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FORMULATION AND EVALUATION OF INDOMETHACIN FAST DISSOLVING TABLETS USING PEANUT HUSK POWDER AS SUPERDISINTEGRANT

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ABSTRACT

Naturally occurring herbal excipients are always interesting and show many advantages during drug formulation. The excipients are acknowledged to play substantial role in the quality of drug products. Binders and disintegrants are the two critical categories of excipients used in the manufacturing of solid dosage forms. The objective of the current work was to examine the utility of peanut husk powder as a disintegrating agent in formulating fast-dissolving tablets containing indomethacin. Total six formulations were developed using different disintegrating agents employing wet granulation method. All the pre-compression measurements, including angle of repose, carr's compressibility index and hausner's ratio were determined. Evaluation tests like weight variation, friability, hardness and disintegration test and drug dissolution study were conducted for the formulated tablets. The acquired results were tabulated and analyzed systematically by appropriate methods. The tablets formulated in this study were found to meet the acceptable range of all the quality control tests performed. The formulation prepared with peanut husk powder as disintegrating agent was identified to be the best formulation as it disintegrated and dissolved rapidly. Peanut husk powder developed from natural plant source was found to be a potential superdisintegrant in formulating indomethacin fast dissolving tablets.

Keywords: Fast dissolving tablets, Peanut husk powder, Superdisintegrant, Indomethacin, Wetting time, Dissolution studies

INTRODUCTION

Fast dissolving tablets also called as fast disintegrating tablets, are part of solid unit dosage forms that disintegrate and dissolve in the mouth in few seconds in the absence of drinking water to swallow **[1]**. These dosage forms offer distinct advantage over swallowing capsules and tablets by preventing difficulties related to swallowing in patients especially in pediatric and geriatric patients **[2]**. By utilizing fast dissolving tablets, we can achieve increased bioavailability or quick absorption through pre-gastric absorption of drugs from mouth, pharynx and esophagus as saliva passes down the gastrointestinal tract. Presently, the orally disintegrating tablets market is anticipated to exhibit a compound annual growth rate of 8.5% **[3]**. And these tablets are increasingly being used as an alternative to traditional tablets or capsules. The drug administration through oral route is the best approach in the pharmaceutical business since it is the most cost-effective, safer and easier way of drug administration **[4-5]**.

The disintegrants will be incorporated in to the tablet formulation, to facilitate breakup of the tablet into smaller particles for quick dissolution in an aqueous environment **[6]**. Recently, at lower levels new substances of disintegrants are used more than conventionally and called as "superdisintegrants". These have a nature of super absorbing material with custom-made swelling qualities and shows greater effectiveness even at low concentration **[7]**. Natural materials are easily available as pharmaceutical excipients in the form of a vital source for further development. Rajni Bala *et al.,* designed fast dissolving tablets of Aprepitant by using the gum isolated from c*ordio dichotoma* as a superdisintegrant and it showed promising results when compared with the marketed product of aprepitant **[8]**. *Isapghula* mucilage and Banana powder were also reported as super disintegrants in the formulation of fast disintegrating tablets of Atenolol **[9]**. Jurga Bernatoniene *et al*., prepared fast disintegrating meloxicam tablets using natural polymer chitosan which is a suitable biopolymer to enhance the disintegration process and it showed excellent mechanical strength and disintegrating properties and higher dissolution rate **[10]**. Fast dissolving tablets of piroxicam were formulated utilizing various concentrations of mucilage isolated from the plant *hibiscus rosasinensis* and modified gum karaya as super disintegrants which showed better disintegrating properties than synthetic super disintegrants like sodium starch glycolate, crospovidone etc. **[11]**.

In the present work, the efficacy of peanut husk powder as a disintegrating agent was studied in wet granulation method. The current investigation was aimed at formulation of fast dissolving tablets of indomethacin using peanut husk powder as disintegrating agent. Indomethacin belongs to the category of non-steroidal anti-inflammatory drugs class, which is administered as a therapeutic agent for alleviating pain, inflammation, joint stiffness and fever **[12]**. The drug is poorly aqueous soluble and highly permeable as it is described under the BCS class II drug. The systemic bioavailability of Indomethacin is about 98%. The terminal elimination half-life was reported to be in the range from 2.6 to 11.2 hrs in adults and in neonates it is between 12 and 28 hrs **[13]**. Hence, it was proposed to develop fast dissolving tablets of indomethacin to increase the dissolution rate and bioavailability subsequently.

