ORIGINAL RESEARCH

Evaluation of the sustained release potential of a co-processed excipient in Ibuprofen tablet formulation

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ABSTRACT

Background: The oral route happens to be the most preferred route among the various routes of drug delivery. However, the conventional dosage form has few limitations which could be resolved by modifying the existing dosage form. Sustained and controlled drug delivery systems help to maintain constant plasma drug concentration and retarding the release rate of drug thereby extending the duration of action.
Objectives: To develop by co-processing technique a two-component excipient and evaluate its sustained release potential in ibuprofen tablet formulation.
Method: Maize starch (MS) was co-processed with polyvinylpyrrolidone (PVP), acacia powder (ACA) and hydroxypropyl methylcellulose (HPMC) respectively at a ratio of 60:40 using the co-fusion method. The granules so formed were analyzed for flow properties and compatibility tests based on; angle of repose, flow rate, bulk and tapped densities (BD/TD), Hausner ratio (HR) and Carr's Index (CI), Differential Scanning Calorimetry (DSC) and Fourier Transform Infra-red (FTIR) spectroscopy. The tablets were evaluated after compression by direct compression.
Results: The co-processed excipient (CE) had excellent flow properties as compared to the physical mix (PM). The DSC thermograms and FTIR spectra of CE when compared with their individual excipients and that of the drug, showed a similarity in their endothermic peaks respectively but for some slight difference showing compatibility and no new compound was found because of co-processing. The tablets had acceptable values for weight variation and disintegration time. Tablets of Batch XII B were of good quality regarding weight, hardness, disintegration time and friability by meeting the British Pharmacopoeia specifications.
Conclusion: This study concluded that the two-component excipients developed improved the functionality of the single components. Conversely, the co-processed excipients did not exhibit good sustained release property but would be better employed as conventional tablets or prepared as a sustained release matrix formulation.

Keywords: Co-processed technique; Co-processed excipient; Sustained release; Ibuprofen; Flow properties; Drug delivery

INTRODUCTION

Oral drug delivery is the most widely used and most commonly accepted form of drug administration due to its advantages of simplicity, painlessness and self-administration as well as the design of proper dosage form is an important element to

accomplish this[1]. Sustained release, prolonged action, sustained action, controlled release, extended action, timed release and depot dosage form are terms used to identify drug delivery systems that are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose[2]. The formulation of a sustained release tablet could be achieved through co-processing.

Co-processing involves two or more excipients interacting at sub particle level with an objective to provide a synergy of functionality improvements and masking the undesirable properties of individual excipients. Commercial examples of co-processed excipients include Ludipress®, Cellactose® and Starlac®[3]. Co-processing is generally conducted with an excipient that is plastic and another, brittle. Sun reported co-processing performed with a large amount of brittle material and a little amount of plastic material, as exemplified in Cellactose in which 75% lactose (brittle material) was co-processed with 25% cellulose (plastic material)[3]. This combination is aimed at preventing the storage of too much elastic energy during compression thereby resulting in a small amount of stress relaxation and a reduced tendency of capping and lamination.

Therapeutic agents that are easily absorbed from the G.I.T with a short half-life, eliminated quickly from the blood circulation, narrow absorption window known as oral controlled release formulations have been developed to release the drug slowly into the G.I.T

The controlled release dosage forms cover a wide range of prolonged action formulations that release the drug continuously at the specific site for a predetermined time and rate.

Meanwhile, the sustained release dosage form is a well characterized and reproducible dosage form designed to control drug release profile at a specified rate to achieve desired drug concentration either in blood plasma or at target site. This system provides actual therapeutic control that would either be temporal (time related), spatial (site related) or both[4].

Direct compression is a process by which the tablets are compressed directly from a powder blend of active pharmaceutical ingredient (API) and suitable excipients [5]. Pharmaceutical materials vary in their direct compression behaviour. For instance, it is well known that microcrystalline cellulose (MCC) goes through plastic deformation during compression while dibasic calcium phosphate dihydrate deforms mainly by fragmentation. Most materials are somewhere between these extremes; thus, the ideal mixture of excipients has to be found in order to get the right balance between brittle fracture and plastic deformation[5].

