry granules and blended manually in a closed polythene bag. The tablet granules were compressed into tablet on a tablet punching machine employing 10 mm round and flat punches.

2.3.2 Direct Compression

The process of tableting of a blend of ingredients without a preliminary granulation or aggregation process is known as direct compression. The blend contains the active pharmaceutical ingredient mixed with one or more excipient. Only a few, about 20 % drugs can be compressed directly into tablets. The rest lacks flow and lubricating properties necessary for the production of tablets by direct compression method. The use of directly compressible excipients yields good tablets for such materials. Although less unit processes are involved, the direct compression process is much influenced by powder characteristics such as flowability, compressibility, and dilution potential. Most formulations contain excipients at a higher concentration than the active drug and hence the excipients plat a critical role to a formulation's functionality and process ability. The physic mechanical properties of excipients such as flowability, compressibility, moisture sensitivity, lubricant sensitivity and machinability are important. Most excipients currently available do not possess these qualities, thus creating the necessity for the development of new high functionality excipients.

Table 5: Formulation of Ibuprofen Tablets.

Formulation Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Formulation of co-processed excipient												
Eudragit RSPO	--	--	--	--	100	100	100	100	100	100	100	100
HPMC	--	--	--	--	25	50	75	100	--	--	--	--
Xanthan gum	90	130	50	130	--	--	--	--	50	75	25	100
Ethyl cellulose	110	150	70	70	--	--	--	--	--	--	--	--
Formulation of Ibuprofen tablet containing co-processed excipient												

Co-processed Excipient	100	100	100	100	100	100	100	100	100	100	100	100
Ibuprofen	200	200	200	200	200	200	200	200	200	200	200	200
MCC	100	100	100	100	100	100	100	100	100	100	100	100
Magnesium Stearate	1 %	1 %	1 %	1 %	1 %	1 %	1 %	1 %	1 %	1 %	1 %	1 %
Talc	1 %	1 %	1 %	1 %	1 %	1 %	1 %	1 %	1 %	1 %	1 %	1 %
Total wt. (mg)	400	400	400	400	400	400	400	400	400	400	400	400

2.4 Quality Control Testing of Tablets

The formulated tablet were tested for drug content uniformity, hardness, friability and disintegration time and dissolution rate as follows.

Monsanto hardness tester was used for hardness of the tablets. Roche friabilator was used for determining the Friability.

2.5 Preparation of dissolution medium

1. 0.1 N Hydrochloric acid (HCL)

- Take a clean dried 1000ml Volumetric Flask
- Add 8.5 ml Conc. HCL
- Add about 700ml water mixed & allow cool to room temperature
- Make up volume 1000ml with water
- Keep the solution for at least 1 hrs. & then carry out Standard

2. pH 6.8 Phosphate Buffer Solution: (0.2M)

- Take a clean dried 1000ml Volumetric Flask
- Add 13.87 gm. Potassium Dihydrogen Phosphate & 35.08 gm. Disodium Hydrogen Phosphate
- Add about 700ml water mixed & allow cool to room temperature
- Make up volume 1000ml with water
- Store in cold place
- pH was adjusted by using pH meter.

3. 0.2 M Sodium Hydroxide (NaOH)

- Take a clean dried 1000ml Volumetric Flask
- Add 4gm sodium hydroxide
- Make up volume 1000ml with water
- Keep the solution for at least 1 hrs. & then carry out Standard

2.6 Evaluation of co-processed excipients

1. Angle of repose

Angle of repose (θ) is the measure of a frictional force in a loose powder. It is nothing but the maximum angle between the surface of the pile powder and the horizontal plane. It is a characteristic property related to inter particulate friction or resistant to movement between the particles. Angle of repose is carried out by allowing the powder blend or the drug powder to pass through the funnel from heap on a base. In this case the base diameter may be off fixed or the diameter of the heap can be taken roughly. The flow of powder is carried either by dynamic or draining method of flow. The dynamic method includes the obstruction of flow and its release from the narrow end of the funnel, the tapings should be unnecessary. The drainage method includes the continuous flow of powder through the funnel on a fixed or rough base. The height of the funnel from the base should be of 2-4 cm and fixed.

Method – A funnel with a stem of inner diameter of 10mm was fixed at a height of 6cm over platform. About 20 gm of granules was slowly passed along the walls of the funnel, till the tip of the pile is formed and touches the stem of the funnel. A rough circle was drawn around the pile base and the radius of the powder cone was measured. Angle of repose (θ) was carried out thrice and average is determined using the formula given. The specifications for angle of repose were given in table. The radius of the circle obtained was measured and the angle of repose was calculated by equation:

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

Where,

ɵ = Angle of repose h = Height of pile r = Radius of base of pile

Table 6: Standard value of angle of repose.

Sr. No.	Angle of repose	Flow
1	25 – 30	Excellent
2	30 – 35	Good
3	35 – 40	Fair
4	40 – 45	Poor
5	45 – 50	Very poor

2. Bulk Density

Bulk density is the ratio of the weight of the powder to the bulk volume it occupies. It is expressed in gm. / ml. 20 gm. of the granules were weighed and poured into the 100 ml measuring cylinder.

This is called as bulked density or pored bulk density which is given as:

Bulk Density (Pb) = Weight of granules (M) (g) / bulk volume Vb (ml)

P = Bulk density
M = Mass of granules
Vb = Bulk volume

3. Tapped Density

An accurately weighed granules from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume

was noted which gave the tapped volume. The TBD of granules was determined by the following formula.