MATERIALS AND METHODS

Indomethacin was procured from Dr. Reddy's laboratories, Hyderabad. The excipients like potato starch, crospovidone, pregelatinised starch, sodium starch glycolate, croscarmellose were procured from yarrow chemical products, Mumbai. Lactose, sodium hydroxide and potassium dihydrogen phosphate, talc, magnesium stearate were procured qualikems fine chemicals. Peanuts were purchased from the local super market. All the remaining chemicals were of analytical grade.

Preparation of peanut husk powder

Peanut husk powder (PHP) was acquired from the ground nuts of *arachis hypogaea.* Peanut seeds were purchased from the local super market. The collected seeds were kept in an oven at 60°C for two hours to roast them. The delicate pink external skin was removed from the seeds by manual scrapping procedure. The obtained husk was cleaned and dried again. It was milled into powder using a mixer grinder. The obtained peanut husk powder was passed through sieve no. 80 and the obtained fine powder was stored in a desiccator.

Drug-excipient compatibility study

The drug and excipient compatibility studies were conducted by using fourier transform-infra red spectroscopy (FT-IR). The FT-IR spectra was obtained from Bruker FT-IR (Alpha T, Germany). It was studied to note any possible reaction between the pure drug and the excipients in the tablet formulation. The pellets containing drug sample and potassium bromide were prepared by the pellet press from the mixture obtained by grinding the solid powder sample with suitable quantity of KBr powder in a dry mortar. The finely grounded powder mixture was introduced into a stainless steel die and it was

compressed between polished steel anvils. The pellets were thoroughly dried and loaded into the sample holder of the Bruker FT-IR instrument. The spectra were observed across the wave number range of 4000 to 500 cm^{-1}.

Swelling capacity

The swelling capacity of PHP and other disintegrating agents was determined according to the following procedure. 1g of the disintegrating agent was taken in a 50 ml capacity measuring jar. 20 ml of purified water was poured into it. The contents of the measuring jar were mixed thoroughly for five minutes and allowed to stand for 24 hours without any disturbance. Swelling capacity is measured as percentage and calculated using the following equation **[14]**.

$$\textbf{Swelling capacity} = (V_2 - V_1) / V_1 \times 100$$

V_2 = the final volume occupied by swollen material

V_1 = the initial volume occupied by the powder

Preparation of tablets

Fast-dissolving tablets of indomethacin were prepared using the wet granulation method. Indomethacin and lactose were weighed and taken in a porcelain mortar and mixed with half of the disintegrating agent for sufficient time (10 minutes). Sufficient quantity of 10% starch paste was added to the mortar and mixed well to get a

Carr's compressibility index and Hausner ratio

The Carr's compressibility index and Hausners ratio are empirical parameters to measure powder flow property. The compressibility index and Hausner ratio were calculated using bulk density (D_b) and tapped density (D_t) as follows **[15]**.

$$\textbf{Compressibility index} = \frac{D_t - D_b}{D_t} \times 100$$

$$\textbf{Hausner ratio} = \frac{D_t}{D_b}$$

Angle of repose

An empirical relationship is there between angle of repose and the ability of the powder to flow. Angle of repose have been used as indirect methods of quantifying powder flowability, because of their relationship with interparticulate cohesion. Angle of repose is determined by fixed height cone method. Angle of repose is defined as the maximum possible angle between the surface of a cone of the powder and the horizontal plane. Angle of repose is determined by the following equation.

$$\textbf{Tan } \theta = \frac{h}{r}$$

where,

θ = Angle of repose

h = Height of the pile

r = Radius of the base of the pile

EVALUATION STUDIES

The prepared tablets were evaluated for weight variation, hardness, friability and drug content. Hardness of tablets was tested using Monsanto hardness tester. Friability of tablets was determined by using friability test apparatus (Sisco). Twenty tablets were weighed and taken in the drum of the apparatus that revolves at 25 rpm and dropping the tablets from a distance of six inches with each revolution. After 4 minutes the tablets were collected, dedusted and weighed again. The percent loss in tablets weight was determined. Weight variation was determined by taking 20 tablets and these tablets were individually weighed using electronic balance (Shimadzu AY 220). The drug content was estimated using UV spectrophotometer (Elico, SL 159) at a λ max of 235 nm with pH 6.8 phosphate buffer as the reagent.

