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FORMULATION AND EVALUATION OF CHEWABLE TABLETS OF IBUPROFEN USING COPROCESSED EXCIPIENTS

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ABSTRACT

In the present work, chewable tablet of ibuprofen were prepared using novel coprocessed excipient consisting of dicalcium phosphate and magnesium stearate, in different ratios. The developed excipient were evaluated for angle of repose, cars index and hausners ratio in comparison with physical mixture of excipient. The angle of repose of developed excipient was found to be less than 20^0, cars index in the range of 10-20% and hausners ratio in the range of 1.10 -1.17. Chewable tablet of ibuprofen were prepared using the coprocessed excipient and evaluated for pre compression and post compression parameters. In vitro drug release pattern were taken in PBS- 6.8 and short term stability study (at 40^0C/75% RH for 3 months),drug excipient interactions (IR,DSC) were studied. Among the designed formulations, the formulation (B1) containing (21:0.5 mixture of dicalcium phosphate and magnesium stearate) emerged as the overall best formulation, based on drug release characteristics in PBS-6.8 compared to other formulation. Short term stability studies on promising formulation indicating that there were no significant changes in drug content and in vitro drug release. Thus successful development of a novel coprocessed excipient and formulation of chewable tablet of ibuprofen fulfils the objective of work.

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Introduction

Oral drug delivery is the most desirable and preferred method of administering therapeutic agent for their systemic effects. Oral medication is considered as the first trend investigated in the discovery and development of new drug entities and pharmaceutical formulations, mainly because of patient acceptance. In terms of drug delivery and drug absorption, the oral route is unique due to its comfortable administration, control over both spatial and temporal drug release and better drug absorption from site. The tablet is one of the most preferred dosage form because of its ease of manufacturing, convenience in administration, accurate dosing, stability compared with oral liquids and more tamperproof than the capsule. The bioavailability of drug is dependent on in vivo disintegration, dissolution and various physiological factors.

Most of the substances lack some important characteristics of an ideal excipient. Coprocessing is a novel concept of altering excipient functionality by retaining the favourable attributes and supplementing with newer ones, by processing the parent excipient with another excipient. Coprocessing is based on the novel concept of two or more excipients interacting at the subparticle level, the objective of which is to provide a synergy of functionality improvement as well as masking the undesirable properties of individual. Coprocessing excipients leads to the formation of excipient granules with superior properties compared to physical mixtures of component or individual components.This allows production of high-functionality excipients to the formulator's advantage. The high functionality can be in terms of improved process ability such as flow properties, compressibility, content uniformity, dilution potential, and lubricant sensitivity, or improved performance such as disintegration and dissolution profile.

A majority of the solid dosage forms contain multiple excipients, which opens up a wide window of opportunities by way of combining existing excipients to achieve the desired set of performance characteristics. However, the development of such combinations is a complex process because one excipients may interfere with the existing functionality of another excipient. Over the years, the development of single-bodied excipient combinations at a subparticle level, called coprocessed excipients, has gained huge importance.

In the present investigation, an attempt was made to coprocess dicalcium phosphate a diluent and magnesium stearatea lubricant assuming that the resultant coprocessed excipient would have improved functionality of both diluent as well as lubricant. The reasons for selection of dicalcium phosphate is its property of a creamy mouth feel that is useful for chewable tablet formulations. Magnesium stearate is used as lubricant and is added in formulation for improvement of flow property. Thus co-processing of dicalcium phosphate with magnesium stearate will result in to a coprocessed excipients that may exhibit the properties of both dicalcium phosphate (mouthfeel) and magnesium stearate (better flow property).

Rational behind developing chewable tablets is that it is useful for administration of large tablets to children and adults who have difficulty in swallowing solid dosage forms. Chewable tablets are chewed and thus mechanically disintegrated in the mouth. The drug is, however, normally not dissolved in the mouth but is swallowed and dissolved in the stomach or intestine. These tablets are often employed when the active ingredient is intended to act in a localized manner, rather than systemically. Thus, chewable tablets are used primarily to accomplish a quick and complete disintegration of the tablet – and hence obtain a rapid drug effect or to facilitate the intake of the tablet. It was also thought of formulating chewable tablets because it was expected that Dicalcium phosphate may perform better on the front of increased mouth feel a property required to be present with the chewable tablets.

