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EFFECT OF INCREASING BINDER CONCENTRATION ON THE RELEASE PROFILE OF IBUPROFEN TABLET

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ABSTRACT

Introduction: A pharmaceutical binder essentially holds together the ingredients of any solid oral dosage form that is formulated by wet granulation or dry granulation, roll compaction or even direct compression, the binder ensures integrity and is crucial to stability across the formulation lifetime. Binders are added to the tablet formulation to impart plasticity as well as to increase interparticulate bonding strength in the tablet and also increases the degree of consolidation or compaction while decreasing the brittle fracture tendency during tableting.

Aim: The aim of this study was to produce ibuprofen tablets by wet granulation and to assess the suitability of varying the concentration of low-cost and commercially available binders (acacia and gelatin) and to determine the release profile.

Method: Acacia and gelatin at 5% w/w and 10%w/w were applied as binders in formulating ibuprofen tablets using the wet granulation technique. The resultant granules were evaluated for their micromeritic properties and compressed into tablets. Evaluation of the ibuprofen tablets for their physical properties and dissolution studies were done using British Pharmacopoeia methods.

Results: The results obtained showed that ibuprofen granules were flowable and compressible. The compressed ibuprofen tablets had good physical properties: minimal weight variation (490±0.01 – 510mg ±0.01), hardness (4.20 ±2.00 – 8.70±0.57 KgF), disintegration time (3.8±0.1 – 11.8±0.01) min and friability (0.1±0.03 – 0.6±0.03) %. The dissolution of ibuprofen tablets complied with British Pharmacopoeia criteria.

Conclusion: Acacia and gelatin served as good binders in ibuprofen tablet formulations but acacia performed better than gelatin in terms of crushing strength.

Keywords: Binder, acacia, gelatin, ibuprofen tablets.

INTRODUCTION

Tablets as a solid dosage form, comprises of medicaments usually with excipients compressed or molded into circular shapes with convex faces, flat or other suitable shapes. Their formulation is done so as to release the active ingredients in a way that will achieve the desired effects. Aside from the active ingredients, there are a number of inert materials simply known as excipients that are either mixed with medicaments or added to granules and these include

Archives of Pharmaceutical Sciences and Biotechnology Journal
Volume 2 Issue 2 June 2022, Page 157 - 169 ISSN: 2971_611X
APSBJournal

disintegrants, glidants, binders and lubricants[1].

Tablets are the most commonly used dosage form due to their advantages like availability, easy administration, good stability, and low price.

As a result of the difficulty involved in converting drug powders into satisfactory tablets, it is often necessary to incorporate excipients, which provide adequate compressive characteristics. These excipients include binders, diluents, glidants and lubricants. Binders are responsible for providing adequate mechanical properties to pharmaceutical tablet formulations by promoting the bonding properties between the different components of the powder mixture[21]. Powders and granules are bound together by binders in wet granulation and compression processes, respectively. Binders are now being investigated for their bioadhesive properties in drug formulation.

There are four major sources of binders that are used in tablet formulation. They include binders from plant sources, animal sources semi-synthetic binders and synthetic binders[2]. Binders obtained from plant sources could be gotten from sap, rhizome, leaves, root, fruit or seeds from the plant[3]. These include natural gums, starches, and dried fruits, those from animal sources include chitin, gelatin, lecithin, and lactose. Binders that are naturally-derived but have been chemically modified are referred to as semi synthetic binders[4]. Examples are cellulose derivatives such as hydroxymethylpropyllcellulose, sodium carboxy-methylcellulose, ethylcellulose, hydroxypropyl methylcellulose (HPMC) and methylcellulose[4,5] while synthetic binders are those binders that are derived from pure synthetic organic chemical substances. Examples of synthetic binders are poly methacrylate, polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), polyvinyl alcohol[5].

