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Development of extended release formulation for 5-amino salicylic acid using Co-agglomeration technique

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ABSTRACT

5- Amino Salicylic Acid (ASA) is an anti-inflammatory drug used to treat inflammation of the digestive tract ulcerative colitis and mild-to-moderate Crohn's disease and a high-dose drug that has poor flow and compression properties and thus presents formulation problems. In this study the tabletting properties of extended release Co-agglomerates of ASA-HPMC prepared by solvent treated agglomeration method was investigated. The flow and packing properties of agglomerates, represented in terms of the angle of repose and change in tapping density, were much improved due to the spherical shape and smooth surface. Furthermore, spherical agglomerates possessed superior strength characteristics and were compressed into compacts having considerable hardness without capping at high compaction pressure. From the calculated Heckel's parameter, it was demonstrated that the spherical agglomerates of the drug showed better particle arrangement in the compression stages. Kawakita analysis revealed better packability of the agglomeratd drug compared to the conventional drug. In this study the ASA-COAG complies with the USP requirements i.e. % drug release in acid stage 1 should not be more than 10% and for buffer stage, after 5 hrs, drug release should not be less than 80%.

Keywords: Mesalamine**,** Co-Agglomeration technique, Flowability, Packability, Compactibility.

INTRODUCTION

Excipients are increasingly being recognised for the critical role they play in pharmaceutical products. HPMC products are widely used in extended release drug-delivery applications (1-2). This excipient offer flexibility in formulation and function for preparation of oral tablet dosage forms.

The HPMC matrix tablet is generally produced either via direct compression, wet granulation or in recent past a third method has been introduced called spherical agglomeration process. In wet granulation, the active ingredients and excipients are mixed together and then agglomerated with a wetting solution. This mixture is then dried and granulated. In spherical agglomeration, the solvent change method, the solution of the drug in a good solvent is poured in a poor solvent

under controlled condition of temperature and speed to obtain fine crystals. These crystals are agglomerated in the presence of bridging liquid. In direct compression, the dry ingredients are blended to a homogenous mixture and put directly into the tablet press. However, in many cases, drug-HPMC mixtures (especially if high dose drug) do not have adequate flow characteristics for tableting or direct die filling (3).

In general, wet granulation process is commonly employed to produce HPMC based granules with a high degree of compressibility and good flow characteristics for extended release HPMC tablets (3,4). During granulation numerous processing parameters may affect the quality and integrity of extended release HPMC tablet. Hence, the solvents used for wet granulation agglomeration such as water, ethanol, isopropyl alcohol and methylene chloride should be carefully selected to assure reproducibility of HPMC based granules or tablets (5). Wet granulation with water is widely used but it has drawback as HPMC has a tendency to form gel and lumps in the presence of water (3).

Literature survey has revealed that there are not much data available on the co- agglomeration technique, using solvent change method, to prepare HPMC based extended release spherical agglomerates of candidate drug. In the present work, 5- amino salicylic acid (ASA) was chosen as model drug candidate. Co-agglomeration method was developed by incorporating hydrophilic polymer hydroxylpropyl methyl cellulose (HPMC). The co- agglomerates were evaluated for powder flow, compressibility and release of ASA. These properties were evaluated by comparing the directly compressible HPMC- ASA powder mixture.

Materials

5- Amino salicylic acid was obtained from Swastic Chemicals, Nagpur, India; HPMC K-100 (Colorcon, India) and other materials were purchased from S. D. Fine chemicals (Mumbai, India).

Co- Agglomeration Method

HPMC powder was dispersed in 20 ml of n- hexane, by stirring continuously using mechanical stirrer (at 500, 1000, and 1500 rpm) at room temperature for the specified time (10 min). To it 5-ASA (in proportion of 1:1) was dispersed and stirring was continues to form homogenous mixture. Before separation (using sintered funnel) the co-agglomerated powder, bridging liquid was added. The separated powder was left to dry at room temperature away from light. The dried co-agglomerate powder (ASA- COAG) was stored in plastic bag.