The disintegration time was noted by using disintegration test apparatus (Electrolab). Six tablets were randomly selected from each formulation. One tablet was placed in each tube of disintegration apparatus and the test was carried out without discs, in distilled water at 37±5°C. The mean and standard deviation of time to disintegrate for six tablets was calculated and reported.

Wetting time and water absorption ratio

A piece of tissue paper folded in double was placed in a petri dish containing 6 ml of distilled water mixed with a few drops of water soluble dye. Then a tablet was placed at the center of the wet tissue paper. The time required for the distilled water to diffuse from the paper throughout the entire tablet surface was recorded using a stop watch. Then wetted tablet was weighed. The water absorption ratio (R) was calculated using the following formula **[16]**.

$$R = \frac{100 \times (W_a - W_b)}{W_b}$$

where, W_a = Weight of tablet after absorption

W_b = Weight of tablet before absorption

Dissolution studies

Dissolution study for Indomethacin fast dissolving tablets was conducted using LABINDIA, D5-8000 dissolution apparatus and paddle method at 50 rpm. The dissolution medium used was 900 ml pH 6.8 phosphate buffer maintained at 37±5 °C. In the test, 5 ml samples were collected at stipulated time points and they were analyzed by UV spectrophotometer at 235 nm **[17]**. An equal volume of the fresh medium was replaced into the dissolution basket to maintain same level of the volume. This study was performed on three tablets and the average with standard deviation was calculated.

RESULTS AND DISCUSSION

Peanuts are rich protein food source that contain many vitamins, minerals. Peanut oil is deemed edible and used for cooking in the kitchen. Peanut skin contains an abundant amount of natural antioxidants and a high amount of dietary fiber **[18]**. Milling the skin of the seeds of the plant a*rachis hypogaea,* a finely textured and light brown colored powder was obtained. In our earlier studies, conducted in our laboratory peanut husk powder was employed as a low-density excipient in formulating floating matrix tablets of ramipril **[19]**. The results presented in **Table 1** shows that peanut husk powder possess a bulk density of 0.284gm/cc and tapped density of 0.461 gm/cc respectively. From this data it is observed that it possess lower weight when compared with other disintegrating agents employed in this study, the respective values are also reported in the same **Table 1**.

Swelling capacity is a critical factor to understand the disintegration ability of a disintegrating agent. Peanut husk powder does not show any significant swelling property and pregelatinised starch shows the highest swelling capacity as given in **Table 1**. The swelling capacity of the various disintegrating agents in the increasing order is peanut husk powder < crospovidone < potatostarch < croscarmellose < sodium starch glycolate < pregelatinised starch. FTIR overlay spectra are shown in fig 1. Indomethacin exhibited characteristic peaks at 1692cm^{-1}, 1625cm^{-1}, 1575cm^{-1}, 1479cm^{-1}, 1261cm^{-1}. Similar peaks were also identified in the spectrum of formulation F6. This indicates that the excipients utilized are compatible with indomethacin.

Six formulations were designed as shown in **Table 2** and the respective tablets were prepared by wet granulation method. The pre-compression reports of the powder blend evaluation were shown in **Table 3**. The angle of repose ranges from 25.59 to 31.65 signifying good flow property. The carr's compressibility index values are in between 12.27 to 16.28 signifying good flow property. Hausner ratio values are lower than 1.25 which indicated that the powder blend exhibited good flow which is an essential requirement for tablet compression.

The results of evaluation studies of the experimental prepared tablets were reported in **Table 4** under post-compression parameters. The tablets showed adequate hardness to withstand rigors in transportation and handling. The observed friability values were less than 1%, indicating that they were well within the acceptable limits. The results of weight variation test indicated that the variation between weights of different tablets is below the acceptable limits. The obtained drug content results indicate that the values were

not less than 90% and not more than 110% of the stated amount of indomethacin. The disintegration time and wetting behavior of the tablets were reported in **Table 5**. The formulation containing peanut husk powder showed the least disintegration time and the formulation comprising potato starch showed larger disintegration time. The disintegration time of the prepared tablets in the increasing order was peanut husk powder < crospovidone < sodium starch glycolate < croscarmellose < pregelatinised starch < potato starch. Although pregelatinised starch showed the highest swelling capacity **(Table 1)** its disintegration ability was not at the same order. The time taken for wetting and water absorption ratio of all the formulations were shown in **Table 5**. Formulation F6 (peanut husk powder) showed faster wetting due to capillary action. Maximum water uptake was shown by F6 formulation. Higher water uptake leads to faster disintegration of tablets. Based on the swelling capacity results shown in table 1, the six disintegrating agents employed in this study were classified into two groups. Pregelatinised starch, sodium starch glycolate, croscarmellose showed large swelling capacity and peanut husk powder, potato starch and crospovidone showed very low swelling capacity. Different types of disintegrating agents might function with different mechanisms of their own. From the preceding results and discussion, it is evident that peanut husk powder was found to be a superior disintegrating agent i.e. superdisintegrant and the mechanism of disintegration might be due to wicking and high rate of water uptake **[20-21]**.