Ibuprofen is a drug which possesses analgesic and anti phlogistic (antipyretic and anti-inflammatory) properties. It is a member of the non-steroidal anti-inflammatory drugs (NSAIDs). It is readily absorbed from the gastrointestinal tract and has an onset of action of approximately 30 – 60 min with a duration of action of 6 - 8 h. The mechanism of action is by inhibiting a class of enzymes called cyclooxygenases (COX). Cyclooxygenases catalyze the synthesis of prostaglandins. Prostaglandins mediate the responses of pain, inflammation etc. as negative effects to the body. One of its derivatives, prostacyclins acts by preventing aggregation of blood platelet and as a vasodilator from where it has the role of inflammation. Thromboxane, another derivative, is produced by platelet cells and unlike prostacyclins are vasoconstrictors and facilitate blood platelet aggregation[7]. Enhancement of dissolution rate for poorly water-soluble drugs like ibuprofen is the need of the hour in the formulation design of orally administered dosage forms by wet granulation to get improved bioavailability and rapid onset of action8.

Ibuprofen tablets in the market are found to exhibit one tablet defect or the other. These defects include hardness variation, capping, weight variation, cracking. These defects indirectly affect the efficacy of the tablet in delivering the drug. These problems are usually caused by inappropriate use of binders in tablet formulation[6].

Archives of Pharmaceutical Sciences and Biotechnology Journal
Volume 2 Issue 2 June 2022, Page 157 - 169 ISSN: 2971_611X
APSBJournal

Gelatin, a valuable protein, obtained from collagen-containing materials such as skins and bones of animals and fish. It has a wide range of applications in the food, cosmetic, photographic and pharmaceutical industries because of its unique physicochemical and technological properties. Gelatin has been used as an emulsifier, colloid stabilizer, foaming agent, fining agent and biodegradable packaging material with foods[7]; in injectable drug-delivery microspheres, as a matrix for implants, and in intravenous infusions in the pharmaceutical field; as an application for manufacturing hard and soft capsules, plasma expanders and in wound care[22].

Acacia is made up of loose aggregates of sugars and hemicelluloses, very complex, with a molecular weight of approximately 240 000 - 580 000. This aggregate consists of an arabic acid nucleus having calcium, magnesium, and potassium along with the sugar's arabinose, galactose, and rhamnose connected to it. Acacia is mainly used in topical and oral pharmaceutical formulations as a suspending and emulsifying agent, often in combination with tragacanth. It is also used in the preparation of lozenges and pastilles and as a tablet binder, although if used incautiously has the capacity to produce tablets with a prolonged disintegration time. Desta *et al*, characterized the physicochemical properties of *Acacia etbaica* gum and evaluating its suitability as a binding agent in granules and tablet formulations in comparison with two reference binders, acacia BP and PVP, using paracetamol as a model drug and it was concluded that the gum of *Acacia etbaica* could be explored as an alternative excipient for its binder effect in granule and tablet formulations[24]. Acacia has also been evaluated as a bio adhesive in novel tablet formulations and modified release tablets[18].

The aim of this study was to produce ibuprofen tablets by wet granulation and to assess the suitability of varying the concentration of low-cost and commercially available binders (acacia and gelatin) and to determine the release profile.

MATERIALS AND METHODS

Materials

Ibuprofen powder, maize starch BP (Philip Harms Reagent, England), Talc (Roquett Pharmaceuticals, England), magnesium stearate (Gurr Chemicals GPR, Germany), gelatin, acacia (BDH Chemicals Ltd, England), hydrochloric acid (May and Baker Chemicals Ltd, England) Prosolv SMCC (JRS PHARMA GMBH &Co.KG), distilled water.

Preparation of granules

The wet granulation method was employed in the preparation of granules according to the method of Rubinstein *et al* [23]. Ibuprofen granules were prepared with the ingredients shown in Table 1. The quantity of each ingredient that was required for the production of 100 tablets from the granules was calculated, weighed out (except talc and magnesium stearate), added using the doubling up technique, blended to homogeneity and wet granulated using solutions of gelatin and acacia as the granulating fluid. The granules were formed by wet screening the damp mass of ibuprofen and the other excipients through a 2 mm sieve, dried in the oven (Gallenkamp, England) at 60 ˚C for 1 h, rescreened through a 1 mm sieve, further dried at 60 ˚C in the

Archives of Pharmaceutical Sciences and Biotechnology Journal
Volume 2 Issue 2 June 2022, Page 157 - 169 ISSN: 2971_611X
APSBJournal

oven until a constant weight was attained. The granules were stored in an air-tight container 24 h before evaluation[24].

