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Evaluating the Flow and Release Profiles of Ibuprofen Formulations by Increasing the Binder Concentration

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article.

Abstract

Background: Tablets must be able to release the active drug in the gastrointestinal tract for absorption. The release profile of solid pharmaceutical dosage formulations can be quantified by assessing the disintegration and dissolution times tests. Binders are adhesives either from sugar or polymeric material that are added to tablet formulations to provide the cohesiveness required for the bonding together of the granules under compaction to form tablets.
Objective: The objective of the study was to formulate and assess ibuprofen tablets using different concentrations of binders (Acacia and Gelatin).
Methods: The granules were prepared using wet granulation method and analysed for flow properties based on USP/NF protocols. After granule compression, the tablets release profiles were thereafter assessed via the tablet dissolution and disintegration tests.
Results: Weight variation, thickness and diameter were within the acceptable values for all batches indicative of a uniform flow. Batches with binder concentrations of 10 % and 20 % failed disintegration test due to a disintegration time above 15 min while the release rate for batches 1 and 4 was about 88 % in 60 min as against the other batches whose release rate was less than 50 % in 60 min as a result of increasing their binder concentrations.
Conclusion: The study concluded that increasing the concentration of acacia and gelatin above 5% led to a decrease in percentage of drug released and an increase in disintegration time above 30 mins because 5% batches gave the best release profiles.
Keywords: Binder concentration; Flow profile; Release profile

INTRODUCTION

Ibuprofen as the drug of choice, is a well- known non-steroidal anti-inflammatory drug (Abraham and KI., 2005). Ibuprofen usually at low dose can be compared to aspirin and paracetamol in effectiveness for the indications normally treated with over-the-counter (OTC) medications (Moore, 2003). Also, it is used as an anti-pyretic, analgesic and anti-inflammatory agent (Fischer *et al.,* 2009). Recemic ibuprofen and the S (+)-enantiomer are mostly used in the treatment of mild to moderate pain as indicated in dysmenorrhoea, migraine, headache, post-operative and in the management of rheumatoid arthritis, osteo-arthritis, spondylitis and soft tissue disorders (Potthast *et al.,* 2005 and Tan *et al.,* 1999). Furthermore, dentists have always relied on ibuprofen and other nonsteroidal anti-inflammatory drugs for treating acute and chronic orofacial pain (Moore and Hersh, 2001).

The wet granulation method is the most widely used process of agglomeration in the pharmaceutical industry which involves wet massing of the powder blend with a granulating liquid, wet sizing and drying. The advantages are that, powders can be handled mechanically without loss of mix quality, particle size and sphericity are increased as well as improving flow and uniformity of powder density (Damodar *et al.,* 2014). Conversely, the limitations include its high cost

in terms of labour, time, energy, equipment, and space requirements as well as loss of material during various stages of processing (Kassem and El-Sayed, 2014).

Adhesives that are included in tablet formulations for providing the cohesiveness required for the bonding together of the granules to form tablets when compressed are referred to as binders. Binders are either sugar or of polymeric materials. They are simply classified as natural polymers (acacia, tragacanth, gelatin) or synthetic polymers (polyvinylpyrrolidone, methyl & ethyl cellulose etc) (I.P, 2007). For orally administered and poorly soluble drugs like ibuprofen, the rate by which absorption takes place is often determined by the rate of dissolution. This rate of dissolution can be increased by ensuring an increase in the surface area of available drug using various methods like micronization, complexation and solid dispersion (Martin, 1993). Drug dissolution can also be influenced by disintegration time of the tablets implying that faster disintegration of tablets delivers a fine suspension of drug particles with a resultant higher surface area and faster dissolution (Yong *et al.*, 2005).

Acacia can be described as a complex, loose aggregate of sugars and hemicelluloses which consist essentially of an arabic acid nucleus to which are connected calcium, potassium and magnesium, along with the sugars namely arabinose, galactose, and rhamnose (Patil, 2015) while gelatin is a generic term for a mixture of purified protein fractions obtained either by partial acid hydrolysis (type A gelatin) or by partial alkaline hydrolysis (type B gelatin) of animal collagen obtained from pig and cattle bone, cattle skin (hide), pig and fish skin. Gelatin may also be a mixture of both types A and B (Alomi, 2016).

The objective of this work was to study both the flow profiles and release profiles of ibuprofen tablet formulations by increasing the concentration of the binder using the wet granulation method.