The dissolution studies for indomethacin fast dissolving tablets were conducted for 10 minutes and the plots of cumulative percentage of drug dissolved was presented in fig 2. In all the formulations, over half of the labelled drug content was released within initial two minutes, except for formulation F1 and F2. The rapid release of the drug in formulations F3-F6 might be attributed to the bursting effect of the superdisintegrant. About 100 % of the drug was dissolved within ten minutes in F5 and F6 formulations which contain crospovidone and peanut husk powder respectively. Only 72.30 % of the drug was dissolved in formulation F1 containing potato starch. The dissolution rate of the tablets in the increasing order was found to be F1 < F2 < F4 < F3 < F5 < F6. These observations were similar to the results of the earlier work carried out on the drug, ondansetron hydrochloride and reported from our laboratory **[22]**. Formulation F6 was found to be the best formulation in the present study.

Table 1: Physical properties of disintegrating agents

Superdisintegrant	Bulk Density (gm/cc)	Tapped Density (gm/cc)	Swelling Capacity (%)
Potato starch	0.454	0.614	32
Pregelatinized starch	0.545	0.787	82
Croscarmellose	0.474	0.774	47
Sodium starch glycolate	0.742	0.847	81
Crospovidone	0.324	0.475	21
Peanut husk powder	0.284	0.461	17

Table 2: Formulae of indomethacin fast dissolving tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Indomethacin	150	150	150	150	150	150
Lactose	74	74	74	74	74	74
Disintegrant (20mg)	PS	PGS	CCS	SSG	CP	PHP
Talc	3	3	3	3	3	3
Magnesium stearate	3	3	3	3	3	3
Total	250	250	250	250	250	250

PS= Potato starch PGS= Pregelatinised starch
CCS= Croscarmellose SSG= Sodium starch glycolate
CP= Crospovidone PHP= Peanut husk powder

Table 3: Pre-compression parameters of powder blend

Formulation	Angle of repose (θ)	Compressibility index (%)	Hausners ratio
F1	27.87±1.54	15.75±1.52	1.21±0.71
F2	31.65±2.15	15.16±1.23	1.24±0.32
F3	29.14±1.20	16.28±1.71	1.22±0.35
F4	28.05±1.47	15.45±1.64	1.17±0.74
F5	26.13±1.46	13.46±1.78	1.14±0.78
F6	25.59±1.25	12.27±1.59	1.13±0.49

Each value represents mean ± SD (n=3)

Table 4: Post-compression parameters of prepared tablets

Formulation	Hardness (kg/cm^2)	Friability (%)	Weight variation (mg)	Drug content (%)
F1	3.6±0.5	0.65±0.5	149.18±2.3	97.65±0.5
F2	3.7±0.5	0.74±0.4	147.89±1.7	98.56±0.7
F3	3.1±0.4	0.85±0.8	150.45±2.5	96.43±0.6
F4	4.2±0.6	0.94±0.3	150.17±2.2	99.16±0.8
F5	3.7±0.4	0.57±0.4	149.26±1.6	96.76±0.4
F6	3.9±0.5	0.58±0.4	148.58±2.5	98.25±0.5

Each value represents mean ± SD (n=3)

Table 5: Disintegration and wetting properties of prepared tablets

Formulation	Disintegration time (sec)	Wetting time(sec)	Water absorption ratio (%)
F1	185.6±8.45	123.8±6.42	94.38±1.66
F2	123.7±7.23	96.4±7.36	94.52±2.25
F3	96.4±7.56	73.8±5.46	95.45±1.41
F4	66.2±6.59	86.8±7.85	97.44±1.70
F5	34.7±6.30	66.7±3.26	96.41±1.40
F6	29.8±4.42	56.8±4.47	98.48±1.55

Each value represents mean ± SD (n=3)