Table 1: Ibuprofen Tablet Formula

	BATCHES			
Ingredients	I	II	III	IV
Ibuprofen (40%)	20g	20g	20g	20g
Prosolv	21.5g	19g	21.5g	19g
Maize Starch (10%)	5g	5g	5g	5g
Acacia (5%,10 %)	2.5g	5g	0.0	0.0
Gelatin (5%, 10%)	0.0	0.0	2.5g	5g
Talc (1%)	0.5g	0.5g	0.5g	0.5g
Magnesium stearate (1%)	0.5g	0.5g	0.5g	0.5g
Total (g)	**50**	**50**	**50**	**50**

Key: Batch I: Acacia 5%, Batch II: Acacia 10%, Batch III: Gelatin 5%, Batch IV: Gelatin 10%

Granule Flow Rate

The flow rate of ibuprofen granules was determined according to the method of Enauyatifard *et al*[6]. From each batch of granules, 10 g was allowed freely through the orifice of a funnel mounted vertically by means of tripod stand and clamp. The time taken for each batch of granule to completely pass through the funnel was recorded. The flow rate (Fr) was calculated using the formula:

$$Fr = \frac{weight\ of\ granules\ (g)}{time(\text{sec})} \quad \ldots\ldots\ldots (1)$$

Angle of Repose

This is the maximum angle possible between surface of pile of powder or granules and the horizontal plane. A funnel was fixed at a height approximately of 2-4 cm over the platform.

The loose granules was slowly passed along the wall of funnel, till the cone of the powder formed. The angle of repose is determined by measuring the height of the cone of granules and radius of the heap of the granules and this was done in triplicate using the formula [25]:

$$\text{Tan } \Theta = \frac{h}{r} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (2)$$

Where h = height of the heap, r = radius of the base of the pile.

Bulk and Tapped Densities

A 10g quantity of the granules was weighed and gently poured into a 50 ml measuring cylinder. The volume attained after the granule was poured into the cylinder was taken as the bulk volume. The procedure was repeated three times and the mean bulk volume determined. The weight of powder divided by the bulk volume of powder is known as the bulk density.

Bulk density = weight of sample in gram/volume occupied by the sample ....(3)

Archives of Pharmaceutical Sciences and Biotechnology Journal
Volume 2 Issue 2 June 2022, Page 157 - 169 ISSN: 2971_611X
APSBJournal

To determine the tapped density, the measuring cylinder containing the granules was tapped gently but continuously on a smooth wooden platform until there was no further reduction in volume. This occurred after about 100 taps. The procedure was repeated three times and the mean tapped volume was determined.

Tapped density = weight of the granules/ mean tapped volume……. (4)

Carr's Compressibility Index
This was derived by the application of the formula,

$$CI = \frac{TD-BD}{TD} \times 100 \ldots\ldots\ldots\ldots\ldots (5)$$

TD=Tapped density, BD=Bulk density

Sieve Analysis of Granules: The particle size analysis was carried out on a vibratory sieve shaker (Endecott) for 10 min, using 500 to 75 µm mesh sieves. From the plots of powder weight retained (%) versus mesh size (µm), particle size distribution parameters, such as the mean particle diameter was determined[25]

$$\% \text{ retained} = \frac{Final\ weight - initial\ weight}{Total\ weight\ taken} X\ 100 \ldots\ldots (6)$$

Preparation of Tablets

The die cavity of the tabletting machine (Erweka AR 400 Germany) was adjusted to accommodate granules corresponding to the target tablet weight of 400 mg as stated in Table 1 above. The pressure settings of the machine were also adjusted to 7 MT with a punch size of 12 mm. The granules of the various batches were first lubricated with magnesium stearate and talc. They were compressed at the same weight and pressure settings. A total of 100 tablets were produced from each batch of granules. The tablets were allowed to stand for 24 hours before evaluation to allow for elastic recovery.