Direct compression Mix of ASA and HPMC

Direct compression mix of ASA and HPMC at different levels of Drug: HPMC ((1:0.5 and 1:1; ASA-DRY I, and ASA-DRY II respectively) was prepared in laboratory mortar and pestle and stored in plastic bag.

Powder characterization

Particle size distribution

Particle size distribution of the powders was determined by sieve (mesh) analysis using laboratory sifter equipped with series of 6 screens and a pan. An approximate 10 gm sample was tested for total sifting time of 5 min. The method was carried out in triplicate (n=3).

Determination of particle shape parameters

The particle shape in the present work was measured by using Motic (optical) microscope with an attached digital camera (Olympus). The microscope was used to create 10 images, at a

magnification of 10X or 40X. From the microscope images, approximately 100 particles were analyzed using the Image-Pro Plus software to determine the particle descriptors of major and minor axis length and perimeter. Aspect ratio and irregularity were calculated from these particle descriptors using equations

Aspect Ratio = b/l (1)
Irregularity P/l (2)

In these equations *b* represents the length of the minor axis, *l* is the length of the major axis, and *P* is the perimeter.

Static Angle of Repose

The static angle of repose flowability test was performed following the procedure described in literature (6). A conical funnel was mounted with its stem 6 cm from the horizontal surface. Between 50 and 100 grams of powder were poured through the funnel, enough that the top of the resulting pile reached the funnel outlet. The angle measured on the right and left hand sides of the pile were averaged to give a single static angle of repose. The angle of repose can be obtained from equation

$$\text{Tan } \theta = h/0.5d \quad (3)$$

Where h- height of the cone and d- diameter of the cone. The method was carried out in triplicate (*n*=3).

Hausners Ratio and Carrs Index

The Hausners Ratio and Carrs Index are both calculated from compressibility data (7). The test powder is gently loaded through a funnel into a 100 ml cylinder and weighed to calculate its bulk density. Next, the cylinder is tapped in a single platform tapped density meter till no change in the volume of powder is observed. The Hausner ratio is calculated from equation (4) and the Carr Index from equation (5), where BD is the powder bulk density and TD is the powder tapped density (8). The method was carried out in triplicate (*n*=3).

HR = TD/ BD (4)
CI= TD-BD/TD x 100 (5)

Porosity

The porosities of the ASA- COAG and ASA-DRY I, and ASA-DRY II powder were calculated from their bulk and true densities. The porosity of the powder was calculated from true density of the powder using the following equation:

Total Porosity (E) = 1- Bulk density/ True density (6)

Packability

Sample packability was assessed by analysis of the tapping process with the Kawakita (Eq. 7) (9) and Kuno (Eq. 8) (10) methods, and using the parameters a, b, and k in the equations.

$n/C = 1/(ab) + n/a.$ (7)
$C = (V_o - V_n)/V_o,$
$a = (V_o - V_\infty)/V_o.$
$\rho_f - \rho_n = (\rho_f - \rho_o) \cdot \exp(-kn)$ (8)

Where: a is the degree of volume reduction when the tap number is infinity, b and k are constants for the apparent packing rate, V0 and Vn are the volume in the initial loosely packed and the nth tapped state, and ρ0, ρ n, and ρ f are the apparent density in the initial state, the nth tapped state, and the most densely packed state.

Compact Preparation of Powder

Compact compression was performed on R&D tablet press tablet (model M/C-12 STN, Cemach Machineries Ltd, India). Six different compaction forces (from 1 ton to 6 ton) were used for ASA- COAG and ASA-DRY I, and ASA-DRY II powders. The compact tablets were of 450 mg and 600 mg of powder and a flat-faced punch with a diameter of half inch (D-tooling) was used. The punch and die were lubricated with magnesium stearate before punching. Each compact was weighed accurately, and its dimensions (diameter and thickness) were measured with vernier caliper apparatus.