Tapped density = Total Weight of granules/ Tapped Volume

4. Hausner Ratio

Hausner ratio is the ratio between tapped density and bulk density. Hausner ratio less than 1.25 indicates good flow properties while Hausner ratio greater than 1.25 shows poor flow of granules.

Table 7: Standards for Hausner Ratio.

Sr. No.	Hausner Ratio	Flow
1	1.2 – 1.3	Excellent
2	1.3 – 1.4	Good
3	1.4 – 1.5	Fair
4	1.5 – 1.6	Poor

5. Carr's Index

After determining the poured bulk density, the granules were then tapped mechanically for 100 times a constant volume called tapped bulked density. Using poured bulk density and tapped bulk density the percentage compressibility of granules were determined, which is given as Carr's compressibility index.

$$\text{Carr's Compressibility Index} = \frac{\text{Tapped bulk density-poured bulk density}}{\text{Tapped bulk density}}$$

Poured bulk density = Mass of granules / Untapped volume of packing

Tapped bulk density = Mass of granules / Tapped volume of packing

Table 8: Standard value of Carr's Index.

Sr. No	Carr's Index	Flow
1	05 - 15	Excellent
2	12 – 16	Good
3	18 – 21	Fair
4	23 – 25	Poor
5	35 – 38	Very poor
6	More than 40	Extremely poor

6. Granular Friability (F)

10gm of the sample was placed in a Roche friabilator and rotated for 4min at 25rpm. The sample sieved through 60# screen and measure the co-processed excipients retained on the sieve.

F= Initial wt – Final wt / Initial wt*100

< 1% Indicates resistance to loss of weight due to fracture and abrasion during transportation

2.7 Evaluation of Ibuprofen tablets

Pre-compression parameters

The prepared co-processed excipients were uniformly mixed with model drug and other tablet ingredients mixer and the pre-compression characteristics were determined (as described for coprocessed excipients).

1. Bulk density, Tapped density

Bulk density, Tapped density of mixture 20gm of the sample was filled in a 100ml measuring cylinder and tapped 50 times. The initial and final volumes were measured. The densities were calculated as below formula.

Bulk density = W/ V0

Where W is the weight of polymer and V0 is the bulk volume of the polymer.

Tapped density = W /Vf

Where W is the weight of powder, Vf is the tapped volume of the powder.

2. Hausner's Ratio, Carr's Index

The pre-calculated tapped densities and bulk densities are used in the following equations to determine HR and CI to evaluate the compressibility characteristics and flow property.

Hausner's ratio (HR) = Tapped density/ Bulk density

Carr's index (CI) = (Tapped density - Bulk density) / Tapped density

3. Angle of Repose

Fix a glass funnel at 2.5cm height (fix) using a burette stand and place a graph paper below. 20gm of sample is allowed to flow through the funnel. The circumference of the pile formed is marked with a pencil and the average diameter is measured.

Θ = tan-1 (h/r)

Where 'h' is the height of pile and 'r' is the radius of pile

2.8 Post-compression parameters

1. Appearance

Tablet from each formulation were randomly selected and organoleptic properties such as color, taste, and shape were evaluated. The results are shown in table 18.

2. Hardness test

Hardness (diametric crushing strength) is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during coating, packaging transportation and also during patient handling. The degree of hardness varies with the different manufactures and with the different types of tablets. The permissible limit for sustained release tablets is 4-12 kg/cm^2. The hardness of tablets for fast dissolving tablets is usually kept low for easy disintegration in the mouth. The hardness was tested using Pfizer or Monsanto hardness tester. The results are shown in table 18.

3. Thickness

The thickness of tablets was determined using a vernier caliper. Three tablets from each batch were used, and

average values were calculated. The results are shown in table 18

4. Weight variation test

This is an important in-process quality control test to be checked frequently (every half an hour). Corrections were made during the compression of tablets. Any variation in the weight of tablet (for any reason) leads to either under medication or overdose. So, every tablet in each batch should have a uniform weight. 20 tablets were weighed individually. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (7.5%). The following % deviation in weight variation is allowed. The results are shown in table 18

Table 9: Percentage Weight Deviations.

Sr. No.	Average Weight	% Difference
1	130 mg or less	10
2	130 – 324 mg	7.5
3	324 mg and greater	5

5. Friability test

Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. This in-process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. Roche friabilator was used to measure the friability of the tablets. It was rotated at a rate of 25 rpm. Ten tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting from free fall of tablets within the chamber of the friabilator. After 100 rotations (i.e. in 4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively. Permitted friability limit is 1.0%.

The % friability was then calculated by,

Percentage friability = Initial weight- Final weight / Initial weight ×100

Acceptance criteria for % friability % weight loss should be less than 1%. The results are shown in table 19.

6. Content uniformity (Drug Content)

Content uniformity was determined by accurately weighing 10 tablets and crushing them in mortar with the help of a pestle. Then an accurately weighed quantity of powder equivalent to 25 mg of drug was transferred to a 50 ml volumetric flask. Then added few ml of methanol and made up-to 50ml with methanol. The solution was filtered through whatman filter paper. 10 ml of the filtrate was diluted to 100 ml with Methanol. Then 1 ml of the resulting solution was again diluted to 10 ml with Methanol. The absorbance of the resulting 10 □g/ml solution was recorded at 225nm.