Literature reveals that the use of various excipients like HPMC, sodium alginate, carrageenan, xanthan gum, etc. has shown a sustained release of drug and thus increased the duration of action for long hours.

Prajapati *et al,* developed controlled-release tablet of Zolpidem tartrate by using polyethylene glycol (PEG 6000) as melt binder, Hydroxypropyl methylcellulose (HPMC K4M) and Polyvinylpyrrolidone (PVP K30) as matrixing agent and filler, respectively, which would release the drug for prolonged period of time [6].

Starches when modified, can significantly enhance their swelling and flow properties which initially constitute their weaknesses as well as yielding tablets of low crushing strength-friability ratio but co-processing it with HPMC, PVP, ACACIA known for their cohesive property and ability to impart mechanical strength would yield substantial benefits as reported by Okunlola[7].

Acacia is an odourless and colourless dry gum obtained from the stems and branches of species of acacia tree and is composed of loose aggregates of sugars and hemicelluloses[8]. The main constituent of the gum is arabic acid, that is chemically associated with arabinose, galactose and rhamnose, as well as metals such as calcium and magnesium. It is used in the pharmaceutical industry as an emulsifying

and stabilizing agent mainly for oral and topical formulations. Other uses include tablet binders, suspending and viscosity increasing agent, and in the formulation of lozenges[8].

Polyvinylpyrrolidone, also known as povidone or PVP, is employed in the pharmaceutical industry as a synthetic polymer vehicle for dispersing and suspending drugs. It has multiple uses, a film former for ophthalmic solutions, as a binder for tablets and capsules, aids in flavouring liquids and chewable tablets, and as an adhesive for transdermal systems[9].

The aim of this is to investigate the sustained release potential of the excipient system via co-processing technique using ibuprofen as the model drug.

MATERIALS AND METHODS

Materials

Maize starch powder BP (Kermel®, Tianjin chemical reagent Co., Ltd, China), Acacia powder USP (Loba chemie® Pvt Ltd, India), Polyvinylpyrrolidone powder (BDH Chemicals Ltd, England) Ibuprofen powder BP (Pure Chem Products Ltd, Neeham Market Suffolk, England) Distilled water, all other materials and solvents, used were of analytical grade.

Preparation of co-processed excipient

The primary excipients were co-processed using the co-fusion method as reported by Adeoye and Alebiowu[10]. Corn starch powder and polyvinylpyrrolidone powder (Batch XII A), corn starch powder and acacia powder (Batch XII B), corn starch powder and hydroxypropyl methylcellulose powder (HPMC) (Batch XIIC) in the ratio 60:40 obtained as the best ratio from the preliminary dilution potential studies done, were fused together by dispersing them in distilled water and heated in a water bath to 40˚C. The dispersion was then stirred for 15 min at the same temperature to form a paste. The resulting paste was then dried at 40 ˚C in a hot air oven (Gallenkamp, B.S size three, England) for 2 hours before screening with 1.5 mm sieve, finally dried for 10 min then passed through a 500 µm sieve and stored in a screw-capped bottle. The physical mix was also prepared by co-grinding method.

Powder characterization

Angle of repose

Twenty (20 g) grams of the powder from each batch was poured into a plugged funnel. The height and diameter of the static heap of powder were taken using a ruler and the angle of repose was calculated. Bulk and tapped densities, Carr's index and Hausner's ratio were determined. Flow rate being the time taken for the powder to flow was noted and computed.

Compatibility Studies

Fourier Transform- Infrared Spectroscopy

The Fourier transform- infrared (FT-IR) spectrum of the sample, was recorded from 4000 – 650 cm^{-1} on an IR spectrometer (Shimadzu FTIR 8400s, USA). This was done by using potassium bromide (KBr) discs prepared from the mixture of the sample and dried KBr in the ratio of 1:200.

Differential Scanning Calorimetry (DSC)

A DSC study of the samples was conducted using DSC, (Mettler Toledo, Germany). DSC cell was purged with 50 mL/min dry nitrogen. Accurately weighed samples (2- 4 mg) were heated in aluminium pans in temperature range of 25- 250 ˚C at a heating rate of 20˚C/min[9]. Prior to analysis, calibration of the instrument was performed using zinc (Zn) and indium (In).