Compact characterization of ASA- COAG and ASA-DRY I, and ASA-DRY II

Heckel Analysis

The following Heckel's equation (11) was used to analyze the compression process of agglomerated crystals and wet granules, and assessed their compactibility.

$$\text{In } [1/(1-D)]=KP+A \qquad (9)$$

Where, D is the relative density of the tablets under compression Pressure, K is the slope of the straight portion of the Heckel Plot. The following equation gives the intercept obtained by extrapolating the straight portion of the plots.

$$A=1n\ [1/(1-D_0)]+B \qquad (10)$$

Where, D_0 is the relative density of the powder bed when P=0. The following equation gives the relative densities corresponding to A and B.

$$D_A=1-e^{-A} \qquad (11)$$

$$D_B=D_A-D_0 \qquad (12)$$

Tablet Elastic Recovery Test

Each powder was placed, 450 mg, in a die with 12 mm diameter and compressed under 6 tons (Hc) pressure. The thickness and diameter of each tablet at initial and after 24 h of ejection (He) was measured. Following equation was used to calculate the elastic recovery ratio (ER).

$$ER=[(He - Hc)/Hc]x100 \qquad (13)$$

About 24 h after the tablet was ejected, its weight, diameter, and thickness were measured, and its apparent density ρa calculated.

Compact Hardness, Tensile strength, Friability and Disintegration time

Tablet hardness was determined using a Monsanto hardness tester. The tensile strength (*T*) of the compact was calculated using the following equation:

$$T = 2F/\pi Dt \qquad (14)$$

in which *D* and *t* are the diameter and thickness of the compact, respectively, and *F* is the force fracturing the compact.

The friability values of the tablets were determined using a Roche-type friabilator. It was rotated at 25 rpm for 4 min. Percent friability was calculated using the following equation:

$$\text{Friability} = ([W0 - W]/\ W0) \times 100 \qquad (15)$$

In which *W*0 is the weight of the tablets at time zero before revolution, and *W* is the weight of the tablets after 100 revolutions.

The disintegration times of the tablet formulations were determined using a tablet disintegration test apparatus (Veego, Mumbai).

Content Uniformity

The tablet of 5-ASA were ground to fine powder and mixed thoroughly. A quantity of powder equivalent to 10 mg of the drug was transferred to 10 ml volumetric flask and dissolved in 0.1 M HCl and then pipette out 1 ml and dissolved in 100 ml of 0.1 M HCl to produce concentration of j10 ug / ml and the spectrum of the final sample was recorded against 0.1 M HCl as blank at 232 nm.

In-vitro dissolution studies

The in vitro dissolution studies were carried out using eight station USP type II dissolution apparatus. The study was carried out in first 2 h using 500 mL (at 100 rpm) of 0.1 N HCl. This step was followed by using 900ml of 6.8 phosphate buffer at 50 rpm for 1h. Finall y the study was continued using 900 ml of 7.2 buffer at 50 rpm. In all the stages temperature was maintained at 37 ± 0.5^0C thermostatically. At predetermined time intervals, 5mL of samples were withdrawn and the amount of drug released was determined Spectrophotometrically by measuring gabsorbance at 232 nm.

RESULTS AND DISCUSSION

Preparations of co-agglomerates

It was found that co-agglomeration was possible. The particle size distribution of the agglomerated powder was determined by the parameters that depended on the stirring rate and the time of stirring. It was observed that less the initial time of stirring and larger stirring rate resulted in no or smaller size agglomerates. More time of stirring and slower stirring rate was favorable in the building-up of agglomerates with a closed structure (**Figure 1)**. On the basis of above results the agglomerates preparation was optimized considering stirring rate of 500 rpm and stirring time of 1 h and this agglomerate powder now onwards would be named as ASA-COAG for further characterization.