Materials and Methods

Ibuprofen was received as gift samples from Cipla Pvt. Ltd, Goa, India. Dicalcium phosphate, Talc, magnesium stearate, Potassium dihydrogen phosphate, Sodium hydroxide were purchased from Loba Chemie, Mumbai, India. Strawberry flavor and Sodium saccharin was obtained as gift sample from Research Lab, Islampur. All chemicals and reagents were of analytical grade and were used as such.

Experimental/ Methodology

Preparation of Coprocessed Excipient

The coprocessed excipient were prepared by solvent evaporation method. A blend of dicalcium phosphate and magnesium stearate (in the ratio of 1:0.5,1:1,1:1.5.1:2) was added in 70:30 ml of ethanol:water mixture. The beaker containing excipients mixture was kept on magnetic stirrer at 50 rpm speed and temperature was maintained between 60 to 80^{o}C for 24 h till the complete solvent was evaporated. Precaution was taken that a beaker containing excipients mixture was wrapped with aluminum foil after solvent evaporation till furher processing to prevent microbial growth. The wet coherent mass was air dried for 2 to 3 h till it was completely dried. The dried coprocessed excipient was sifted through # 44 mesh sieve, again dried for 30 min. at the temperature of 40^{0}C and stored in airtight container till further use. In the coprocessing of excipients, diluent concentration was taken as 70% while different concentrations of magnesium stearate i.e. 0.5%,1%,1.5% and 2% were taken. Co-processing of magnesium stearate and dicalcium phosphate was carried as per concentrations given in table no.1:

Table No.1 - Excipients ratio for coprocessing

Dicalcium phosphate (gm)	Magnesium stearate (mg)				Solvent
	0.5%	1%	1.5%	2%	
21	150	300	450	600	Ethanol: Water (70:30)

Preparation of Ibuprofen Chewable Tablet

All the ingredients except glidants and lubricant were weighed accurately and passed through sieve no 40, and were taken in morter and mixed thoroughly for 15 min. A small quantity of starch paste (5%) was added to make cohesive mass. This cohesive mass was then passed through a sieve no 20 or 22 then weighed quantity of glidant and lubricant was added. The prepared granules were dried at 40^0C for 30 min. in hot air oven (Singhal Scientific**,** Mumbai.). This blend was compressed by using 11 mm round flat - faced punch using 12 station multitooling tablet compression machine (Rimek II, Karnavati Eng. Ltd, Ahmedabad).

Table No.2 – Formulation of ibuprofen chewable tablet by wet granulation method

Ingredients	Formulations							
	A1	**A2**	**A3**	**A4**	**B1**	**B2**	**B3**	**B4**
Ibuprofen	100	100	100	100	100	100	100	100
Coprocessed excipient	-	-	-	-	352.5	355	357.5	360
Dicalcium phosphate	350	350	350	350	-	-	-	-
Magnesium stearate	2.5	5	7.5	10	-	-	-	-
Mannitol	32.5	30	27.5	25	32.5	30	27.5	25
Talc	5	5	5	5	5	5	5	5
Strawberry flavor	5	5	5	5	5	5	5	5
Sodium saccharin	5	5	5	5	5	5	5	5
Total	**500**	**500**	**500**	**500**	**500**	**500**	**500**	**500**

Evaluation of ibuprofen chewable tablet

Thermal Analysis

Differential scanning calorimetry (DSC) is performed of drug, dicalcium phosphate, magnesium stearate, coprocessed excipient, representative formulations A1 and B1. DSC measurements were done on a Mettler-Toledo DSC 821e, Switzerland and samples were heated up to 200^0.

Fourier Transform Infrared (FTIR) Spectral Studies:

Fourier Transform Infrared (FTIR) Spectral data were taken on a Pharmaspec 17010,shimadzu, japan instrument to find out the chemical stability of the excipient. FTIR spectra of the drug, dicalcium phosphate, magnesium stearate, coprocessed excipient, representative formulations A1 and B1were obtained. spectral scanning was done in the range between 4000-400 cm^{-1}.