METHODOLOGY

Materials and methods

Materials used in the study were ibuprofen powder, gelatin (May and Baker Ltd, Dagenham, England), acacia (Loba chemie®, Pvt Ltd, India), microcrystalline cellulose, maize starch (BDH Chemical Ltd, England) etc.

Methods

Granules containing 200 mg of ibuprofen were prepared by the various formulae using the wet granulation method shown on table 1. The drug, diluent and disintegrant in required quantities were properly mixed and granules were prepared by using the different binder solutions. The cohesive mass was passed through mesh number 1.6 mm and dried at a temperature of 40 ^{O}C in hot air oven (Gallenkamp). The dried mass was passed through mesh number 1.0 mm and to this was added lubricant and glidant (magnesium stearate, and talc) well mixed and then compressed into tablets. The tablets were prepared by compressing granules using 12 mm punches on an Erweka AR400 single punch tableting machine at pressures between 5 and 7 MT.

Evaluation of granules

Bulk and tapped densities, carr's compressibility index, angle of repose, hausner's ratio, flow rate, particle size analysis (Martin, 1993; Fiese and Hagen., 1987; Ansel *et al.*, 1995; Staniforth *et al.*, 2007).

Table 1: Ibuprofen tablet formula

	ACACIA (g)			GELATIN (g)		
	Batches					
Ingredients	I	II	III	IV	V	VI
Ibuprofen (40%)	20	20	20	20	20	20
Microcrystalline cellulose (q.s)	21.5	19	14	21.5	19	14
Maize Starch (10%)	5	5	5	5	5	5
Acacia & gelatin (5 %, 10 % 20%)	2.5	5	10	2.5	5	10
Talc (1%)	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium stearate (1%)	0.5	0.5	0.5	0.5	0.5	0.5
Total (g)	50	50	50	50	50	50

Determination of Powder Properties

Particle size analysis was carried out using the sieve method. Test sieves ranging from 75 - 500 µm were arranged in descending order beginning with the largest sieve on top. 20 g of the sample was placed on the 500 µm sieve and allowed to vibrate for 10 mins in the Endecott sieve shaker. The powder retained on each sieve was weighed and the mean particle size determined using the formula given below:

Mean particle size

$$= \frac{\Sigma(\%\ retained\ on\ each\ sieve \times sieve\ size)}{100} \quad \text{.....(1)}$$

Twenty grams (20g) of sample was placed in the Erweka flow rate apparatus and allowed to flowthrough the funnel's orifice. The time taken for the powder to flow through the funnel's orifice was recorded. The flow rate was calculated using the equation given below and the mean of three determinations was recorded.

$$\text{Flow rate} = \frac{weight\ of\ powder\ in\ grams}{time\ in\ seconds} \quad \text{....(2)}$$

The angle of repose was determined using the fixed funnel method. A clean glass funnel was clamped on a retort stand such that the height from the tip of the funnel to the base was 7 cm into which 20 g of the sample was poured and was allowed to flow freely under the influence of gravity. A conical heap of powder was formed. The parameters of height and radius were measured off and used to determine the angle of repose.

$$\Theta = \tan^{-1}(h/r) \quad \text{..... (3)}$$

h = height of the pile in cm; r = radius of the pile in cm

Also, twenty (20) grams of the granules was gently poured into a 50 ml graduated cylinder through a funnel. The volume of the granules was then determined and the bulk density (BD) was calculated. The graduated cylinder was tapped from a height of 25 mm and the final reduction in volume was measured after attaining a constant volume after which the tapped density (TD) was calculated. Hausner's ratio and Carr's index were estimated by incorporating the values of bulk and tapped densities in the equations given below:

$$HR = TD / BD \quad \text{..... (4)}$$

$$CI = \frac{TD - BD}{TD} \quad \text{..... (5)}$$

Where TD is tapped density; BD is bulk density

Evaluation of tablet properties

Weight variation test

Some 20 tablets randomly picked from each batch was weighed using Mettler P163 balance (Mettler Instruments, Switzerland), and the average mass was determined. The percentage deviation from the average mass was calculated (B.P, 2004).

Crushing strength determination

Twenty tablets taken randomly from each batch were tested for hardness using Monsanto hardness tester (Monsanto Chemical Co., USA). The average hardness (kgF) and standard error were calculated for each batch.