Evaluationof Tablets Uniformity of Weight Test
Twenty (20) tablets were randomly selected and individually weighed on an electronic balance (Mettler balance P 165, Greifensee-Zurich). The mean weight and the percentage coefficient of variation of each tablet were calculated. The percentage coefficient of variation was calculated for each batch using the formula:

$$\% \text{ Coefficient of variation} = \frac{Standard\ deviation}{mean} X\ 100 \ldots\ldots\ldots\ldots (7)$$

Uniformity of Diameter andThickness
Five tablets randomly selected from each batch were evaluated by measuring the diameter and thickness using a vernier caliper (Drapper Ltd, West Germany) individually. The mean diameter and thickness were then calculated and the standard deviation derived for each batch.

Hardness Test

Five (5) tablets were selected at random and the mean hardness determined using a Monsanto hardness tester (Eagle Scientific Limited, England).

Friability Test

Ten tablets were randomly picked from each batch and were collectively weighed. They were then placed in a Roche friabilator (Eagle Scientific Limited, England) and operated for 4 minutes at a speed of 25 revolutions per minute. The tablets were then dusted and

Archives of Pharmaceutical Sciences and Biotechnology Journal
Volume 2 Issue 2 June 2022, Page 157 - 169 ISSN: 2971_611X
APSBJournal

reweighed and the percentage friability calculated according to the following equation:

$$Fr = \frac{Initial\ weight - final\ weight}{Initial\ weight}\ X\ 100 \ldots\ldots\ldots (8)$$

Disintegration Time Test

The disintegration rate of six tablets randomly selected from each batch was individually determined using the basket method in a B.P specified apparatus (Erweka) and in a medium of 0.1 N HCL at 37 ± 0.5°C. The mean disintegration time was calculated.

In-vitro Dissolution Test

In-vitro dissolution test was carried out using the Erweka dissolution testing apparatus. The dissolution medium was 1000ml of Phosphate buffer which was maintained at 37°C. The machine was operated at 50 revolutions per minute. Samples removed for analysis were replaced with 5 ml fresh aliquots of the Phosphate buffer. The withdrawn samples were filtered and diluted before the absorbance reading was carried out using UV-Visible spectrophotometer (Romter, UV-1650PC, Shimadzu, Europe). The wavelength of maximum absorption used was 221nm. The per cent drug released at varying time intervals was determined from the slope of the calibration curve and plotted against time to generate the dissolution-time profile.

RESULTS AND DISCUSSION

In the present study an attempt has been made to formulate and evaluate ibuprofen tablets using the wet granulation method. A total of four batches were prepared (Table 1). The study revealed that pre-compression parameters like angle of repose (27.5° – 33.2°), bulk density (0.28 – 0.32 gm/ml) and tapped density (0.33 – 0.43 gm/ml), compressibility index (11.6 – 17.6 %), Hausner's ratio (1.13 – 1.21) were also found to be within limit, indicating excellent flow property and compressibility (Table 2). Bulk density is an indication of the packing characteristics of powders and granules. Powders with high bulk density have an advantage in tableting because of increased volume of fill in the die cavity of tableting machines[8]. Also, the tapped density was seen to be greater than the bulk density. This is expected due to the elimination of voids as a result of tapping. The bed diminished in volume since the void is eliminated[9, 11].

All the post compression parameters like tablet thickness, hardness, weight variation test, disintegration and friability tests were performed. Both Hausner's ratio and Carr's index are derived from the bulk and tapped densities of the granules and are also used to estimate the flow of granules. Values of Hausner's ratio of 1.2 or below indicate good flow. Higher values represent cohesiveness of powders which result in poor flow. Granules containing 5% acacia as binder possessed the least Hausner's ratio of 1.13, while those containing 10% gelatin exhibited the highest Hausner's ratio of 1.21. Conversely, granules containing 5% and 10% acacia had the least and highest values of Carr's compressibility of 11.6 and 17.6 % respectively. This may be attributed to the results of the bulk and tapped densities that is normally proportional to the number of spherical particles present in the bulk, and inversely proportional to the size of particles[7,16].

