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Formulation & Evaluation of Aceclofenac Fast Dissolving Tablets Using Foam Granulation Technique

Anas Bahnassi[*a], Diana Zidan[b]

[a] *ISRA University,Kingdom of Jordan*

[b] *Center of Health Studies, Syrian Arab Republic*

Address for Correspondance: abahnassi@gmail.com

ABSTRACT: Orally dissolving tablets (ODT) provides a patient compliance solution for patients swallowing difficulties. Foam granulation is a newer technique that promises better distribution of the granulating system and better properties of the produced tablets. Aceclofenac (anti-inflammatory and analgesic) was selected as the model drug. The poor hydrophilicity of the drug results in variable dissolution rate and poor bioavailability. In this study, we tried to prepare aceclofenac ODT using the newer technique and various types of disintegrants, glidants, and lubricants. The resulted tablets were evaluated for hardness, friability, weight variation, in vitro disintegration time, and wetting time. All the formulation showed acceptable disintegration time. It was concluded that the prepared aceclofenac ODT by foam granulation technique using selective range of excipients can provide a dosage form with better patient compliance and effective therapy.

KEYWORDS: Fast Dissolving Tablets; Foam Granulation; Aceclofenac; Physical Characterization.

INTRODUCTION

Granulation has been impacted over the years as an important unit operation by which small powdery particles are agglomerated into larger entities called granules [1]. Changes such as the refinement of high shear granulators and fluid bed processors have enabled a faster and more accurate process monitoring [2, 3]. There are many reasons to perform granulation in the pharmaceutical industry, including: enhancing flowability, mixing properties, and granules appearance for the purpose of enhancing fine powder physical and chemical properties. Most solid dosage forms are prepared using traditional wet granulation process to enhance powder flowability during tableting [4]. Although pharmaceutical companies successfully use wet granulation to prepare drug formulations, it is an equipment-intensive and worker-intensive manufacturing step [5]. Besides, granules prepared using traditional wet granulation lack the distribution uniformity, especially when hydrophilic polymers are used [4, 5].

Orally dissolving tablets (ODT) are characterized as a solid dosage form which is able to dissolve in the oral cavity in less than a minute without the need of water [6], yet it has adequate tensile strength to withstand the different steps of the manufacturing process [7, 8]. Another challenge facing the manufacturing of ODT is the hygroscopicity, which prevents it from maintaining physical integrity under normal conditions of temperature and humidity [9]. The individual dose of each ODT for the prospective drug cannot exceed 400mg for hydrophilic drugs and can go as low as 60mg for hydrophobic drugs [10]. A newer granulation technology was

introduced recently based on delivering aqueous binder mixture using a high-shear and fluid-bed wet granulation applications. A foam generator can be set up with a binder solution tank and high-sheer granulator to introduce the binder as a foam rather than spraying or pouring in binder onto a moving powder bed. It provides the advantage of uniform distribution of the granulating mixture on the resulting granules [11].Foam granulation is easy to scale up and does not require expensive flame proof area or special equipment. It provides easy and efficient particle coverage within short time and excellent flow of the formed granules which makes it superior to the other methods currently used like spray liquid binders [12].

Aceclofenac has been shown to have potent analgesic and anti-inflammatory activities similar to indomethacin and diclofenac, and better safety profile due to its preferential Cox-2 inhibition, An ODT formulation has been suggested of aceclofenac to provide better patient compliance using traditional wet granulation and direct compression [13]. In this study we will apply the new foam granulation technique and investigate the physical and mechanical properties of the resulted granules.

MATERIALS & METHODS

Aceclofenac, Sodium Lauryl Sulfate (SLS), Avicel (PH 102), Aspartame, and Croscarmellose sodium (CMS) obtained as a gift sample from Al-Hikma Jordan Pharmaceuticals (Amman, Jordan). Mannitol direct compression grade, supplied by Roquette (Lestrem, France). Urea analytical grade, Sodium Starch glycolate; Explotab low pH & high pH were supplied by JRS (Sigma Aldrich, St. Louis, MO, USA). Plasdone XL100 was supplied from ISP (Baar, Switzerland). Colloidal silicon dioxide; Aerosil 200, 300, 380 and R972, were supplied from Evonik (Frankfurt, Germany). Hydroxypropyl cellulose (HPC) was supplied by BASF Company (Ulm, Germany). Sodium Lauryl sulfate, from Fisher Scientific (Pittsburg, PA, USA). Magnesium stearate was supplied by Kirsch pharma company (Salzgitter, Germany). All other materials used were of pharmaceutical or analytical grade.