Formulation Studies

Tablets were formulated using ibuprofen as the model drug. The co-processed excipient was used to prepare tablets by direct compression (Table 1). The target tablet weight was set at 500 mg and a batch size of 100 tablets at 5 -7 Metric tonnes was prepared for each formulation using the Erweka AR400 single punch tableting machine (G.M.B.H Heusenstamin Kr. Offenbach, Germany).

Tablet evaluation

The tablets were evaluated for the following: weight uniformity, crushing strength, friability, disintegration and dissolution tests.

Table 1: Formula for Ibuprofen (200 mg) tablets

Ingredients	Batch XIIA (Maize starch + PVP)	Batch XIIB (Maize starch +Acacia)	Batch XIIC (Maize starch + HPMC)
Co-processed excipient	295	295	295
Ibuprofen	200	200	200
Magnesium stearate	5	5	5
Total (mg)	500	500	500

RESULTS

Flow indicators like Angle of repose, Carr's index (CI) and Hausner's ratio (HR) were used in this study to assess powder flow as shown on (Table 2) below. The table revealed that batch XII A had the highest difference (0.14 g/ml) between bulk and tapped densities compared to batch XII B (0.12 g/ml) and batch XII C (0.06 g/ml)

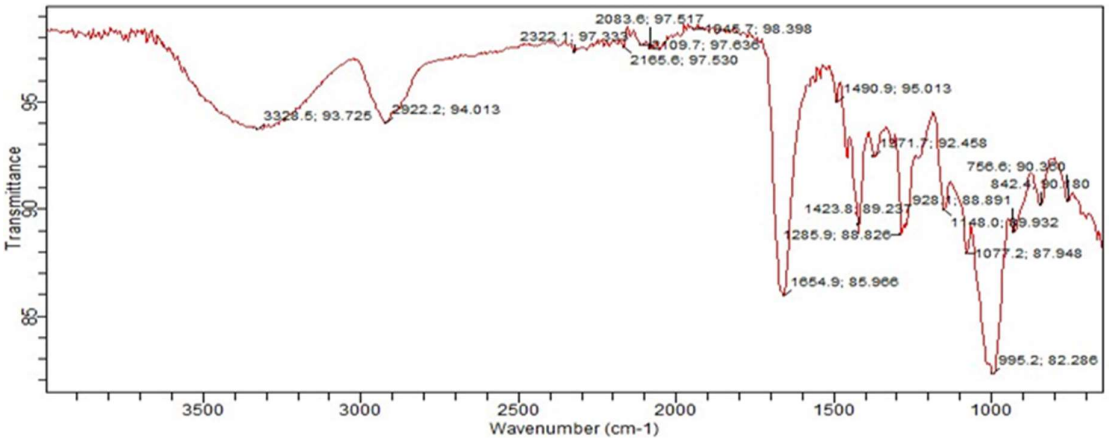
Table 2: Powder Analysis of Co-processed excipients

Parameters	Batch XIIA (Maize starch + PVP)	Batch XIIB (Maize starch +Acacia)	Batch XIIC (Maize starch + HPMC)
Flow Rate (g/sec)	4.3	7.8	5.5
Angle of repose (˚)	20.4	18.9	19.8
Bulk density (g/ml)	0.71	0.83	0.80
Tapped density (g/ml)	0.85	0.95	0.74
Hausners' ratio	1.19	1.14	1.11
Carrs' index (%)	16.01	12.5	10

