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Magnesium stearate is an incompatible excipient for aspirin in wet granulation producing non-linear degradation

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Abstract

Excipients are materials added along with therapeutic agents; and incompatibility between excipients and therapeutic agents affect the final outcome of the product. Aspirin is an ester and is prone to hydrolysis. This study focus on the effect of magnesium stearate as an excipient on stability of aspirin in granules. For that an accelerated degradation study was done on aspirin-magnesium stearate containing granules. For that, aspirin containing granules were sequentially mixed with increasing concentration of magnesium stearate to develop different test samples and they are type 1 (T1), type 2 (T2), type 3 (T3) and type 4 (T4) granules and heated at 70°c for 2 hours and evaluated the drug content. The drug content of untreated samples was found to be 168mg estimated by UV/Vis spectroscopy. The assay of different granules were for T1- 77.11%, T2- 96.7%, T3- 58.02% and T4- 53.80% respectively. The results show that, in these granules prepared by wet granulation process, the aspirin is degrading in a non-linear manner as the drug content increases and followed by decreasing. Overall, the study shows that magnesium stearate is an incompatible excipient for aspirin, varying in a non-linear manner, in granules as a lubricant.

Keywords: Drug-excipient incompatibility, material, degradation, Aspirin, magnesium stearate, granulation

INTRODUCTION

Excipients are pharmaceutical materials added along with the therapeutic agents[1,2]. The mixture of drug and excipients are granulated to prepare various unit solid dosage forms such as granules, tablets and capsules[1,2]. Incomaptibility of the therapeutic agent due to excipient affects the therapeutic outcome[3,4]. The various therapeutic agents currently being explored are drugs, proteins, peptides and gene. Improving the stability of the final product by optimizing the composition/process requirements helps in extending the shelf-life of the product[3,4].

A pharmaceutical dosage form is a combination of active pharmaceutical ingredient and the excipients which aid in manufacturing with required product attributes such as content uniformity, reproducibility stability, easy of administration; enabling required biological effects[1]. An ideal excipient must be pharmacologically inert that fulfill the functions of the formulation, provide required stability and produce optimum bioavailability of the drug [1,2]**.** It is important to assess the possible incompatibility between the drugs and various excipients for developing a market stable, effective and reproducible product, for that drug-excipient incompatibility studies are conducted[3,4]**.** Interaction between drug and excipients will results in physical and chemical instability and bioavailability issues that can affect therapeutic efficacy and safety [3,4]**.**

Magnesium stearate is commonly used as a lubricant[5] with granules in tablets, and granules in capsules in pharmaceutical industry. During blending, it will form a layer between drugs and excipients which will prevent the friction and bonding[5]. Aspirin is a non-steroidal anti-inflammatory agent (NSAID) which is used to treat a number of disease conditions including fever, pain, cardiovascular and inflammatory disease conditions such as rheumatoid arthritis[6]. Granulation process is widely adopted for solid dosage forms because of advantages, in processing[7], safety[8,9] and efficacy[10]. The process optimization of the granulation, improves the functional efficiency of resulting granules[7-10]. Aspirin granules are prepared by wet granulation process[15], where aqueous liquid solution will be added to the powder blend, such as starch paste. Aspirin, being an ester degrades faster in presence of water[11]. Other excipients also can accelerate the degradation process of active ingredients[12] and that affects bioavailability[5]. Magnesium stearate is the magnesium salt of stearate, which is often used as anti-adherent and lubricant which reduces the friction of the granules [5].

Aspirin and magnesium stearate reaction rate follows a zero order reaction[13]. Wherein, aspirin forms a complex with alkali cation magnesium and the resulting solvated molecule is susceptible for degradation[13]. In addition, magnesium stearate can affect the physical properties of the product mix.[14] All these studies are done at higher stoichiometric ratio by mixing the powder of aspirin and magnesium stearate in solid[14] or solvated conditions[13,15]. However, usually, this high level of exposure between drug and excipients may not be happening in granules used for preparing the tablets because, the aspirin containing dried granules are mixed with magnesium stearate powder added as a glidant, wherein, magnesium stearate is presented at the outside of granules. Thus, it is important to know at actual processing conditions and composition how the chemical stability of aspirin is affected in presence of magnesium stearate. This work attempts to see the stability of aspirin in granules mixed with varying concentrations of magnesium stearate in actual concentrations. The studies show that, the stability of aspirin is decreasing in a non-linear fashion.