7. Dissolution Studies

The release rate of Ibuprofen from tablets was determined using United States Pharmacopoeia (USP) type II (paddle) apparatus, 900 ml of phosphate buffer, pH 6.8 at 37 ± 0.5°C and 50 rpm. 1ml of solution was withdrawn at time intervals of 15min, 30min, 45min, 1, 2, 4, 6, 8 and 12 hrs. The medium was replaced with the same amount of fresh dissolution media each time. The then solutions made up to 10 ml with the dissolution media. Absorbance of the samples was measured at 225 nm for Ibuprofen tablets using UV-Visible double-beam spectrophotometer. The drug content was calculated using the equation generated from standard calibration curve. The cumulative % drug release was calculated. The results were shown in the table 20.

Table 10: Details of Dissolution Test.

Dissolution test apparatus	USP II (Paddle)
Speed	50 rpm
Time interval	0.5, 1, 2, 4, 8, 10, 12, 14 h
Medium used	Phosphate buffer, pH 6.8
Temperature	37 ± 0.5 ^{O}C.

8. Solubility studies

Aqueous solubility of Ibuprofen as a function of pH was determined in different physiological media. Solubility of drug was studied at different pH range i.e. pH 1.2 (0.1 N HCl), pH 4.5 (Phosphate Buffer), pH 6.8 (Phosphate Buffer), pH 7.4 (Phosphate Buffer).

Table 11: Range of Solubility.

Sr. No	Descriptive Term	Approximate volume of solvent in milliliters per gram of solute
1	Very soluble	Less than 1ml
2	Freely soluble	From 1 to 10 ml
3	Soluble	From 10 to 30 ml
4	Sparingly soluble	From30 to 100 ml
5	Slightly soluble	From 100 to 1000 ml
6	Very slightly soluble	From 1000 to 10000 ml

9. Stability studies

The International Conference on Harmonization (ICH) Guidelines titled, "Stability testing of New Drug substance and products" (Q1A) describes the stability test requirements for drug registration application in the

European Union, Japan and the United States of America.

The stability study was performed for the optimized batch formulation ambient (40°C, 75% RH) conditions for 1 months and the % CDR at 12 hr. was determined for 0 days, 15 days and 1 month

10. Moisture content

Initially 5 gm. of weighed granules were taken and kept for drying at 105°c for a required time in an oven. Then removed and again reweighed and note as final weight. The difference in weight was note as moisture content.

Moisture content = Initial weight- Final weight / Initial weight ×100

11. Assay

Weigh and powder 20 tablet. Weigh quantity of powder containing about 0.5g of Ibuprofen, extract with 60ml of chloroform for 15 min and filter. Wash the residue with three times. Each of 10ml of chloroform and gently evaporate and to dryness in current of air. Dissolve the residue in 100ml of ethanol. Previously neutralize to phenolphthalein solution, and titrate with 0.1M sodium hydroxide using phenolphthalein solution as indicat.

3. RESULTS AND DISCUSSION

3.1 Pre-formulation study

3.1.1 Identification of pure drug (Ibuprofen)

3.1.1.1 Organoleptic characteristics of the pure drug (Ibuprofen)

The organoleptic characteristics pure drug sample of Ibuprofen was found as follows:

Table 12: Preformulation Studies.

Test	Specification
Appearance	White fine powder
Odour	Odour less disintegration
Taste	Tasteless
Water solubility	21 mg/L
Melting Point	77^0C

3.1.1.2 Pre-compression parameter of pure drug

The result for the Pre-compression Parameter of Pure Drug was observed as below table 13

Table 13: Pre-Compression Parameter of Pure Drug.

Sr. No.	Parameter	Ibuprofen	Observation
1	Bulk Density	0.649 g/ml	--
2	Tapped Density	0.682 g/ml	--
3	Carr's Index	10.58 %	Free-flowing
4	Hausner's Ratio	1.12	Good flow
5	Angle of Repose	24.52	Excellent

The Study of Pre-compression characteristics of the pure drug indicates that the given sample of Ibuprofen drug exhibits good flow properties and good compression characteristics.

3.1.1.3 Melting Point

The melting point of Ibuprofen was found to be 76^OC in the range of 72 – 77^OC which complies with the standard reference values.

3.1.1.4 UV- Spectrum

The λmax of Ibuprofen was taken on UV visible Spectrophotometer (Shimadzu, UV-1800, Japan) by scanning a diluted solution that was prepared in a range of 10-50 µg/ml and analyzed the solution and absorbance were taken. In phosphate buffer pH 6.8 λmax of Ibuprofen found at 225 nm wavelength. Hence drug Ibuprofen is pure.

3.1.1.5 FT-IR Spectrum

The FT-IR study showed that there are no significant changes observed in the position of specific absorption bands of groups and bonds.

3.2 Analytical Method Development

3.2.1 Preparation of standard calibration curve

Determination of absorption maxima (λ max) of the drug sample (Ibuprofen)

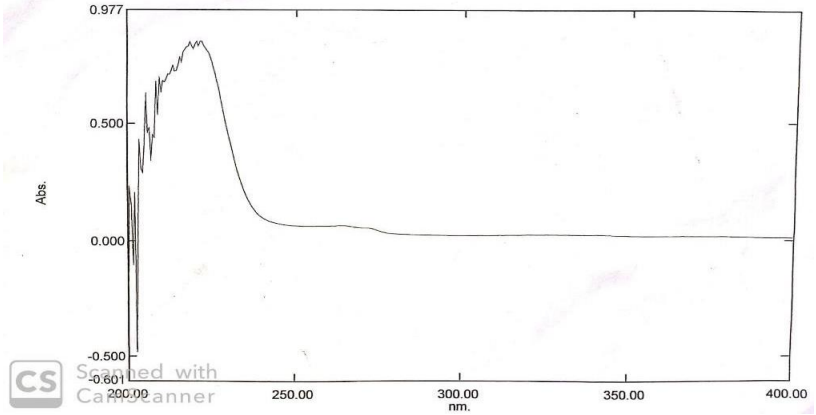

Fig. 9: Spectra of UV Absorption maxima (λ max) of the drug sample.