Preparation of the granules

Foam granulation process utilizes a high shear, double jacketed granulator (Chitra, India) equipped with mixer impeller and chopper set at 300 rpm and 1300 rpm, respectively. A 10% w/w HPC stock solution was prepared by dissolving HPC in water with gentle stirring overnight then dissolving the specified amount of urea that was different according to the formulation as shown in **Table (1)**. HPC foam was generated utilizing the same concepts previously described by Keary and Shesky [12]. The compressed air and liquid flow rates were adjusted to achieve a ≥90% foam quality, according to Eq.(1):

$$Foam\ Quality = \frac{Rate\ of\ Air\ Flow - Rate\ of\ Liquid\ Flow}{Rate\ of\ Air\ Flow}$$

Air flow rate and liquid flow rate were 2.0 L/min and 0.1 L/min, respectively. The rate of addition of the foamed granulating fluid was kept at a rate ranging between 55 and 65 g/min using a peristaltic pump. The foam was homogeneously dispersed into the powder during granulation.

The prepared granules were dried in a hot-air convection oven at 60 °C for 6 h to a loss on drying (LOD) value not exceeding 2.0%. The LOD of the granules was determined using a Mettler DSC HFT-2000M Moisture balance (Columbus, OH). Samples of approximately 2.0 g were dried to constant weight at 105 °C for 10 min.

Preparation of the ODT

The glidant (Aerosil) and lubricant were added to the granules and mixed for 2 minutes using three dimensional blender of 5 liters capacity (Hualian, China). The lubricated granules were set for compression using a rotary compressor (Karnavati Engineering Ltd, India) equipped with 8 mm diameter tools in which the tablet weight was adjusted to 300 mg and containing 100mg of aceclofenac.

Table (1): The composition of the four different formulations of aceclofenac ODT prepared by foam granulation

Component	Formula (mg/tablet) unless indicated otherwise			
	F1	**F2**	**F3**	**F4**
Aceclofenac	100	100	100	100
Sodium Lauryl Sulfate (SLS) Lubricant	12	12	0	0
Magnesium Stearate (MS) Lubricant	0	0	6	6
Disintegrant type	Croscarmellose Sodium (CMS) 20mg/tablet	Explotab 30mg/tablet	Plasdone XL100 30mg/tablet	Croscarmellose Sodium (CMS) 40mg/tablet
Disintegrant (%)	6	10	10	12
Aspartame Sweetener	2	2	2	2
Glidant type	Aerosil 300 32mg/tablet	Aerosil 300 28mg/tablet	Aerosil R972 34mg/tablet	Aerosil 380 30mg/tablet
Urea (mg/tablet) In granulating fluid	18	24	6	6
Urea %	6%	8%	2%	2%
Mannitol (MN)	58	78	81	58
Microcrystalline Cellulose (MCC)	58	26	41	58
ODT Total Weight	300	300	300	300
MN/MCC	1	3	2	1

Characterization of the prepared granules

The granules were inspected visually using an optical microscope. The true densities of dried, sieved granules were determined using a helium pcynometer (Micromeritics, Norcross, GA, USA). True densities used in the solid fraction calculations were the average of a triplicate. Hausner ratio, Carr's index, flow rate, and angle of repose were calculated.

Table (2): Physical characteristics of the aceclofenac granules prepared by foam granulation

Parameter	Formula			
	F1	**F2**	**F3**	**F4**
Bulk Density	0.36	0.40	0.38	0.40
Tapped Density (g/cc)	0.49	0.52	0.50	0.52
Hausner Ratio	1.36	1.30	1.32	1.30
Carr Index (%)	26	24	24	23
Angle of Ribose	31.3	30.9	28.1	26.6
Flow Rate (g/sec)	1.7	1.0	0.8	0.6

Evaluation of the final ODT

The physical characteristics of the final tablets were determined by applying the conventional tablets tests [13,14]; including visual inspection, thickness, friability, hardness, weight uniformity, drug content, in addition to *in vitro* disintegration test.

Thickness

Tablet thickness was measured right after compression using dial thickness caliper (Mitutoya, Japan). Tablets weight uniformity test was performed according to USP-34 standard test.

Friability

Ten tablets were weighed and placed in a standard friabilator (Pharmatest, Germany) .Twenty preweighed tablets were rotated at 25 rpm for 4 min. The tablets were dedusted and reweighed and the percentage of weight loss was calculated. The percentage friability of the tablets was measured as per the following equation; Eq (2):

$$Friability = \frac{Initial\ Weight - Final\ Weight}{Initial\ Weight} X100$$

Percentage was determined according to the standard USP-34 test using Friability tester.