X-ray diffraction studies:

X-ray diffraction studies of dicalcium phosphate, magnesium stearate and coprocessed excipient is performed. XRD measurements were done on a PW 1729, Philips, The Netherlands.

Average weight and weight variation:

For weight variation test IP (2007) procedure was followed. Twenty tablets were taken and their weight was determined individually and collectively using single pan electronic balance (AR 0640, Ohaus Corp. USA). The average weight of the tablets was determined from collective weight. From the individual tablets weight, the range and percentage standard deviation was calculated. Not more than 2 tablets should deviate from the average weight of tablets and the maximum percentage of deviation allowed. In direct compression of tablet, uniform weight of tablets represents appropriate powder flow and uniform die fill.

Hardness:

Hardness exhibits tensile strength of tablet. The force needed to fracture the tablet by diametral compression is referred as crushing strength of tablet. Hardness is a deformation property of a solid. The hardness of the six tablets from each formulation batch was determined using Monsanto hardness tester.

Friability:

Friability test indicates physical strength of compressed tablets. During handling tablets are subjected to stresses from collisions and tablets sliding towards one another and other solid surfaces, which can result in the removal of small fragments and particles from tablet surface. The result will be progressive reduction in tablet weight and a change in its appearance. Test for tablet Friability was carried out according to I.P 2007, according to which friability below 1% passes the test. Tablets from each formulation were tested for friability using Roche Friabilator (Rolex Scientific Engineers Limited). Twenty tablets were weighed initially and

transferred to the Friabilator. The instrument was operated at 25 rpm for 4 minutes. The tablets were reweighed and percentage loss was calculated using formula:

Drug content uniformity:

Twenty tablets were taken in morter and trituted with the help of pestle. A quantity equivalent to 10 mg was taken in 100 ml (100 µg/ml) volumetric flask and to it 100 ml PBS-6.8 was added. From this stock solution 1 ml aliquote were taken and diluted to 10 ml with phosphate buffer-6.8 (10 µg/ml).Finally the absorbances of prepared solution was measured against blank (PBS pH 6.8) at 221 nm using UV visible spectrophotometer (Pharmaspec 1700)

***In vitro* disintegration time:**

In the present study disintegration test was carried out on six tablets using the apparatus specified in USP (Electrolab disintegration apparatus USP). The distilled water at $37^0C \pm 2^0C$ was used as a disintegration media and time in minutes taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in minutes.

***In vitro* dissolution study:**

In vitro dissolution of the chewable tablets was carried out preferably in two forms: Intact (In case the dosage form is accidently swallowed) and partially crushed (to simulate chewing). The USP describes procedure for dissolution testing. Apparatus-I (Rotating basket) of the USP protocol may be appropriate for testing of partially crushed dosage forms while apparatus-II (Rotating paddle) may be suitable for testing whole tablet form. Rotating speed is kept at 100 rpm and the 900 ml phosphate buffer of pH 6.8 as medium at 37.0 ºC $\pm$ 0.5 ºC. Aliquots (1ml) were withdrawn at intervals of 10 min for 60 and 120 minutes respectively for crushed and intact tablet. The amount of ibuprofen in solution was determined spectrophotometrically at 221 nm. Sink conditions was maintained throughout the study.

Stability study:

The chewable tablets were packed in aluminium foil and stored under the following environmental conditions for a period as prescribed by ICH guidelines for accelerated studies.

i) 40 ± 1^0C and RH 75% ± 5%

The tablets were withdrawn at end of 30, 60 and 90 days and evaluated for parameters including disintegration time and dissolution study etc.

Results and discussion

Characterization of coprocessed excipient

Differential scanning calorimetry (DSC) analysis

A sharp endothermic peak at 192.13^0c is observed for dicalcium phosphate (fig.1) whereas a sharp endothermic peak for magnesium sterate was observed at 123.66^0c (fig.2) corresponding to their melting points in their thermograms respectively.