3.2.2 Calibration curve of Ibuprofen

Table 14: Calibration curve of Ibuprofen in phosphate buffer pH 6.8

Concentration (µg /ml)	Absorbance
0	0.000
10	0.136
20	0.244
30	0.398
40	0.549
50	0.736
Slope	0.0145
Intercept	0.0185
R2	0.9931

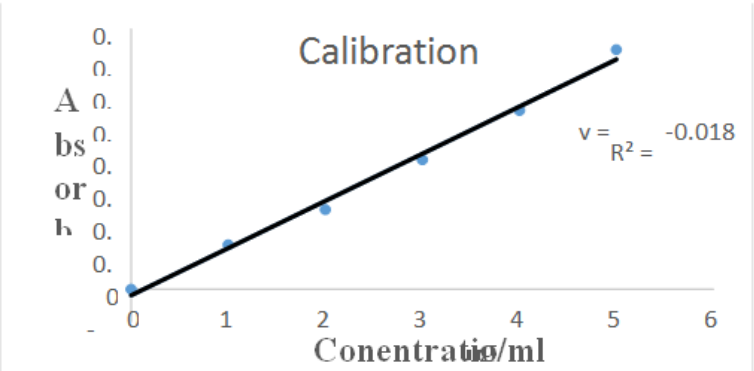

Fig. 10: Calibration Curve of Ibuprofen in Phosphate Buffer pH 6.8.

Table 15: Calibration curve values of Ibuprofen in Ethanol

Concentration (µg /ml)	Absorbance (nm)
0	0.000
10	0.142
20	0.268
30	0.429
40	0.512
50	0.612
Slope	0.0135
Intercept	0.0026
R2	0.9949

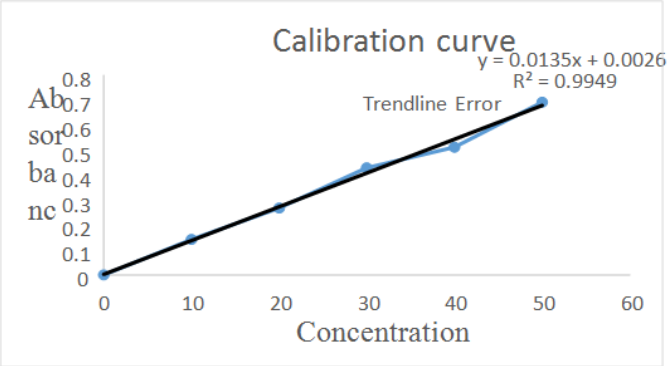

Fig. 11: Calibration Curve of Ibuprofen in Ethanol.

- Preformulation studies showed the drug is colorless, highly soluble in water, melting point of 75 - 77 ^{O}C. **(Table 12).**
- Ibuprofen was scanned in the UV wavelength region of 400-200 nm from absorbance maxima (λ max). The absorbance maximum was found to be 225 nm. **(Fig 9).**
- The standard curve was plotted and it shows the r2 of 0.9931 **(Table 14, Fig 10)** which obeys Beers Lamberts Law in concentration range of 10 - 50 µg/ml.
- The standard curve was plotted and it shows the r2 of 0.9949 **(Table 15, Fig 11)** Which obeys Beers Lamberts Law in concentration range of 10 - 50 µg/ml

3.3 Compatibility Studies

Attenuated Total Reflectance Spectrum (ATR)

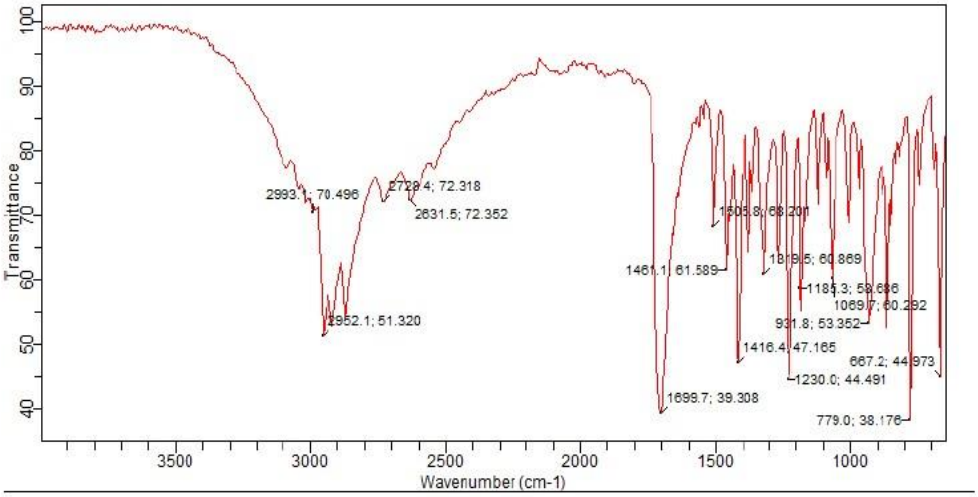

Fig. 12: ATR Spectrum of Ibuprofen Pure Drug.