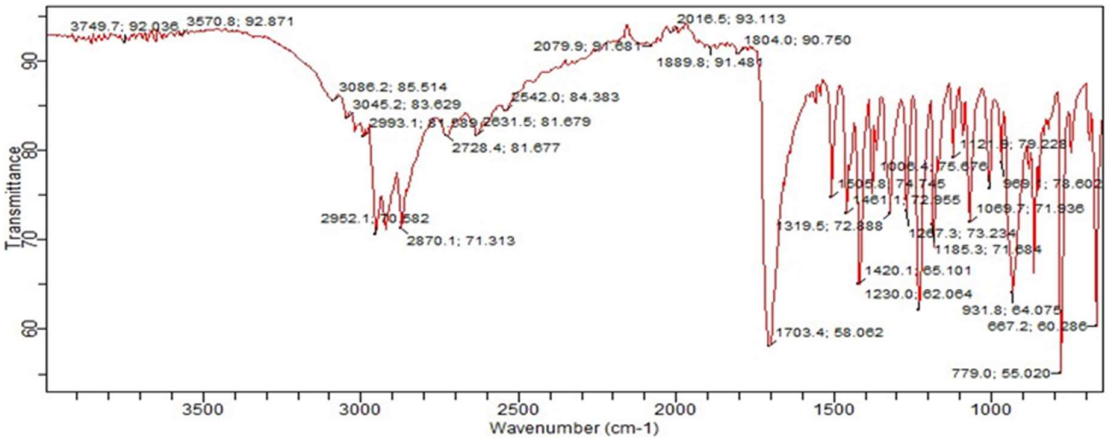
Key: Maize starch/ Polyvinylpyrrolidone (MS/PVP); Maize starch/ Acacia (MS/AC); Maize starch/ Hydroxypropyl methylcellulose (MS/HPMC)

Figure 1 shows the plots of M/S+PVP(CE), IBU, and M/S+PVP(CE)+IBU showing the individual spectrum respectively

MS +PVP



IBU



MS +PVP+ IBU

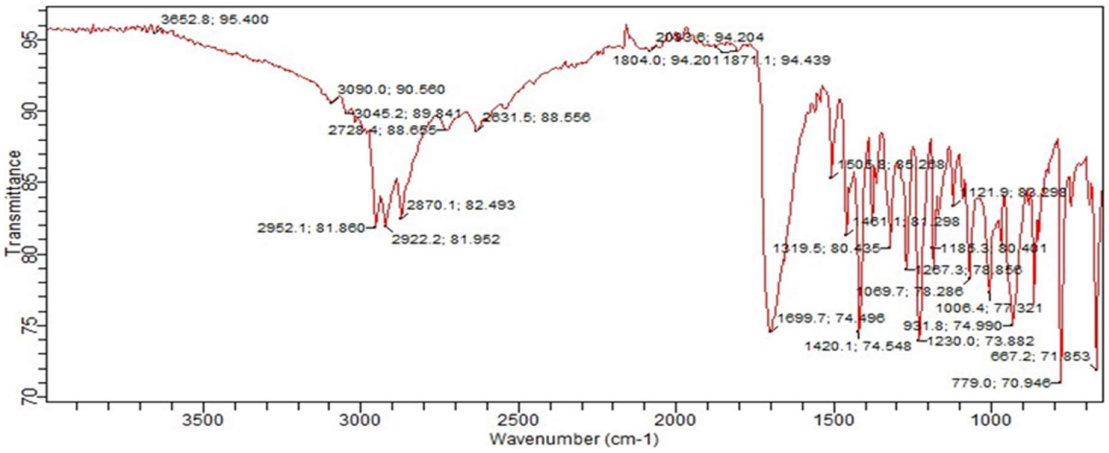
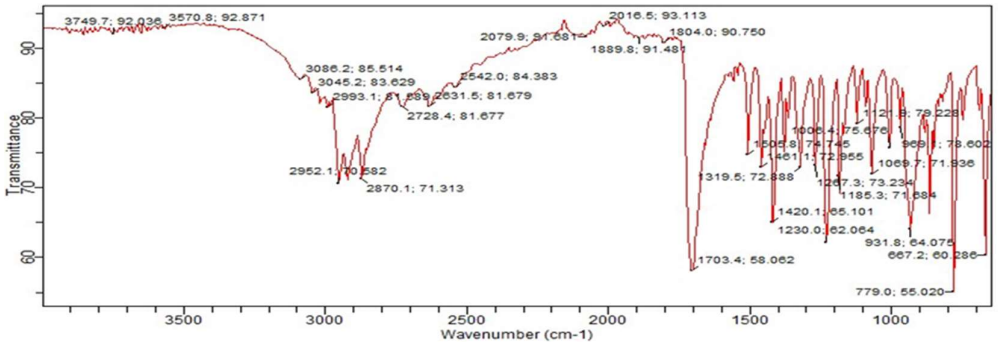