In the thermogram of coprocessed excipient two endothermic peaks were obtained (fig.3) close to the melting point of dicalcium phosphate and magnesium sterate, indicating the separate existence or just physical blending of them and rules out any chemical interaction between them. Thus from the DSC thermogram of coprocessed excipients, it is clear that there was a physical interaction and that to at subparticle level and no any chemical interaction was evident.

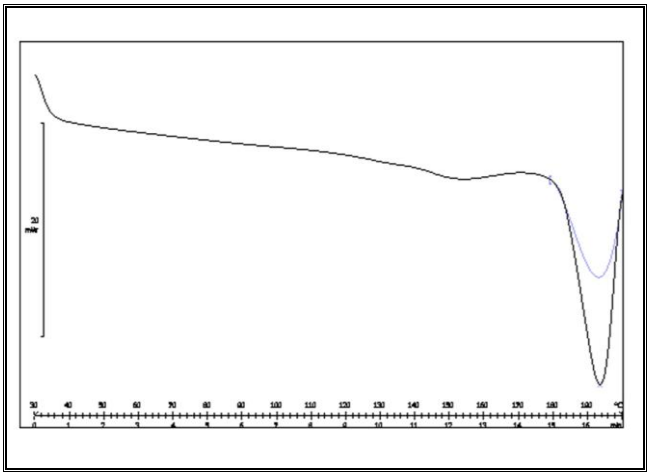

Figure No. 1: DSC thermogram of Dicalcium phosphate

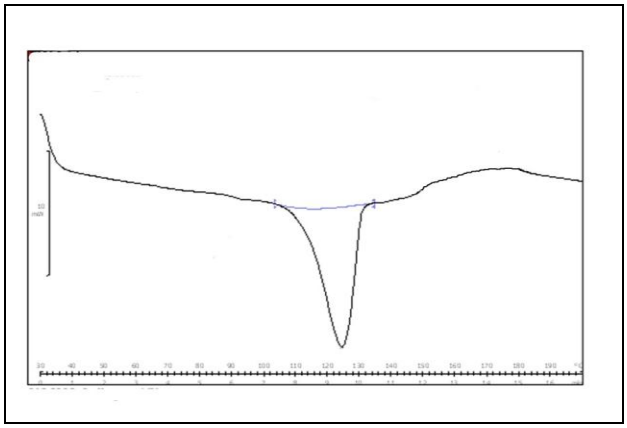

Figure No.2: DSC thermogram of Magnesium sterate.