Table 16: Functional group and IR region of Ibuprofen.

IR Region (Wave number, cm-1)	Functional Group
2993.1, 2952.1	C - H stretching
2728.4	H-C=O: C-H stretching
2631	O-H Stretching
1699.7	C=O stretching

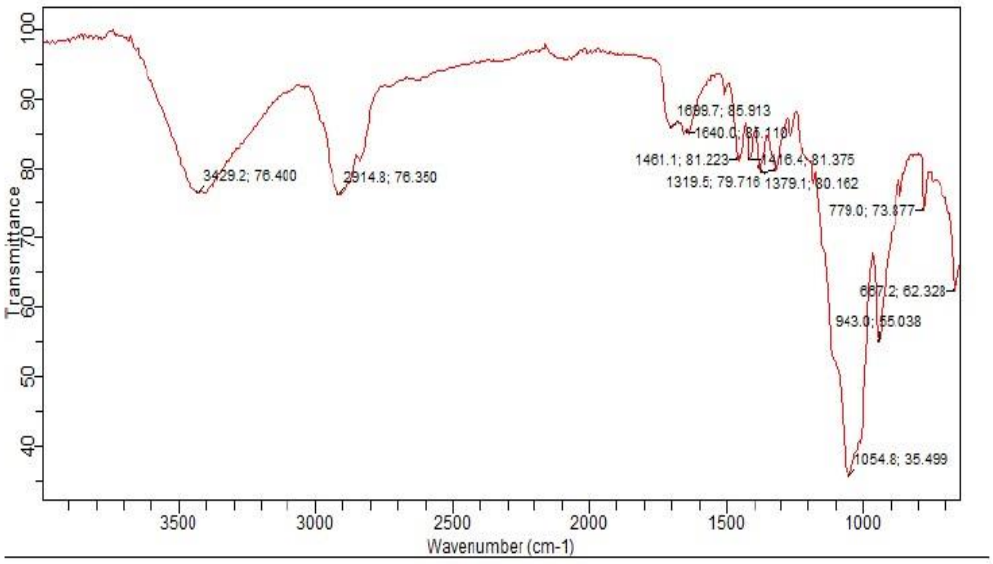

Fig. 13: ATR Spectrum of Ibuprofen + HPMC.

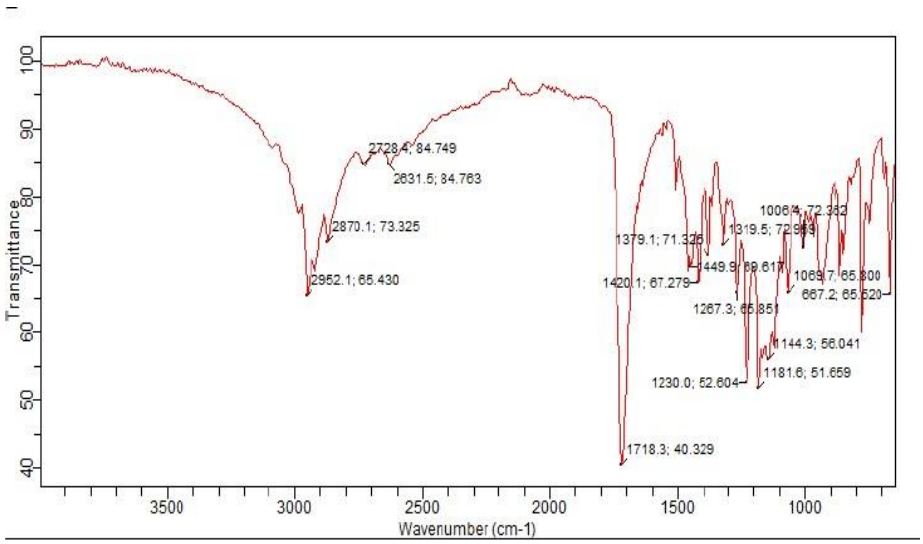

Fig. 14: ATR Spectrum of Ibuprofen + Eudragit RSPO.

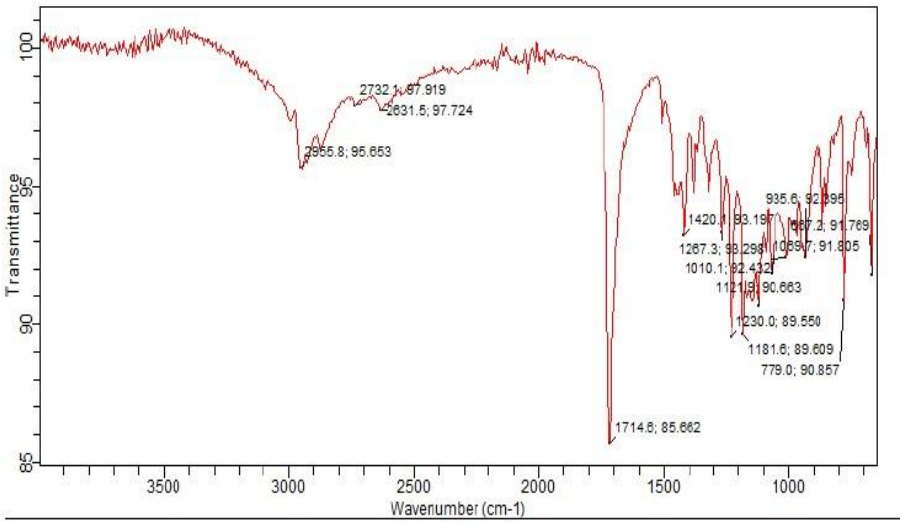

Fig. 15: ATR Spectrum of Ibuprofen + Ethyl Cellulose.