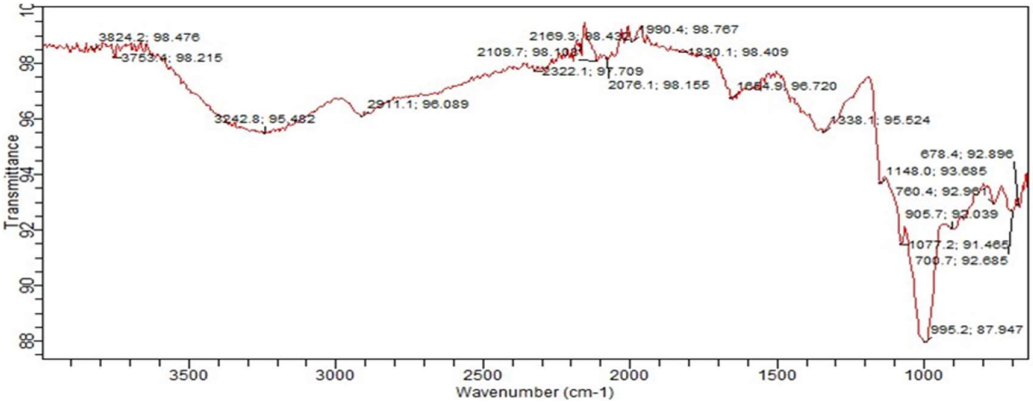
Figure 1: FTIR spectra of MS+PVP, IBU and MS+ PVP +IBU
Key: MS – maize starch, PVP –polyvinylpyrrolidone and IBU - ibuprofen

Figure 2 represents the individual spectrum for IBU, IBU+MS+AC(CE) and M/S+AC(CE); respectively

IBU



M/S+AC(CE)



IBU+MS+AC

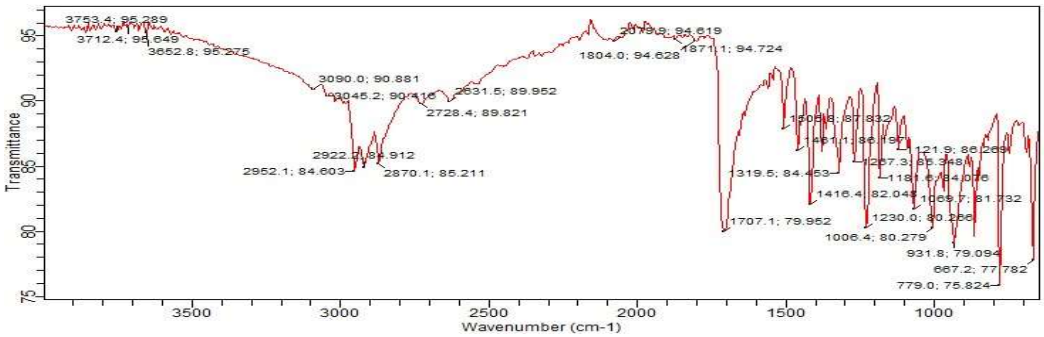
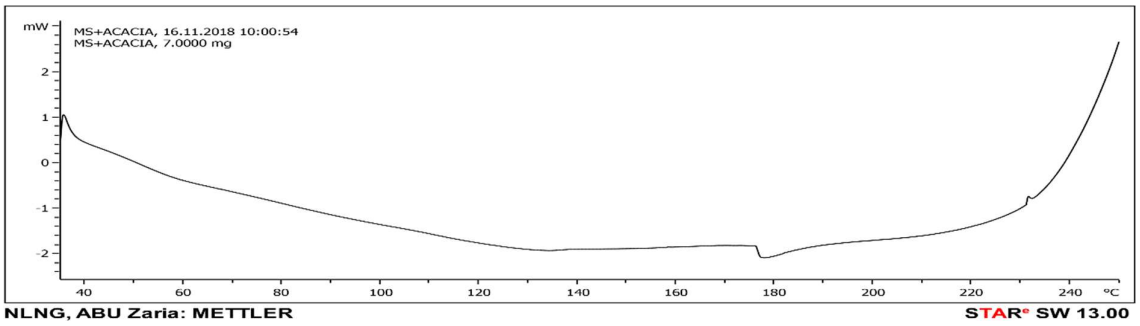