Friability test

Twenty tablets were taken randomly and weighed accurately and placed in a friabilator (Erweka, Germany). After 100 rotations, the tablets were removed and reweighed accurately. The loss in mass was determined.

Disintegration test

One tablet was placed in each tube of the basket rack assembly and a disc was added on each tube. The rack was immersed in distilled water at 37 ± 2ºC and the apparatus (Erweka, Germany) was operated at a frequency rate between 29-32 cycles per minute. The time taken for the tablets to disintegrate and pass through the screen was recorded (B.P, 2004).

Dissolution studies

The drug-release profile of ibuprofen was determined using the Erweka dissolution apparatus. 900ml of phosphate buffer pH 7.2 solution was used as dissolution medium. 5 ml sample was withdrawn, filtered and diluted after 5, 10, 20, 30, 45 and 60 minutes and the absorbance determined at a wavelength of 221 nm. The amount of drug released with time was determined using the equation, y = 0.0673x + 0.0077, and a graph showing the relationship between percentage drug released against time was plotted.

Data and Statistical Analysis

All experiments were performed in replicates for validity of statistical analysis. Results were expressed as mean ± SD. ANOVA was performed on the data sets generated using SPSS®16. Differences were considered significant for p-values < 0.05.

RESULTS AND DISCUSSION

The results of the granule properties are presented on Table 2. The values obtained for particle size ranged from 329 – 473 µm with batch VI having the largest particle size. There was a corresponding increase in particle size as the concentration of the binder was increasing across the batches. Particle size is one of the principal determinants of powder behaviour such as flow ability, packing and consolidation, compaction etc, and it is therefore one of the most common and important areas of powder characterization. As a result of the impact of particle size on powder performance, it is of paramount importance in selecting excipients to develop or improve formulation.

Angle of repose is an indication of flowability of a substance whether powder or granule. This is dependent on the cohesive nature of the powder/granule and the value is expected to be high if the powder is cohesive and low if the powder is non-cohesive (Staniforth and Aulton, 2007). The angle of repose of Batches I-IV indicated excellent flow properties since it fell within the range (25^{o}-30 ^{o}). Also Batches I to III (acacia) followed a trend of increase in angle of repose with increase in binder concentration unlike for gelatin. Batch VI indicated good flow property which falls between the ranges (30^{o}-35^{o}).

The tapped density is usually higher than the bulk density (Apeji *et al*, 2013; Mohammed *et al.,* 2020) and this is due to diminished void spaces as a result of a change in the bulk volume by the rearrangement of packing geometry of the particles resulting in a tightly packed powder bed (Staniforth and Aulton, 2007). The above was observed across all Batches. Batches I, II and III yielded a compressibility index of 19%, 6% and 7% respectively. This result corresponds with standards which indicate Batch I granules as having a fair flow property and Batches II and III as excellent flow property. Batches IV, V and VI yielded a compressibility index of 12%, 10% and6% respectively. The Batches all fell under the range of values for excellent flow property which is between 5 and 15% except for Batch I (B.P, 2004). This thus indicates that Batches II, III, IV, V and VI had excellent flow properties and Batch I had a fair flow property. For the Hausner's ratio, all Batches exhibited excellent flow properties following a result between 1.1-1.2.

Table 2: Granule properties

Granule properties	Batch I	Batch II	Batch III	Batch IV	Batch V	Batch VI
Granule size (µm)	399	412	449	329	442	473
Angle of repose (^{O})	22 (4.2)	24 (1.6)	27 (2.4)	30 (2.4)	26 (3.5)	32 (2)
Flow rate (g/sec)	3.31(0.6)	3.52(1.2)	4.58(1.8)	2.63(0.2)	4.25(1.6)	5.34(2.1)
Bulk density (g/ml)	0.27(3.6)	0.32(2.2)	0.34(2.0)	0.31(3.6)	0.30(0.5)	0.30(0.9)
Tapped density (g/ml)	0.33(1.1)	0.34(1.4)	0.36(2.3)	0.35(0.7)	0.34(3.4)	0.31(0.1)
Carr's index (%)	19	6	7	12	10	6
Hausner's ratio	1.2	1.1	1.1	1.1	1.1	1.1

Key: Batches I, II and III= 5%,10% and 20% acacia respectively
Batches IV, V and VI = 5%,10% and 20% gelatin respectively.