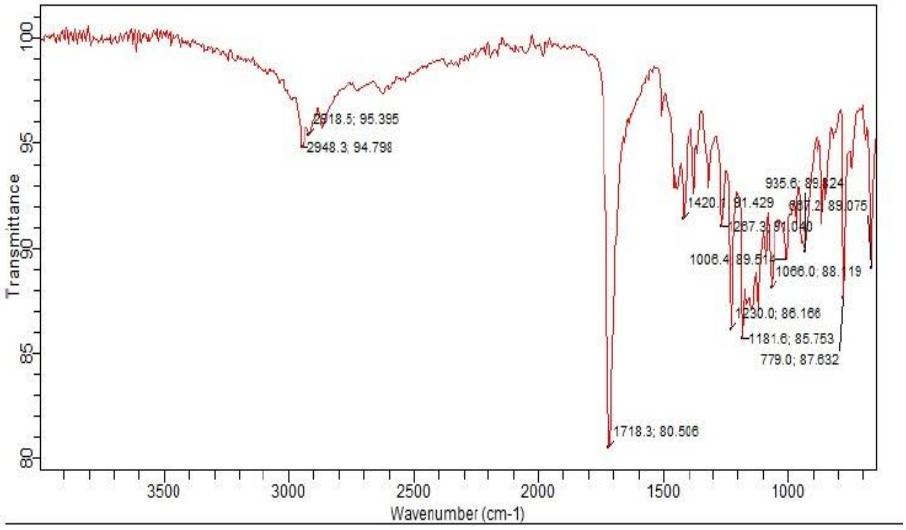

Fig. 16: ATR Spectrum of Ibuprofen + Microcrystalline Cellulose.

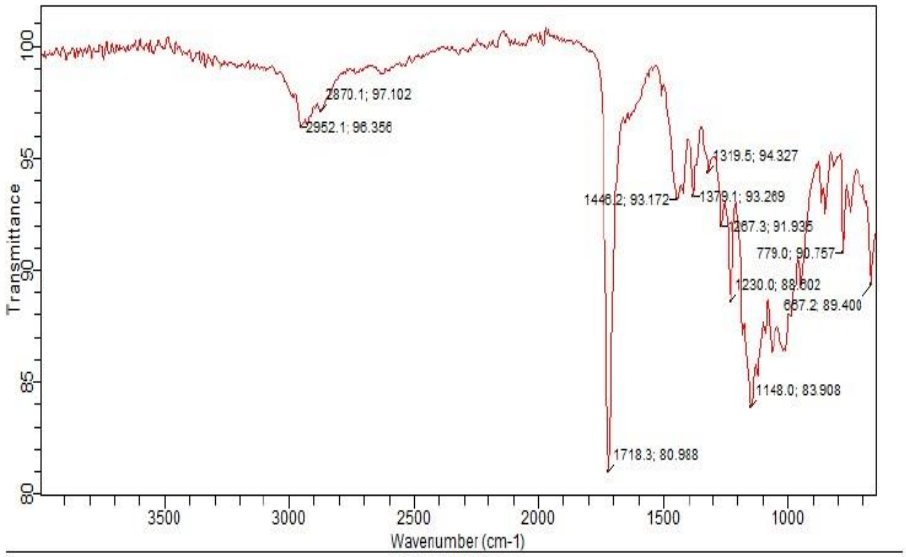

Fig. 17: ATR Spectrum of drug + Xanthan Gum.

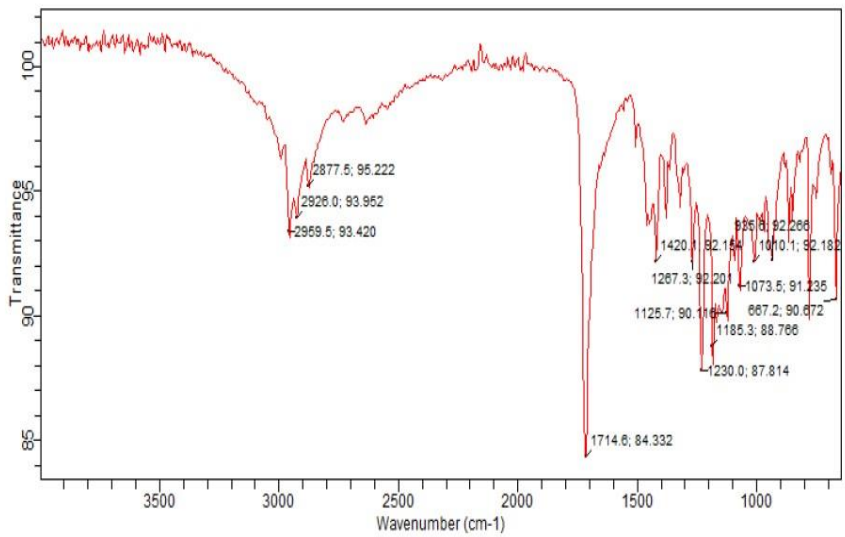

Fig. 18: ATR Spectrum of physical mixture (Drug + HPMC+ Eudragit RSPO+ Ethyl Cellulose+ Microcrystalline Cellulose + Xanthan Gum).