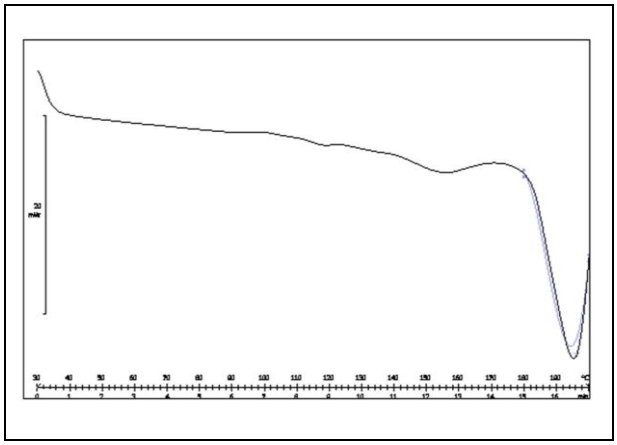

Figure No.3 : DSC thermogram of coprocessed excipient

FTIR spectroscopy

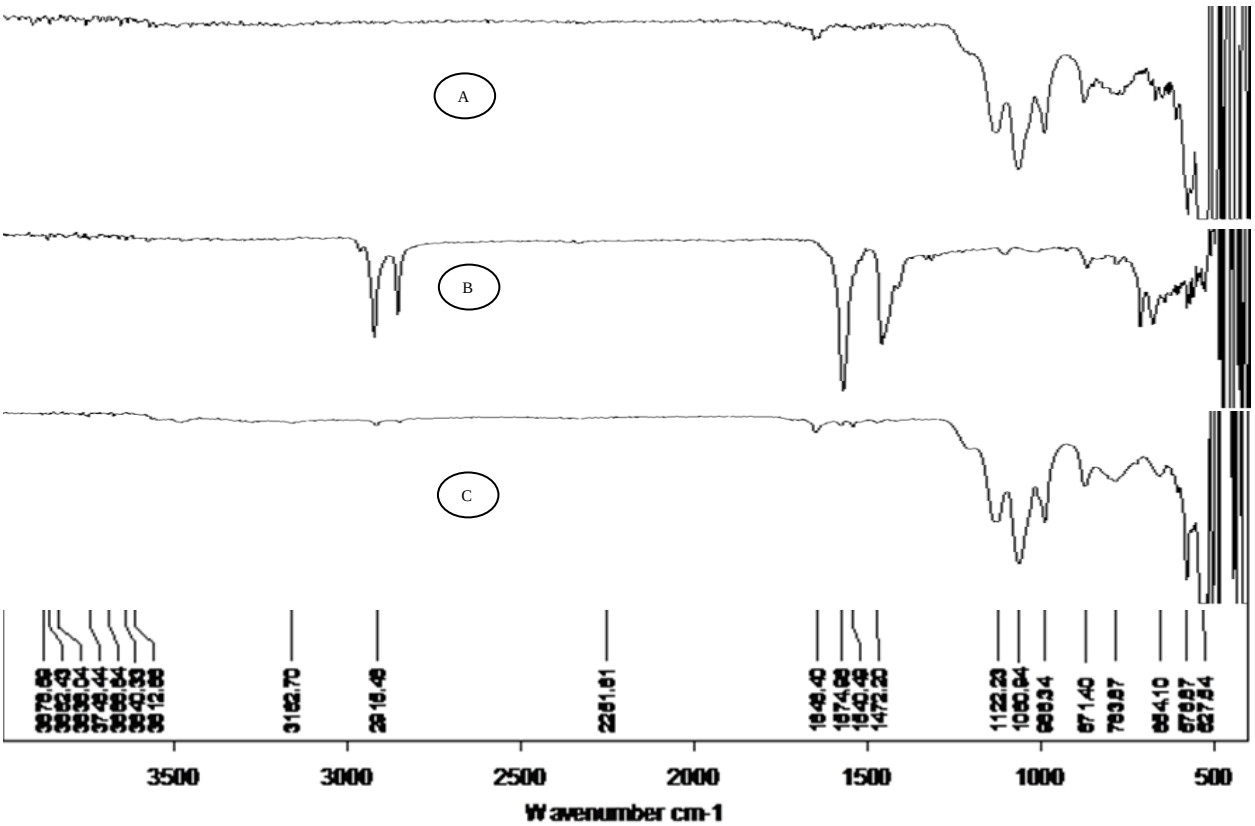

Fig.No.4 - Overlain FTIR spectrum of A) Dicalcium phosphate B) Magnesium stearate C) coprocessed product

After observation of FTIR characteristic peaks of dicalcium phosphate, magnesium sterate and coprocessed excipient it was observed that, except characteristic peaks of dicalcium phosphate and magnesium sterate there was no any additional peak in FTIR spectrum of coprocessed excipients, which revealed that there was no any chemical interaction or modification in coprocessed excipient during entire coprocessing reaction.

X-ray diffraction study:

The XRD pattern of dicalcium phosphate showed intence and sharp peak at intensity 739 which indicated its crystalline nature, while XRD pattern of magnesium stearate showed small peaks at intensity 167 which indicated its amorphous nature. XRD plot of coprocessed product showed peaks at intensity 670, reporting that there was a decrease in the crystalinity of coprocessed excipient.

Crystanility value was compared by means of relative decrease in crystanililty value. Crystallinity was determined by comparing sharp intense representative peak height in the diffraction patterns of individual excipient with coprocessed excipient. dicalcium phosphate showed sharp peak of intensity 739, while coprocessed product showed sharp peak of intensity 670. The relative degree of crystallinity (*RDC*) was calculated according to equation:

$$RDC = I_{Sample} / I_{reference}$$

Where I_{sample} is the peak height of highest intensity of sample i.e. coprocessed product and $I_{reference}$ is the peak height at the same angle for the reference i.e. dicalcium phosphate with the highest intensity.