Angle of repose is used to estimate the flow of powders and granules. Generally, granules possessing repose angles in the range of 25 – 30° usually exhibit good flow. Angle of

Archives of Pharmaceutical Sciences and Biotechnology Journal
Volume 2 Issue 2 June 2022, Page 157 - 169 ISSN: 2971_611X
APSBJournal

repose is a parameter used to predict the flow property of powders and granules. The results of the angle of repose values obtained for the various batches are in conformity with those of the flow rate of granules. This is in conformity with the work of Elsabbagh *et al*, [10].

The results for the physical properties of ibuprofen tablets containing the various binders are shown in Table 3. Here, the hardness values of batches of ibuprofen tablets are 5% > 10% for tablets containing acacia, respectively. The corresponding hardness values for those made with gelatin are 5% < 10% respectively. Friability is another mechanical property of tablets specified by the official compendia, and is expected not to exceed a value of 1.0%. It is a surface deformation of tablets, which could occur as a result of the morphology of the tablet, as the rougher the surface of the tablet, the more friable it would be. However, it is worthy to note that the tablets batches passed the friability test as shown in Table 3 which were below the 1% limit.

Both hardness and friability values are used to assess the mechanical properties of tablets. They ensure that the tablet is able to withstand the stresses involved in packaging, transportation and handling of tablets without breaking[12,13].

Table 2: Physical Properties of Granules

Properties	Batch I	Batch II	Batch III	Batch IV
Angle of repose (°)	27.5(0.06)	32.5(1.2)	33.2(0.05)	31.6(0.01)
Tapped density(g/ml)	0.43(0.31)	0.34(0.11)	0.33(0.4)	0.38(.3)
Bulk density (g/ml)	0.38(0.01)	0.28(0.01)	0.28(0.04)	0.32(0.1)
Carr's index (%)	11.6(0.05)	17.6(0.13)	15.1(0.04)	15.8(0.67)
Hausners ratio	1.13	1.21	1.18	1.19
Mean particle size (mg)	329.10	328.50	426.70	417.25
Flow rate (g/s)	3.7(0.5)	2.0(0.1)	1.7(0.06)	2.5(0.05)

Although hardness of tablets is not an official test in pharmacopoeias, values of 4 – 8 kgf are generally accepted as adequate to ensure protection from mechanical stress and ensure the integrity of the tablets[14,15]. Tablet thickness is directly related to tablet hardness and can be used as an initial control of this parameter. Tablets which are too thin are liable to break easily while those which are too thick may be difficult to swallow. Manufacturers set limits on the thickness of tablets of various products in order to assure trouble-free packaging of tablets[17,18].

Archives of Pharmaceutical Sciences and Biotechnology Journal
Volume 2 Issue 2 June 2022, Page 157 - 169 ISSN: 2971_611X
APSBJournal

Table 3: Results of the Physical Properties of Formulated Ibuprofen Tablets

Parameters	Batch I	Batch II	Batch III	Batch IV
Mean weight(g)	0.51 (0.01)	0.48 (0.01)	0.51 (0.01)	0.49 (0.01)
Thickness(mm)	3.69 (0.03)	3.88 (0.02)	3.86 (0.03)	3.96 (0.04)
Diameter (mm)	11.94 (0.07)	12.07 (0.05)	11.96 (0.03)	11.94 (0.04)
Crushing strength (kgF)	8.7 (0.57)	5.6 (0.50)	4.2 (2.00)	5.4 (1.10)
Friability (%)	0.6(0.03)	0.4(0.02)	0.1(0.03)	0.3(0.01)
Disintegration time (min)	11.8(0.01)	10.7(0.02)	3.8(0.1)	9.7(0.02)
Dissolution time (hr)	$T_{50\%}$=<10mins $T_{90\%}$=ND		$T_{50\%}$=<10mins $T_{90\%}$=60mins	

The recommendation is that tablet diameter and thickness should not exceed a coefficient of variance of 5% depending on the weight[19]. The results showed that the thickness and diameter of all the batches fell within the accepted range. Hence all batches of tablets passed the tests for uniformity of thickness and diameter. This is in tandem with the work of Canton *et al*[16].