Powder characterization of ASA- COAG and ASA-DRY I, and ASA-DRY II

The physical properties of the ASA- COAG and ASA-DRY I, and ASA-DRY II are summarized in (**Table 1)**. The mean diameters of the agglomerated particles were approximately 40–60 times higher than those of the untreated powder mix.

The flow properties of particulate solids are known to depend on the size, shape and size distribution of particles (12). Aspect ratio varies between 0 and 1, with a low value indicative of

an elongated particle; a perfect circle has an aspect ratio of 1. (**Table 1)** showed that the aspect ratio of ASA-COAG powder was close to 1, indicating spherical shape.

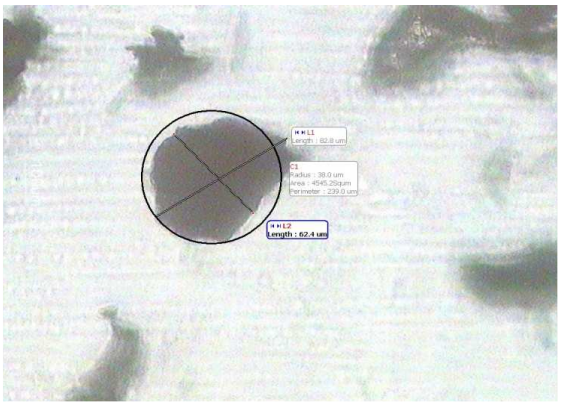

Figure 1: Motic images of – Agglomerated powder ASA-CAOG

According to Cain (7), a static angle of repose greater than 40° indicates a cohesive powder, whereas an angle greater than 50° indicates a very cohesive powder. The angle of repose of ASA-DRY I, and ASA-DRY II clearly shows that they form very cohesive powder.

The bulk density and tapped density of ASA-COAG is lower than those of the ASA-DRY I, and ASA-DRY II indicating more porous nature of powder. The ASA-COAG had a Hausner ratio of 1.2345 and a Carr index of 18.99 %. These measurements indicate increased or good flow property. ASA-DRY I and ASA-DRY II had Hausner ratio of 1.52 and 1.54 whereas a Carr index of 34.51 % and 35.14 % respectively. Both of these measurements are indicative of a cohesive powder [14]. The equations of Kawakita and Kuno were used to analyze the tapping process. The value 'a' in Kawakita equation was lower for ASA-COAG compared to that of the ASA-DRY I and ASA-DRY II, while 'b' in Kawatika equation and 'k' in Kuno equation were both higher for ASA-COAG. This indicates that ASA-COAG had excellent flowability and packability.

Table 1: Physical property of the ASA- COAG and ASA-DRY I, and ASA-DRY II powder

S. No.	Property (n=3)	Formulations		
		ASA-COAG	**ASA-DRY I**	**ASA-DRY II**
1	Mean particle diameter (µm)	1000± 12	300± 22	320± 20
2	Aspect ratio	0.4± 0.01	-	-
3	Irregularity	3.83	-	-
4	Angle of repose(^{0})	18.98± 1.40	45.84± 0.67	46.93± 0.85
5	Bulk Density gm/cm^3	0.246± 0.14	0.3137± 0.1	0.2740± 0.2
6	Tapped Density gm/cm^3	0.3037± 0.12	0.4780± 0.18	0.4225± 0.13
7	True Density gm/cm^3	1.6± 0.13	1.5± 0.10	1.5± 0.15
8	Carr's Index %	18.99± 0.91	34.51± 0. 15	35.14± 0.67
9	Hausner's ratio	1.2345± 0.14	1.5271± 0.12	1.5419± 0.11
10	Porosity	0.847± 0.09	0.791± 0.012	0.818± 0.013
11	a	0.2	0.3562	0.3621
12	b	0.9484	0.6910	0.9798
13	k	0.7202	0.6894	
14	1/b	1.0634	1.4471	1.020
15	Content Uniformity	100.8± 0.58	99.55± 0.54	101.2± 0.32