Interpretation of FT-IR of Ibuprofen and Excipients Mixtures

IR spectrum obtained for drugs with formulation excipients showed characteristics peaks of the drug at their respective wavelength with no major shifts indicating chemical integrity of drug. The drug excipient compatibility study was done by Fourier Transform – Infrared Spectroscopy study, the prominent peaks of Ibuprofen pure drug were shown at C-H at 3100, C=O at 1720, C-N at 1335, H-C=O: C-H at 2830 All peaks are in the range of a group of drug structure, so all the excipients are compatible with the drug.

3.4 Evaluation parameters

3.4.1 Pre Compression Parameters

Table 17: Pre Compression parameters of formulation F1-F12.

Formulation Code	Angle of Repose (θ)	Bulk Density (mg/ml)	Tapped Density (mg/ml)	Carr's Index (%)	Hausner' s Ratio	Granular Friability (%)
F1	22.63	0.470	0.522	15.231	1.21	0.65
F2	22.12	0.492	0.535	10.125	1.07	0.70
F3	24.62	0.501	0.563	12.544	1.29	1.06
F4	23.59	0.477	0.556	13.521	1.15	0.72
F5	22.47	0.486	0.486	12.652	1.08	0.78
F6	24.56	0.465	0.502	14.574	1.19	0.54
F7	26.22	0.482	0.512	12.325	1.18	0.62
F8	25.42	0.496	0.526	12.478	1.26	0.77
F9	24.26	0.452	0.556	14.127	1.31	0.68
F10	25.49	0.507	0.545	15.378	1.46	0.49
F11	23.65	0.488	0.596	14.651	1.37	0.82
F12	25.81	0.499	0.588	15.052	1.44	1.12

The pre compression results were shown in table 17

- The bulk density was found to be in range of 0.452 - 0.507 g/ml.
- The tapped density was found to be in range of 0.486 - 0.596 g/ml.
- The Carr's index and hausner's ratio were found to be between 10.125 % - 15.378 % & 1.07 - 1.46 respectively.
- The angle of repose was in range of $22^0.12'$- $26^0.22'$. From the above results it was found to be the powder blend has good-excellent flow properties.

3.4.2 Evaluation of experimental batches Post Compression Parameters characteristics

Table 18: Post Compression parameters of formulation F1-F12.

Formulation Code	Parameters				
	Average Weight of Tablet in (mg)	Hardness in (Kg/cm^2)	Thickness (in mm)	Friability (%)	Drug Content %
F1	398 ± 3.20	5.1 ± 0.6	4.65 ± 1.34	0.10	82
F2	401 ± 1.41	5.8 ± 1.2	4.11± 1.21	0.06	78
F3	395 ± 3.49	6.1 ± 0.9	3.69 ± 1.38	0.28	86
F4	397 ± 3.26	5.9 ± 1.3	4.16 ± 1.17	0.12	84
F5	400 ± 1.02	6.4 ± 0.8	3.98 ± 1.52	0.09	89
F6	399 ± 2.11	6.3 ± 1.5	4.29 ± 1.38	0.18	81
F7	397 ± 3.41	6.6 ± 1.3	4.02 ± 1.23	0.21	88
F8	399 ± 2.09	5.8 ± 1.6	4.54 ± 1.68	0.28	76
F9	395 ± 3.12	6.2 ± 0.8	4.09 ± 1.24	0.21	89
F10	398 ± 2.56	6.5 ± 1.4	4.38 ± 1.63	0.27	76
F11	397 ± 3.13	6.6 ± 1.1	3.96 ± 1.85	0.22	79
F12	395 ± 3.89	5.9 ± 0.9	3.75 ± 1.78	0.25	89

Post compression results were shown in table 18.

- Weight variation results were found to be within specifications ±5 % as per I.P.
- Hardness of all the formulations lies between 5.1 – 6.6 kg/ cm^2 and all the 12 formulation hardness were compliance the IP limit.

- Thicknesses of the entire tablets were found to be 3.69 mm – 4.65 mm.
- Friability of all the formulations were found to be < 0.10 % and were within specifications and for optimized formulation the friability was found to be 0.18%.

3.5 Characterization of optimized co-processed excipient

Table 19: Evaluation of co-processed excipient optimized batch.

Sr. No.	Formulation F7	Value
1	Angle of repose	$26^{O}22'$
2	Bulk Density	0.482 mg/ml
3	Tapped Density	0.512 mg/ml
4	Carr's Index	12.325 %
5	Hausner' s Ratio	1.18
6	Granular Friability	0.62 %

3.6 Dissolution Studies

Table 20: Dissolution Profiles of formulations F1-F12.