The disintegration times obtained for the batches of ibuprofen tablets were also revealed in Table 3 and the values ranged from 3.80 min for tablets containing gelatin to 11.80 min for those made with acacia. Conventional or uncoated tablets are expected to disintegrate within 15 minutes[20]. The results show that none of the tablets failed the disintegration time test. Disintegration involves the rapid breaking up of tablets into smaller fragments when the liquid penetrates the pores of the tablet[2]. This ensures that a tablet releases its active ingredient when exposed to the appropriate medium[22]. The smaller the granules size, the harder the tablet and subsequently the longer the disintegration time. The concentration of binder is a factor that affects the disintegration time profile[19]. In figure 1, the dissolution profiles of batches containing 5% binder of ibuprofen tablets were taken into account. The dissolution parameters are shown in Table 3. From the T_{50} values obtained, it can be seen that both batches containing acacia and gelatin released the drug almost at the same time from the tablets but for T_{90} gelatin was more promising as acacia could not release beyond 80%. This is because this batch possessed the least concentration of drug and this is in tandem with the work of Canton *et al*[16].

Archives of Pharmaceutical Sciences and Biotechnology Journal
Volume 2 Issue 2 June 2022, Page 157 - 169 ISSN: 2971_611X
APSBJournal

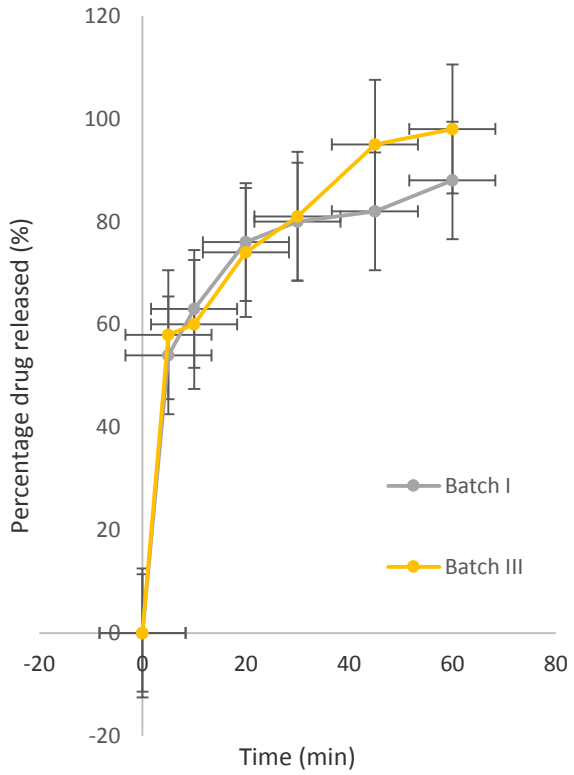

Figure 1: Dissolution profiles for 5% Acacia and Gelatin III

CONCLUSION

The binding property and effect of increase on two commonly used binders in ibuprofen granules and tablet formulations was studied. The binders studied included gelatin and acacia. The binders were incorporated as 5%w/v and 10%w/v in each case. The granules were formulated by the wet granulation technique while the tablets were prepared by compression. The properties of granules evaluated included flow rate, bulk and tapped densities, angle of repose, Hausner's ratio and Carr's index. Tablet properties studied included weight uniformity, hardness, friability, thickness and diameter, disintegration time and dissolution rate.

Results indicated that granules containing 5% acacia possessed flow properties superior to that of gelatin due to higher bulk and tapped densities compared to those containing 10% acacia.

The mechanical strength of tablets containing gelatin, was superior to those made with acacia. In terms of release rate of ibuprofen, tablets containing gelatin were more efficient in releasing the drug, while those made with acacia was the least.

On the basis of these, good ibuprofen tablets could be formulated using gelatin or acacia. On the other hand, increasing the binder concentration of acacia and gelatin to 10 % may not be recommended due to expected poor release respectively.

Authors' Contributions

The authors together declare that all have contributed toward this research work that all the studies were conducted by all the authors together.

Conflicting Interest

Authors declare no conflicting interest.

Authors' Contributions: MBB and AEY were involved in the conceptualization of the paper, MBB, CAP, ZYS and AG drafted and revised the manuscript. All authors approved the final version and accept responsibility for all aspects of the work.

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