Evaluation of tablets

For tablets quality to be accepted or approved for use, conformity to specifications set by these standards (compendial and non-compendial) is very critical. From the result obtained as presented on table 3, the weight uniformity test on the tablets indicated no significant difference ($p > 0.05$) in the weights of tablets from the various Batches and hence conformed to the British Pharmacopoeia (BP., 2003) specification which states 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 %. All the tablets in each Batch had an average weight range of 500mg-525mg which is the BP standard for weight variation of tablets weighing 250mg and greater. Hardness generally measures the tablet crushing strength (Davinder *et al*., 2015). The required standard though non-compendial, of hardness for compressed tablet ranges from 4 to 8 kg. This clearly indicates that all the batches met the required standard for tablet hardness.

A friability test usually determines the ability of tablets to withstand abrasion during packaging, handling, and shipping processes. A maximum weight loss of not more than 1% is generally considered acceptable. (Davinder *et al*., 2015). The tablets from all the Batches had a friability of less than 1% which is acceptable this could be attributed to the increase in binder concentration.

Disintegration time for uncoated tablets should be within 15 minutes implying that tablets which do not comply with this standard failed disintegration test. Batches I and IV passed disintegration test with Batch

I disintegrating faster than Batch IV, it's instructive to note that both Batches have the least concentration which is 5 %. The other Batches were observed to have failed disintegration test. Many factors involved in the tablet's formula and method of manufacture can affect the disintegration time namely: the diluents used, the binder, the nature of the drug, the type and amount of disintegrant, the type and amount of lubricant, as well as the method of incorporation for all of these additives (Rabia Bushra and Nousheen ., 2018). Some fillers add strength and cohesiveness to these tablets therefore affecting the disintegration time.

Table 3: Tablet properties

Parameters	Batch I	Batch II	Batch III	Batch IV	Batch V	Batch VI
Mean weight(g)	0.50 (0.01)	0.51 (0.01)	0.51 (0.01)	0.51 (0.01)	0.50 (0.01)	0.50 (0.01)
Thickness(mm)	3.92 (0.03)	4.03 (0.02)	3.85 (0.03)	4.02 (0.04)	3.70 (0.25)	3.90 (0.12)
Diameter (mm)	12.09 (0.07)	12.06 (0.05)	12.07 (0.03)	12.05 (0.04)	12.04 (0.03)	12.05 (0.03)
Crushing strength (kgF)	7.5 (0.57)	8.75 (0.50)	4.01 (2.00)	7.63 (1.10)	5.5 (3.15)	9.38 (2.61)
Friability (%)	0.39	0.39	0.79	0.39	0.39	0.19
Disintegration time (min)	2	>30	>30	3	>30	>30
Dissolution time (hr)	1	1	1	1	1	1

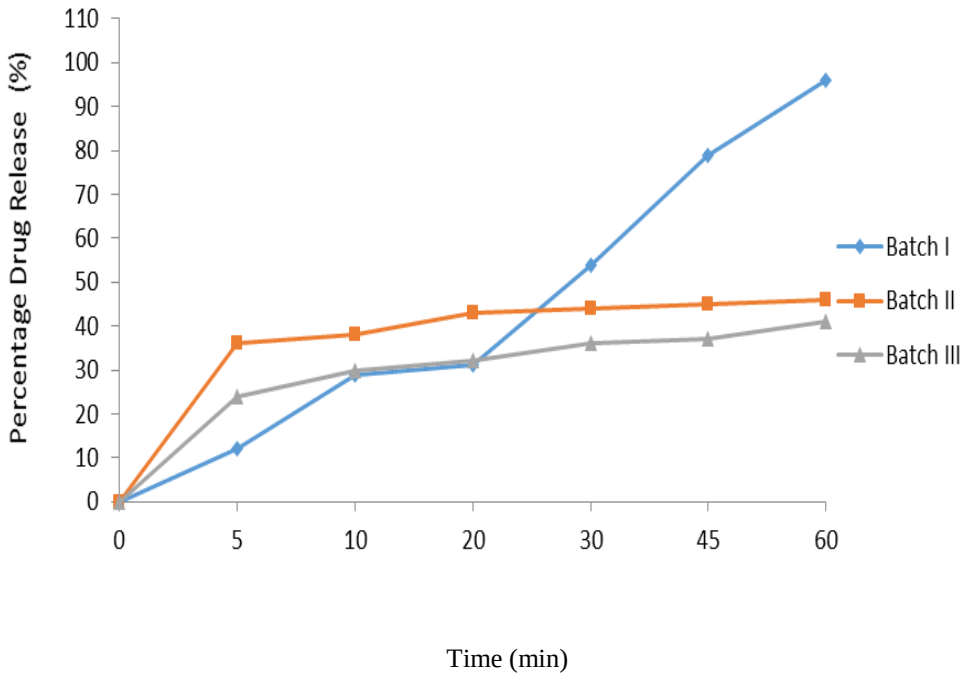

Figure 1: Graph representing the dissolution profile of ibuprofen using acacia as binder