MATERIALS AND METHODS

Chemicals and reagents

Aspirin, Sodium lauryl sulphate and lactose were purchased from Spectrum Chemicals Pvt. Limited, Cochin, Kerala. Starch was obtained from Nice Chemicals Cochin, hydroxyl ethyl cellulose was purchased from Loba chemie, Mumbai and Magnesium stearate was bought from Saphron chemicals, Kochi. All the chemicals and reagents used were of laboratory grade. All the reagents and buffers were prepared as per standard protocol.

Optimization

For preformulation studies, the UV/Vis spectrum (SHIMADZU UV-1800 UV VIS Spectrophotometer) of the aspirin was collected in phosphate buffer (pH 4.4).

Preparation of aspirin granules

The wet granulation of aspirin was done by following the established procedure[15]. Required amount of aspirin and lactose (Table-1) were weighed and mixed by using mortar and pestle. To the mixture, starch paste was added and mixed well. The starch paste was added until a coherent mass was obtained and passed

the coherent mass through sieve no.12 to obtain granules. The granules were dried by using hot air oven for 20 min at 60°C. Then the dried granules were passed through sieve no.24. Granules which reside on top of sieve no. 24 were taken and mixed with half of the fine powder. Finally, added sodium lauryl sulphate, cellulose and magnesium stearate (in various concentrations). The formulation matrix is given in Table-1. The granules were then filled into 3 size capsules with a fill weight 220mg.

Evaluation of granules

Preparation of standard graph

Aspirin (250 mg) was accurately weighed and dissolved in small quantity of 0.1 N NaOH and made up to 250 ml with distilled water. From that, pippeted out 0.5 ml, 1.0 ml, 1.5 ml, 2.0 ml and 2.5 ml in a 10 ml standard flask and made upto 10 ml with distilled water. Measured the absorbance at λ max 254nm.

Drug content analysis

Four types of granules were filled in the capsules and placed in a petriplates and kept in a hot air oven for 2 hours at 70°C. Each capsules, of different types of granules were dissolved in 100ml phosphate buffer (pH 4.4). From this, pipetted out 1ml of stock solution and made upto 10 ml with phosphate buffer. Then measured the absorbance at 254nm. The study was done in triplicate.

Table 1: Formulae for the preparation of granules.

Ingredients	Official formulae	Working formulae
Aspirin	300mg	37.5g
SLS	1mg	1g
Lactose	120mg	7.5g
Starch	24mg	1g
Cellulose	15mg	1.8g
Starch paste	Qs.	Qs.
Magnesium stearate		
Type1	0	0
Type 2	8mg	1.0g
Type 3	12mg	1.5g
Type 4	24mg	3.0g

Table 2: Percentage drug content of three types of granule.

Sl No	Type of granule	Drug content	Percentage drug content
1.	Type 1	129.55±3.39	77.11%
2.	Type 2	162.49±3.37	96.7%
3.	Type 3	97.49±3.34	58.02%
4.	Type 4	90.40±5.24	53.80%