Hardness

The crushing strength of the tablets was measured using a Monsanto hardness tester (Sheetal Scientific Industries, Mumbai, India). Three tablets from each formulation were tested randomly and the average reading was noted. The tablet tensile strength was calculated by using the following equation; Eq (3):

$$Tensile\ Strength\ \left(\frac{N}{cm^2}\right) = \frac{Peak\ Force\ (N)}{Length\ (cm)\ X\ Thickness\ (cm)}$$

Weight Uniformity

Randomly, twenty tablets were selected after compression and the mean weight was determined. None of the tablets deviated from the average weight by more than ±7.5% (USP-34).

Drug Content

Twenty tablets were weighed and powdered. An amount of the powder equivalent to 100mg of aceclofenac was dissolved in 100ml of pH 7.4 phosphate buffer, filtered, diluted suitably and analyzed for drug content at 274 nm using UV-Visible spectrophotometer (UV 160-Shimadzu, Japan)

Wetting time

A piece of tissue paper (12cmx10.75cm) folded twice was placed in a Petri dish (Internal Diameter = 9cm) containing 9ml of buffer solution simulating saliva (pH 7.4). A tablet was placed on the paper and the time taken for complete wetting was noted. Three tablets from each formulation were randomly selected and the average wetting time was noted. The results are tabulated in **table (3)**.

In vitro disintegration test

The *In vitro* dispersion time was measured by dropping a tablet in a 10ml measuring cylinder containing 6ml of buffer solution simulating the buccal cavity fluid (pH7.4) and the percentage released in 15-minute-time was calculated [15].

RESULTS & DISCUSSION

Characterization of the final granules

Granules of aceclofenac with acceptable characterizations were feasible by foam granulation technique table (2). The chemical composition of the four suggested formulations was according to previous studies formulating aceclofenac in ODT [16,17]. Granules were tested for their physical properties. The foam quality for the binder solution composed of HPC and different percentages of urea showed that, the binder solution with low urea content results in fine foam while high urea content results in coarse foam. Scaling up of such formulation shall be much easier than routine wet granulation since the formula is insensitive to the processing variables. Drug's compatibility with other excipients was tested using differential scanning calorimetry (DSC) and infrared spectroscopy (IR).

Table (3): Characterization of the prepared aceclofenac ODT prepared by foam granulation.

Formula	Thickness (mm)	Tensile Strength (N/cm2)	Weight Variation (%)	Friability (%)	Drug Content (%)	Wetting Time (sec)	In Vitro Dis-integration Time (sec)	Cumulative % released after 15
F1	3.53	56.4	0.62	0.45	100.8	67	40	94.4
F2	3.02	65.9	2.10	0.67	101.5	59	35	98.5
F3	3.76	52.9	0.95	0.44	97.9	54	35	100.0
F4	3.52	79.2	1.70	0.18	96.6	34	18	100.0

Characterization of the final tablets

The visual inspection of the final tablets and the compressor dies showed no picking or sticking, **Table (3)** shows the results of the tablet thickness which was used to calculate the tensile strength, weight variation and friability. Tablet weight variation is affected significantly by MN content, MN exhibits crystal change into needle shaped crystals which reflects into poor granules flowability. MN crystallization and polymorphism could have been induced by the moisture content of the granules [18]. The tensile strength represents the strength of a compact after permanent plastic deformation has occurred and gives an indication of the extent of intra-particulate bonding due to true contact areas formed between the surfaces. In evaluating the final compressed tablets, it is noted that the increase in urea percentage content is resulted in higher tensile strength of the produced tablets which may be explained by the ability of urea molecules to form hydrogen bonding between the molecules [19]. Hardness indicates the resistance of a material to permanent plastic deformation under a compressive load and will vary depending on the ductility or brittle nature of the material. Tablets friability is significantly affected by tablet hardness. Increasing tablet hardness is a result of increasing the compression force which result in increasing the bonding of the granules and hence decreasing the tablet friability. Drug content in the prepared compressed tablets were within the acceptable range 90.0 – 110 % according to USP-34.

In vitro disintegration time

In vitro disintegration time was measured by the percentage of drug released after dropping a tablet in a 10ml measuring cylinder containing 6ml of buffer solution simulating the buccal cavity fluid (pH7.4), the results are noted in **table (3)**. It was clear that the enhanced dissolution is related to the hydrophilicity of the excipients used. This ensures wettability as well as rapid uptake of water. In comparison of earlier studies, Aceclofenac ODT prepared by different techniques [16,17] reported slightly shorter disintegration time in comparison to the tablets prepared by foam granulation. This can be attributed to the presence of urea in the newer foam granulation technique.

CONCLUSION

Aceclofenac ODT can be formulated using foam granulation technique. The resulting granules and tablets have acceptable physical characteristics, disintegration time, and drug release rate. This could provide aceclofenac to patients with swallowing difficulties with a new dosage forms that can improve patient's compliance.

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