Time (in hours)	Cumulative % Drug Release											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
00	0	0	0	0	0	0	0	0	0	0	0	0
0.5	20.86	25.36	28.45	29.63	16.53	17.66	20.63	19.53	21.96	24.96	25.86	19.65
1	40.56	55.41	56.32	52.69	24.37	28.63	28.45	24.63	35.68	41.23	32.77	38.89
2	60.52	73.56	79.42	77.16	39.51	40.12	34.96	30.37	50.63	65.85	47.96	59.32
4	82.74	84.34	88.12	83.86	52.12	60.89	50.37	46.31	76.19	82.63	77.56	71.56
6	95.63	96.47	97.56	93.42	69.75	80.64	66.85	59.87	95.36	97.56	92.45	90.78
8					78.54	90.52	72.63	66.91				
10					85.45	95.77	84.96	74.56				
12					94.56	98.56	90.12	89.69				
14					95.63	99.68	96.56	92.63				

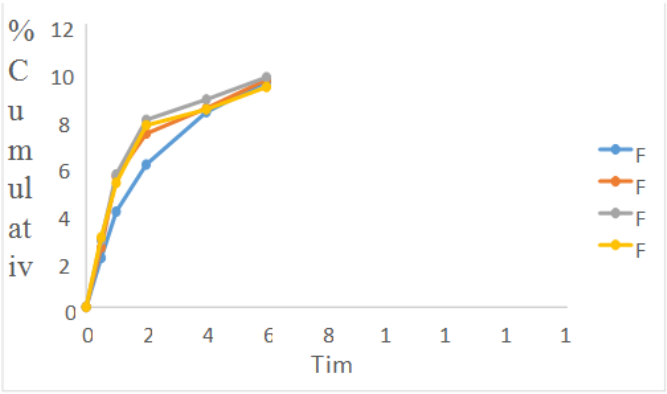

Fig. 19: *In vitro* dissolution profiles of the formulations F1-F4.

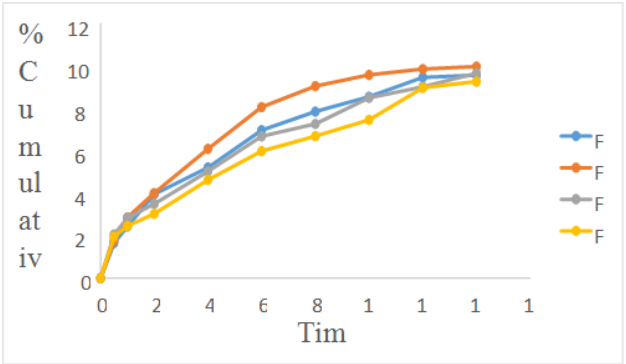

Fig. 20: *In vitro* dissolution profiles formulation F5-F8.

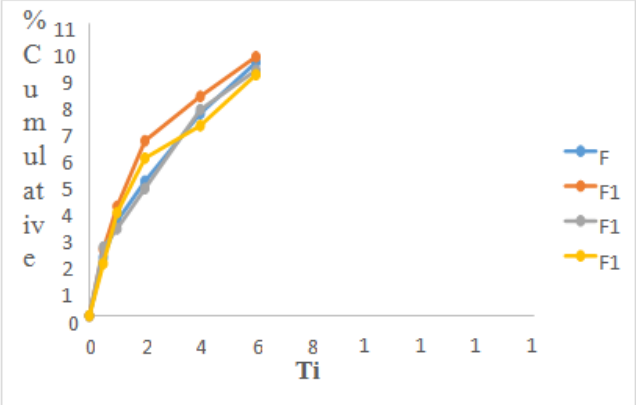

Fig. 21: In vitro dissolution profiles of the formulations F9-F12.

3.7 Selection of optimized batch

From the formulation F1-F12, It was observed that **F6** formulation give better result, in 12 hr. F9 formulation release 98.56%.

Table 21: Formulation for Optimized Batch.

Formulation ingredient	The optimized batch F6 (mg)
Co-processed excipient	
Eudragit rspo	100
HPMC	50
Ibuprofen tablet	
Ibuprofen	200
Co-processed excipient	100
MCC	100
Starch paste	q. s.
Talc	1%
Magnesium stearate	1%
Total	400

3.8 Stability Study

The stability studies were carried out according to ICH to access the drug formulation stability. Optimized F6 formulation was kept in stability chamber at 40°c and RH 75% for 1 month at ambient conditions end of study period, the formulation was observed for change in physical appearance and drug release characteristics. The stability study of an optimized batch F6 are given in table 22

Table 22: Stability Studies [condition 40°C and 75% RH].

Optimized Batch	Parameter		Time (days)	
		0	15	30
F6	% CDR 12 hr.	92.56	93.89	95.60
	Drug content	85.60	85.60	85.60

SUMMARY AND CONCLUSION

Co-processed excipients were evaluation possess good flow properties, direct compression characteristics, suitability for different water-insoluble drugs (BCS Class II), and with release retardant characteristics to obtain sustained release drug delivery systems. Different polymer combinations of water-soluble (natural gums) and water-insoluble polymers (meltable and nonmeltable) were studied at a preliminary level and suitable polymers were selected for further studies. Ibuprofen was selected as a model drug. Ibuprofen is a BCS Class II drug Non-steroidal anti-inflammatory.

Co-processed excipients optimized formulation F6 was by using the wet granulation method. The concentrations of Eudragit rspo and HPMC were optimized. Responses % CDR for %CDR 12hr (6.8pH phosphate buffer) were considered for the evaluation. All the pre- and post-evaluation parameters were found to be within standard permissible limits.

The % CDR for (6.8pH phosphate buffer) optimized F6. While the % CDR 12 hrs. in 6.8 pH phosphate buffer for both the formulations lies in between 98- 99.6%. The similarity factor was calculated using dissolution data for 6.8 pH phosphate buffer as a reference. The study

revealed that the formulations passed the in vitro ADD test.

Stability studies at ambient conditions for 1 months were performed and it was found that both the formulations passed the test.

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