The *RDC* value of corresponding coprocessed excipient was found to be 0.90. Thus the XRD analysis revealed that there was reduction in the diffraction intensity of coprocessed excipient. This indicates reduction in the crystallinity of coprocessed excipient.

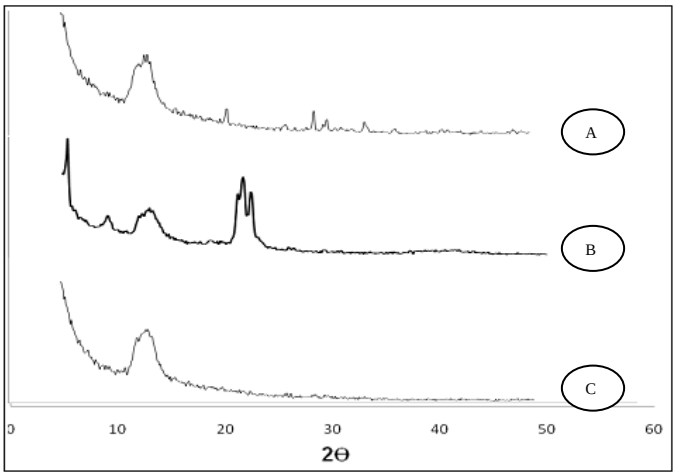

Fig.No.5 - XRD analysis plot of A) dicalcium phosphate B) Magnesium stearate c) coprocessed product

Preformulation studies of coprocessed and non-coprocessed granules:

The blended mixture which was ready for compression, was examined for angle of repose, bulk density, tapped density, Carr's index(CI), Hausner's ratio(HR) and the values for which are as reported in table no.3. According to literature survey powders with CI values between 5% -18% were suitable for producing tablets via direct compression and those with HR values are below 1.25 and angle of repose below 20^0 exhibits excellent flow, while values in between 20^0-30^0 indicate good flow properties.

Table No.3: Preformulation parameters of coprocessed and non-coprocessed granules.

Batch	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose θ (0o)	Compressibility Index (%)	Hausner's ratio
A1	0.3201±0.01	0.3956±0.06	23.20±2.14	18.25± 3.03	1.15± 0.04
A2	0.3128±0.04	0.3705±0.08	25.14±1.14	15.50± 3.13	1.18± 0.04
A3	0.3266±0.03	0.3893 ±0.01	21.39±0.11	19.10± 1.00	1.19± 0.01
A4	0.3142±0.01	0.3819±0.06	20.78±1.99	17.70± 1.78	1.23± 0.01
B1	0.3231±0.01	0.3546±0.02	21.23±1.10	10.87± 0.41	1.10± 0.04
B2	0.3101±0.02	0.3483±0.04	19.57±1.30	13.93± 1.68	1.15± 0.02
B3	0.3176±0.06	0.3562±0.01	15.45±3.79	11.79± 1.65	1.12± 0.01
B4	0.3177±0.09	0.3725±0.01	17.45±1.39	14.68± 1.23	1.17± 0.02

From the Preformulation studies it was clear that all the required properties for formulation of tablets were in the acceptable range. From the results obtained for bulk density, tapped density, angle of repose and hausner's ratio it was clear that the granules were having free flowing ability from hopper in to die cavity and uniform die fill. The values for compressibility index indicating that the granules were having the values in the acceptable range and these blende could be readily compressible. Thus from the above date it was decided to go for compression of granules for producing the chewable tablets of ibuprofen.

X-ray diffraction study:

The XRD analysis of dicalcium phosphate, magnesium sterate and their coprocessed product was carried out to study their morphological pattern.