Compact characterization of ASA- COAG and ASA-DRY I, and ASA-DRY II

In order to achieve uniformity in tablet weight, the feed powder must flow and pack smoothly into the die cavity of the tablet machine. The (**Table 1)**, shows the Heckel constants derived from the plots. The plot for the ASA-COAG shows linearity over the compression range of 2-4 tons, indicating that the mechanism of consolidation of the material were predominantly plastic deformation**.** The slope of the linear portion, K, can be correlated to the crushing strength of compacts; larger values of K usually indicate harder compacts (11). The K values for the ASA-COAG is expected to form harder compacts. On the basis of these findings, it could be concluded that good flowability and packability for agglomerates (ASA-COAG) may be attributed to the spherical shape and the bigger particle size.

As expected, the tensile strength of the ASA-COAG compact was more than the ASA-DRY I and ASA-DRY II compacts (see **Table 2**). This may be a result of the stronger bonds formed between newly formed crystals of agglomerates. A friability study showed lower friability of the tablets prepared from the ASA-COAG, possibly owing to the better compaction of the spherical agglomerates.

Table 2: Compact property of the ASA- COAG and ASA-DRY I, and ASA-DRY II powder

Sr. No.	Property (n=3)	Formulaitons		
		ASA-COAG	**ASA-DRY I**	**ASA-DRY II**
1	Tablet Elastic Recovery Test (%)	0.8450	0.2777± 0.013	0.2272± 0.012
2	Hardness (kg/cm^2)	4.5± 0.013	3.5± 0.12	3.5± 0.13
3	Tensile strength (at 6 tons)	0.0672	0.0361	0.0516
4	Friability (%)	0.012%± 0.013	1.2 ± 0.11	1.69 ± 0.14
5	A	0.089	0.143	0.201
6	slope	0.462	0.171	0.156

In-vitro dissolution studies

In accordance to USP the extended release formulation of Messalamine the % drug release in acid stage 1 should not be more than 10% and for buffer stage, after 5 hrs, drug release should not be less than 80%. In this study the ASA-COAG complies with the USP requirements as shown in **(Figure 2)**.

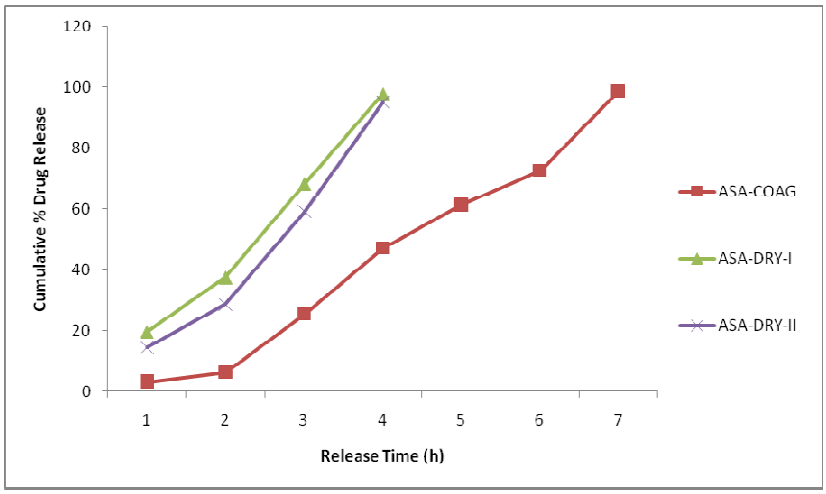

Figure 2: *In vitro* Dissolution Profile of ASA-COAG (■); ASA-DRY-I (▲) and ASA-DRY-II (x).

CONCLUSION

It was concluded that the selected solvent treated method for the formation of agglomerates of model drug improved the powder functionality properties of the of ASA drug powder such as flowability, packability and compactibility. Compacts by direct compression method could be formed successfully of agglomerated powder (ASA-COAG).

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