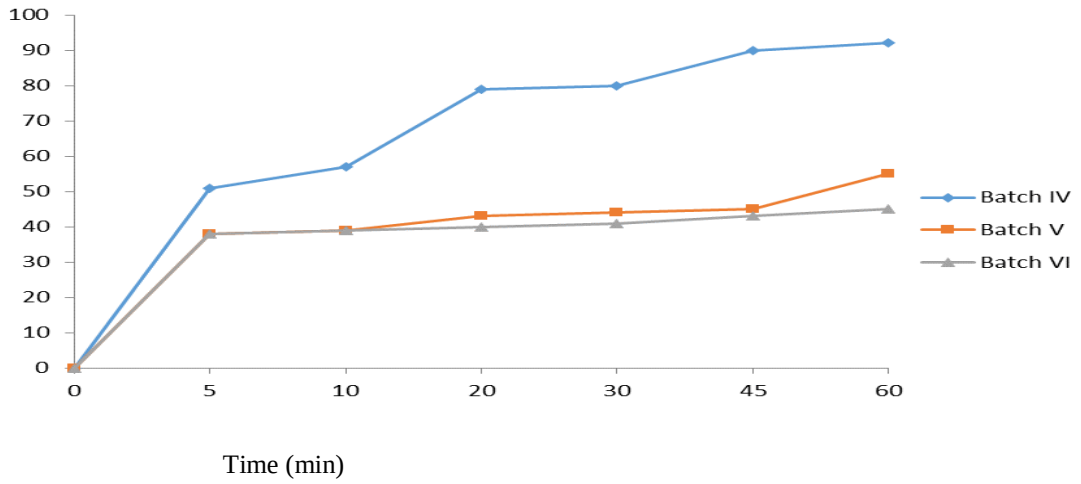

Figure 2: Graph representing the dissolution profile of ibuprofen using gelatin as binder

Dissolution also described as the rate of mass transfer from a solid surface into the dissolution medium under standardized conditions of liquid/solid interface, temperature and solvent composition is a dynamic property that changes with time and describes the process by which a homogenous mixture of a solid or a liquid can be obtained in a solvent. (Davinder *et al.*, 2015). The drug release profile of ibuprofen when the concentration of acacia increased showed that for Batch I, $T_{50\,\%}$ of the drug was released within 30mins and $T_{90\%}$ was released within 60 mins while for gelatin, Batch IV $T_{50\%}$ of the drug was released within 10 mins and $T_{90\%}$ released within 60 mins. It is instructive to note that only the first batches i.e 5% batches had values for $T_{90\%,}$ while there was poor release for the remaining batches. The dissolution of the particles may have been affected by intrinsic properties of the drug, its size and components of its formulation especially increased concentration of binders (Azam and Haider., 2008).

Fischer *et al* (2009) mentioned that the mechanical properties of granules and resultant tablets compressed are determined by the physicochemical interaction of the substrate interfacial layer (contact angle, surface tension and binder concentration). Mechanical properties gave a spike with increasing binder concentration until a limit above which increasing binder concentration would hinder the spread, thus creating weak regions in the compact that would ultimately lead to reduced mechanical strength. Besides, packing densities with high values and dense particles are usually less cohesive than less dense particles of the same size and shape (Staniforth &Aulton, 2007).

CONCLUSION

Granules prepared by wet granulation technique with increased concentration of binder exhibited averagely excellent flow properties as indicated by carr's compressibility index and hausner's ratio. The mean weight, thickness and diameter fell within the standard deviation for tablets. The release profile for the 5 % Batches was impressive while the reverse was the case for the higher binder concentrations (10% and 20%). Therefore, it can be concluded that increasing the concentration of the binders i.e acacia and gelatin above 5% led to a decrease in percentage of drug released.

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