Figure 2: FT-IR spectra of IBU, IBU+MS+AC and MS+AC

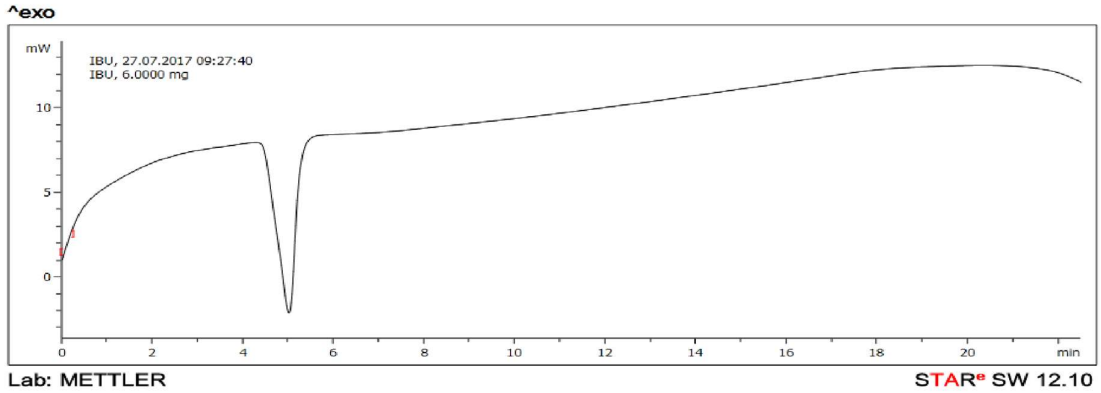
Key: IBU – ibuprofen powder, MS – maize starch and AC - acacia

Figure 3 reveals the DSC thermograms for maize starch and acacia, ibuprofen and maize starch, ibuprofen and acacia combined. Ibuprofen showed a significant sharp peak.

MS+ACACIA



IBU



MS +ACACIA+IBU

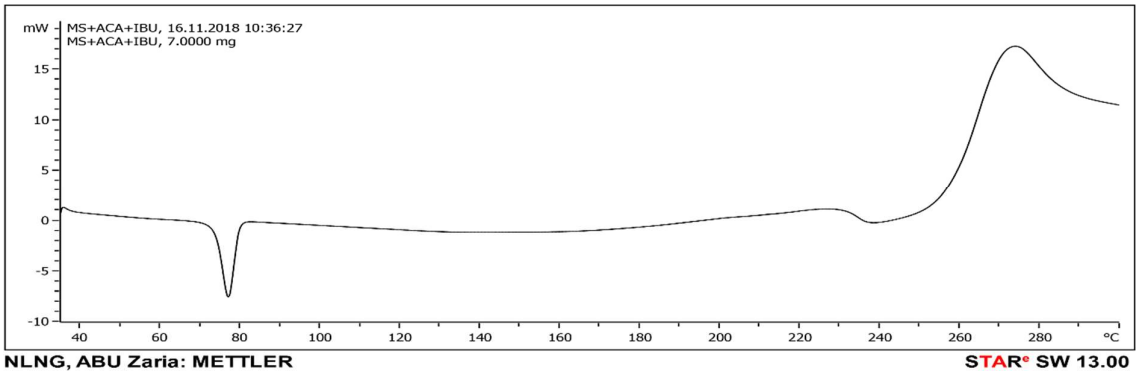


Figure 3: DSC thermogram of MS+ACACIA+IBU, IBU and MS+ACACIA

Key: IBU – ibuprofen powder, MS – maize starch and AC - acacia

The tablet properties for batches XIIA, XIIB and XIIC are presented on (Table 3) below with XIIB having the highest crushing strength. The weight uniformity test on the tablets indicated no significant difference ($p > 0.05$) in the weights of tablets.