Compatibility study:

Compatibility study of drug with excipients was carried out using DSC and FTIR analysis. Results obtained are as discussed below:

Physicochemical evaluation:

Physicochemical evaluation of both coprocessed and non coprocessed formulations was carried out, in that weight variation, hardness, friability, in-vitro disintegration time, diameter, thickness, drug content, and in-vitro dissolution study of tablets was carried out.

Table No.4: Evaluation parameters of Ibuprofen chewable tablet

Batch	Weight variation€ (mg)	Hardness* (Kg/cm2)	Friability† (%)	In-vitro Disintegration Time (min)*	Drug content(%)	Diameter (mm)†	Thickness (mm)†
A1	Passes	5.2±0.11	0.57±0.02	30±1.89	98.52±0.72	11.02±0.5	4.03±0.3
A2	Passes	5.1±0.15	0.60±0.04	32±0.17	98.67±0.56	11.03±0.4	4.07±0.1
A3	Passes	5.1±0.12	0.58±0.01	35±1.41	99.45±0.55	11.07±0.1	4.01±0.4
A4	Passes	5.3±0.10	0.62±0.05	37±1.63	97.84±0.67	11.03±0.5	4.02±0.2
B1	Passes	5.2±0.10	0.47±0.03	26±1.94	99.54±0.56	11.03±0.2	4.03±0.1
B2	Passes	5.4±0.18	0.52±0.08	28±1.87	99.32±0.63	11.04±0.1	4.02±0.4
B3	Passes	5.1±0.02	0.49±0.06	31±1.67	96.29±0.66	11.01±0.3	4.08±0.1
B4	Passes	5.3±0.013	0.59±0.07	34±0.40	98.74±0.60	11.07±0.5	4.01±0.3

Tablets of all formulations pass weight variation test as per IP. None of the tablet was found to deviate from the average weight of tablets. The thickness and diameter of all formulations containing both excipients was found to be uniform as it was obtained in the range of 4.01 to 4.07 mm and 11.01 to 11.07 mm respectively. Drug content of all formulations was observed between 97.84 % to 99.54 %. Hardness test for all formulations was carried out and values obtained were in the range of 5.1 to 5.4 kg/cm^2. Test for friability was conducted for all formulations,

% friability was found to be in the range of 0.47 to 0.62. In vitro disintegration time for all formulations was found to be in the range of 26 to 37 min.

The values for thickness and diameter signify uniformity and it was due to uniformity in die fill, good flow properties, uniform pressure and appropriate punch movement. Drug content for all formulations showed uniformity which indicated that there was was uniform flow and uniform distribution of drug. Weight variation tests for all formulations showed weight variation with deviation less than ± 5, which complies with I.P specification and signifies that there is uniformity in flow of powder blend which led to uniform die fill. Hardness for all formulations was observed to be proper, which signify that tensile strength of all formulations was maintained after direct compression. Friability test for all formulations indicated that % friability was less than 1%, which complies with I.P specification and reveals that all formulations have possessed good physical strength and can withstand the mechanical shocks that can be observed during handling, shipping and transportation.

***In vitro* Dissolution study:**

Two types of in vitro diisslution studies were performed namely the in vitro dissolution study on the intact tablets and second one was the in vitro diisslution study on the crushed tablets. As the chewable tablets are ment to be chewed the second type of dissolution studies were also carried out. The data for the in vitro diisslution studies on intact tablets and crushed tablets are provided in table no.5 and 6 and figure no.6 and 7 respectively.

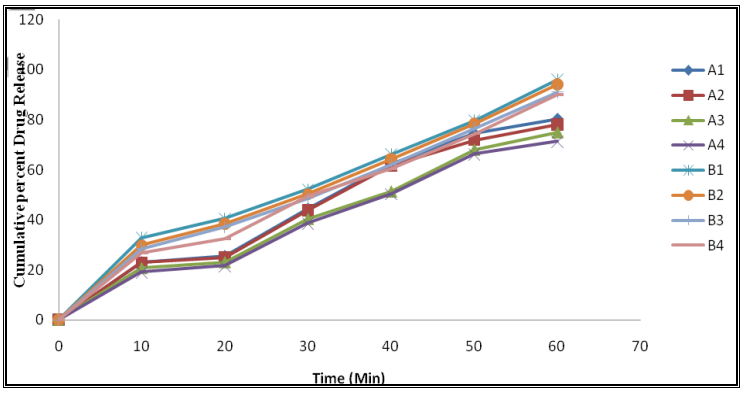

Figure No.6 : Comparative plot of dissolution profiles of crushed ibuprofen chewable tablet