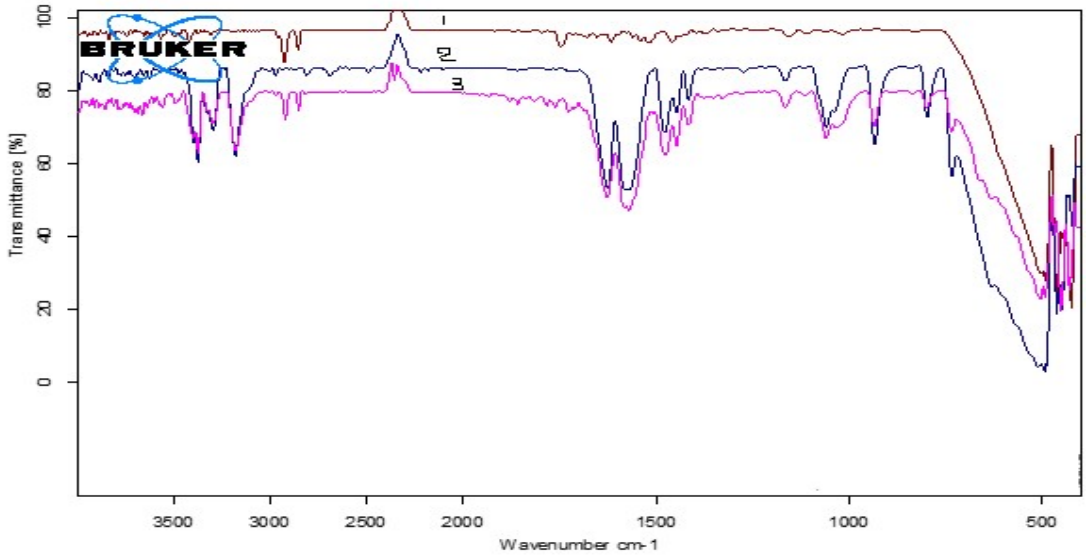

Figure 1: FTIR overlay spectra indicating 1 = Peanut husk powder, 2 = Indomethacin pure drug, 3 = Indomethacin tablet (F6)

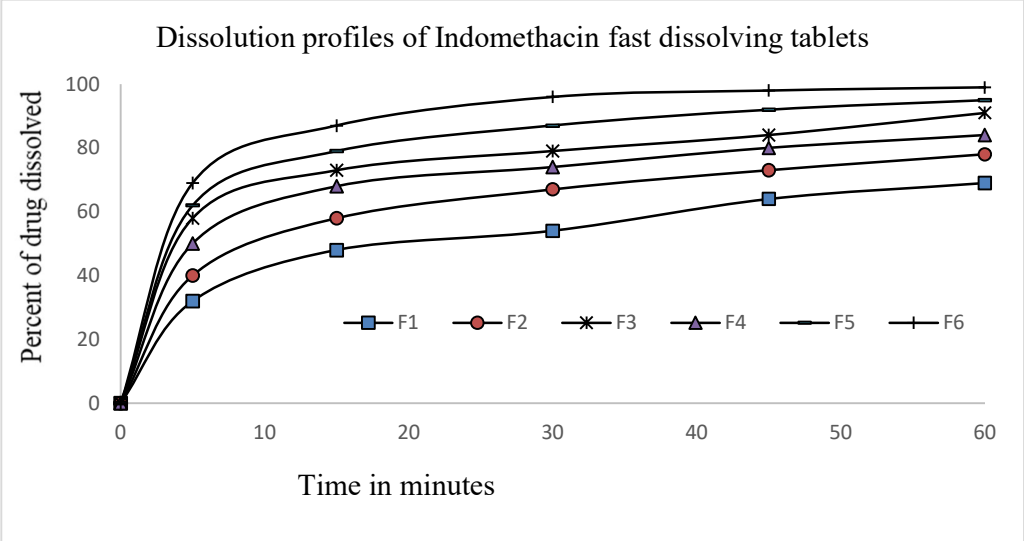

Figure 2: Dissolution profiles of fast dissolving tablets of Indomethacin

CONCLUSION

Peanut husk powder which is safe and procured from natural herbal source is found to be a light weight substance. It is found to be an excellent superdisintegrating agent in formulating indomethacin fast dissolving tablets. The mechanism of disintegration action and efficiency of peanut husk powder are similar to crospovidone, which also does not show any significant swelling property in water. The enhancement in the dissolution rate of indomethacin tablets will have a positive effect on its bioavailability and therapeutic efficacy. Herbal excipients are cost effective and

functionally effective without any side effects.

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