Table 3: Tablet properties evaluated

Parameters	Batch XIIA [Maize starch + PVP] (s.d.)	Batch XIIB [Maize starch +Acacia] (s.d)	Batch XIIC [Maize starch + HPMC] (s.d.)
Mean tablet weight (g)	490 (0.01)	501.5 (0.09)	501 (0.01)
Thickness (mm)	4.68 (0.07)	4.23 (0.06)	4.73 (0.10)
Diameter (mm)	12.09 (0.02)	12.08 (0.02)	12.71 (0.60)
Crushing strength (KgF)	2 (0.00)	3.4 (0.19)	2.3 (0.11)
Friability (%)	5.5	0.3	20.7
Disintegration time (min)	112	111	36
Dissolution time (hrs)	8	8	8

Key: Batch XIIA: MS/PVP; Batch XIIB: MS/ACACIA; Batch XIIC: MS/ HPMC; s.d.: standard deviation

It was seen for all batches as presented on (Figure 4) below, that more than 60 % was released in I hr and maintained between 70 % and 88 % over 7 hr showing that there was no statistically significant difference between them.

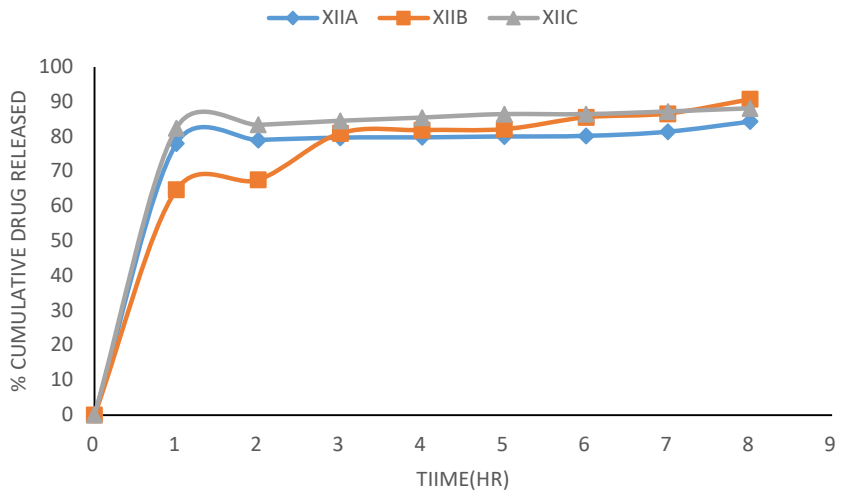


Figure 4: Dissolution profile of Ibuprofen tablets formulated with Co-processed excipients

Brufen retard tab®) as seen in (Figure 5) below showed a release rate of about 40 % in 5 hr and about 80 % in 10 hr.

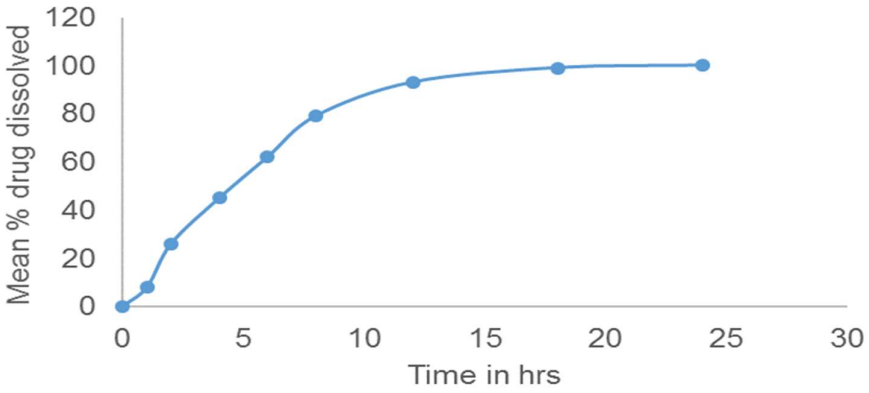


Figure 5: Dissolution profile of Brufen® Retard

DISCUSSION

In the present study sustained release tablets of ibuprofen were formulated and evaluated by direct compression method. The dynamics of working on pharmaceutical excipients to yield high functional ones (contribute at least two functions to the formulation through a single ingredient) can be achieved by looking inwards and developing new chemical excipients, new grades of existing materials, or by new combinations of existing materials. The latter two types are products of what is now called particle engineering[11].