RESULTS AND DISCUSSION

The standard graph of aspirin is given below. It is showing a linearity with r value 0.989. As per the drug content analysis of samples T1, T2, T3 and T4 granules were prepared which contain 0mg, 1mg, 1.5mg and 3mg magnesium stearate as per working formula have the drug content 129.55±3.39, 162.49±3.37, 97.49±3.34 and 90.40±5.24 respectively. All the samples were treated at elevated temperature. In type 2 granule, the degradation was lower than the other three formulations may be because of variation in diffusion properties at this particular concentration. The drug concentration was sequentially decreasing with respect to the magnesium stearate content as per table-2 and figure-2. The type 1 granule does not contain any magnesium stearate, has shown nearly 20% degradation which is only due to the moisture and elevated temperature. In type 2 granule containing 1g magnesium stearate, no degradation was observed. This may be due to the reduction in effect of elevated heat by the magnesium stearate, as part of the heat might be used for its melting. When the magnesium stearate concentration was increased, further degradation was also increased. This may be due to the availability of excess magnesium ions resulting in enhanced degradation and that is further continued even at higher concentration. Overall the degradation profile is non-linear. In solid state there are heat and mass transfer limitations, that is the reason for nonlinear degradation profile of the system [16].

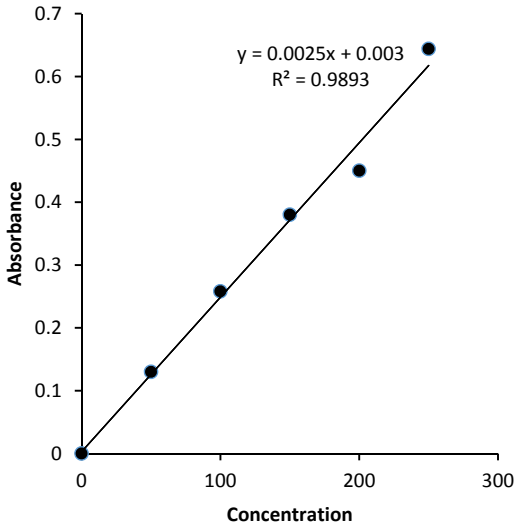

Figure 1: Standard graph of Aspirin

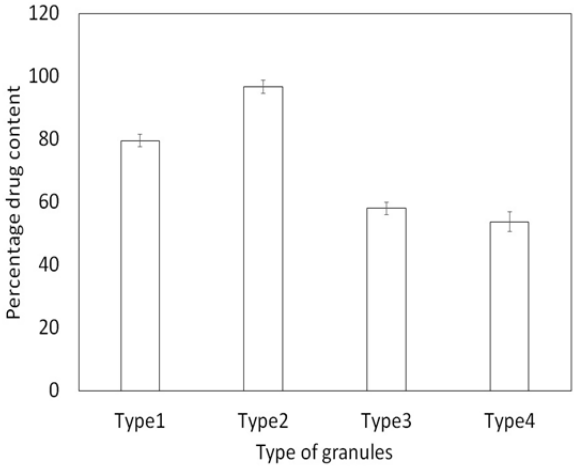

Figure 2: Drug content of three different types of granules with varying amount of magnesium stearate

Earlier it has been demonstrated that aspirin is a sensitive drug for formulation by wet processes[17]. The magnesium stearate appeared to increase the degradation rate of aspirin[13]. For such studies, the drug to excipient ratio was also taken in high weight ratios[13]. This is to accelerate the reaction conditions for tangible evidence of reaction[13]. However, in actual scenario such high exposure is not happening[15]. Also the sequence of exposure of the aspirin to the magnesium stearate happens at the last stage[15]. Engineering the system by pharmaceutical approaches is widely being applied for optimum signal presentation that include improving the stability of drug molecules[18] and optimizing the delivery in various

particulate systems such as granules,[7,8] microparticles[9] and nanoparticles[19,20]. This study aims to mimic the actual ratios and actual formulations during wet granulation in solid state to analyze the drug degradation. The studies show a non-linear degradation profile of aspirin in actual situation. This may be due to variation in diffusion properties in solid state granules, at this concentration. Detailed studies are required for giving mechanistic insights.

CONCLUSION

The aim of this study is to analyze the drug-excipient incompatibility between the aspirin and magnesium stearate in actual formulatory conditions of wet granulation filled in capsule. It shows that, the aspirin degradation is non-linear in actual conditions. It reflects the importance of mimicking the actual processing steps for getting the actual stability scenario of drugs with excipients, it has wider applicability in the area of therapeutic agent- excipient incompatibility. Engineering the materials and process plays an important role in controlling the incompatibility.

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