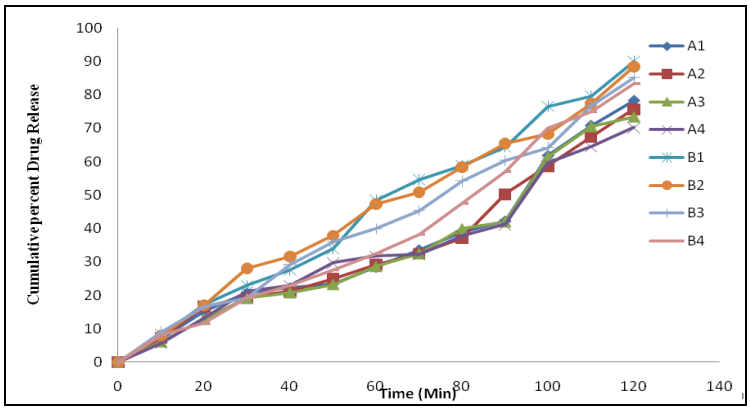

Figure No.7: Comparative plot of dissolution profiles of intact ibuprofen chewable tablet

Stability study:

Short-term stability studies of the optimized formulation indicated that there were slight changes in physical parameters like drug content, disintegration time, and in vitro dissolution studies when stored at temperature and humidity conditions of 40 ± 1^{o}C and 75 ± 5 % RH for three months period.

No significant reduction in the content of the active drug was observed over a period of three months hence shelf life of the formulation could extrapolate to a minimum of two years. However, storage temperature not exceeding 45^{0}C and moisture proof packaging are essential to ensure stability of these formulations.

Conclusion

Compatibility study was performed using DSC and FTIR, which concluded that integrity of representative formulations were maintained as there was no any chemical alteration in between drug and excipients.

The drug release of ibuprofen chewable tablet was found to be dependent of concentration of magnesium stearate. From dissolution study of crushed tablet it can be concluded that Formulation B1 shows 96.00% drug release in 60 min, while formulation A1 showed 80.39% drug release in 60 min, and From dissolution study of intact tablet it can be concluded that Formulation B1 shows 90.01% drug release in 120 min, while formulation A1 showed 78.33% drug release in 120 min. It revealed that formulation containing co-processed excipients showed improved performance compared to physical mixture formulation and it was due to its amorphous nature which shows more solvent affinity due to less degree of crystalline lattice. Hence from the physicochemical evaluations of all chewable tablet formulations, it was concluded that formulation B1 was observed to be optimized formulation. The future for co-processed excipients looks very reliable. With upcoming newer combination of excipients grades and newer methods of coprocessing, co-processed excipients are for sure going to gain attraction in developing novel dosage forms in pharmaceutical industry.

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Abbreviations

Sr.no.	Abbrevations	Full form
1.	cm	Centimeter
2.	cm3	Cubic Centimeter
3.	DSC	Differential Scanning Calorimetry
4.	FTIR	Fourier transform infrared
5.	g/gm	Gram
6.	H	Hour (s)
7.	IP	Indian pharmacopoeia
8.	Kg/cm2	Kilogram per centimeter square
9.	Mg	Miligram
10.	Min	Mintue (s)
11.	Ml	Milliliter
12.	mm	Millimeter
13.	max	Maximum
14.	nm	Nanometer
15.	PBS	Phosphate buffer solution
16.	Q	Cumulative
17.	r2	Correlation coefficient
18.	RH	Relative humidity
19.	rpm	Revolutions Per Minute
20.	SD	Standard deviation
21.	sec	Second
22.	t	Time
23.	UV	Ultra Violet
24.	USP	United States Pharmacopoeia
25.	µg	Microgram
26.	XRD	X-ray diffractometry

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