To obtain a uniform product, the powder blend of API and excipients must of a necessity flow uniformly into the die cavity[12]. Angle of repose less than 30 ˚C is an indication of good flow and it is a function of the cohesiveness of the powder. This was observed in granules of CE batches which were co-processed and had angles of repose within the expected range.

Inter-particle interactions are less significant and the bulk and tapped densities will be closer in value when the powder flows freely. For poorer flowing materials, reverse is the case and a greater difference between the bulk and tapped densities will be observed[13]. Therefore, this corroborates the result obtained in this study.

Drug-excipient compatibility was confirmed by FT-IR analyses. No new functional group or molecule was formed because of chemical interaction between Ibuprofen and the co-processed excipients[14].

Ibuprofen when mixed with CE (MS + ACACIA) as exhibited in the overlay DSC curve, their characteristic peaks were seen at a reduced intensity then a fusion. After the fusion, the DSC curve indicated an initiation of an exothermic process with a positive slope indicating crystallization at 270 ˚C then ended in a complete degradation of the drug at 280 ˚C. This is comparable to the work of Gramaglia and colleagues[15]. This shows the compatibility of IBU with CE. The difference in intensity of the peaks observed in the thermograms can be attributed to the introduction of excipient in the mixture as well as is influenced by the concentration. The overlay of the thermograms for CE showed a similarity in their endothermic peaks but for some slight difference showing compatibility and no serious change or formation of a new compound because of co-processing. This goes a long way to show that co-processing or particle manipulation did not in any way result in the formation of a new compound as obtained in a previous study[15].

The weight uniformity test on the tablets indicated no significant difference ($p > 0.05$) in the weights of tablets and dimensions from the various batches and hence conformed to the British Pharmacopoeia[16] specification,

i.e. that not more than two of the individual weights should deviate from the average weight by more than ±5 % and none should deviate by more than ±10 %. Results of tablet hardness test show values between 2 KgF and 3.4 KgF, since hardness values greater than or equal to 4 KgF is considered to be the minimum for a satisfactory tablet[17], batch XII B showed better hardness value compared to batches XII A and XII C, the low crushing strength of the tablets could be attributed to the hygroscopic nature of the co-processed excipients, this further agrees with the friability result where only tablets of batch XII B met the BP specification of a maximum loss of 1 % of the mass of the tablets tested[18]. For disintegration test, the range was between 36 and 112 mins with batch XIIB having the longest time, this may be due to the crystal habit and tableting behaviour of Ibuprofen in the formulation as documented by Rasenack and Muller[19] where plate-shaped crystals of Ibuprofen were compared with the common needle shaped form. Sustained release indicates an initial release of drug sufficient to provide a therapeutic dose soon after administration and then a gradual release over an extended period. Sustained release formulation describes the slow release of a drug substance from a dosage form to maintain therapeutic response for an extended period. HPMC, in Batch XIIC (hydrophilic) was selected considering its widespread applicability and excellent gelling activity in controlled-release formulations. PVP (Batch XIIA) and Acacia (Batch XIIB) were also selected for their binding, gelling and swelling nature.

The dissolution test revealed that there was no statistically significant difference between them. Also, there was no complete release seen across board for all batches. This disagrees with the work done by Rajyalakshmir and colleagues[1] where the best corresponding plot (Brufen Retard tab®) seen in Figure 5.0, showed a release rate of about 40 % in 5 hr and about 80 % in 10 hr. The difference seen in Brufen Retard tablet® may be attributed to the amount of ibuprofen present (800 mg) and that of HPMC, the tableting method used (wet granulation) aside from the poorly water-soluble nature of ibuprofen, its inclusion in a matrix system and the method of analysis (RP-HPLC).

CONCLUSION

Two component excipients with improved functionalities were prepared. The co-processed excipients exhibited excellent flow properties with a high moisture content and good swelling index when compared to their single excipients. Tablets of batch XII B were of good quality regarding weight, hardness, disintegration time and friability because the official specifications were met. The three batches, XIIA, XIIB and XIIC since they could not compare favourably with commercially available Brufen Retard tablet®, can therefore be put forward as unsuitable excipients for sustained release formulation but would be better employed as conventional tablets or prepared as a sustained release matrix formulation.

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