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Distribution of low dose drugs in granules: Influence of method of incorporation

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ABSTRACT

Variations in content uniformity can cause more problems in low dose drugs than high dose drugs especially if the drug is potent and has a narrow therapeutic index. The study was aimed at investigating the method of incorporation of low dose drugsin formulation and its effect on distribution of Active Pharmaceutical Ingredient (API) in granules. Mixing of API and diluent(s) as well as dissolving the API in binder solution prior to massing of diluent were the two methods of incorporation used. The content of drugs in the various granule sizes was determined by UV spectrophotometer. The result showed that when salbutamol sulphate powder was dissolved in binder solution, increased content was observed as compared to mixing it with the diluent before massing. But the opposite was seen with folic acid powder. Method of incorporation of API contributes to the distribution of low dose drugs in granules.

Keywords: low dose, incorporation, diluent, binder solution, content uniformity.

INTRODUCTION

The potency of both new and currently used drugs necessitates doses as low as 0.025mg e.g. levothyroxine sodium tablet. Variations in content uniformity cause more problems in low dose drugs than in high dose drugs. For instance, a change in drug content of 0.1mg of paracetamol tablets containing 500mg per tablets is only 0.02% increase or decrease which is not significant, and is also within the specification of that drug (5% for tablets of that size). However, the same 0.1mg change in a low dose tablet like misoprostol containing 0.2mg per tablet will cause a very significant dose variation of 50% and depending on the potency, toxicity and therapeutic index, it may cause a lot of problems. Variations in dose of drug have been reported to cause serious and even fatal consequences [1].For low dose solid dosage forms, the particle blend in numbers

sometimes too low to be found in every unit dose, when one or more of these particles are found in a single unit dose, the observed potency can fall outside the desired potency limit [2]. In low dose drugs, diluents constitute over 70% of the granules[3].

Over decades, pharmaceutical scientists in both academia and industry have developed alternative drug delivery systems that target drugs more effectively and efficiently to the therapeutic site[4]. These efforts have led to many new pharmaceutical delivery technologies, including pulmonary systemic delivery, nasal delivery, injectable formulations, and transdermal delivery. However, oral administration is still the preferred route when developing a conventional dosage form[5]. Tablets are solid preparations each containing a unit dose of one or more active ingredients and are obtained by compressing uniform volumes of particles intended for oral administration. The particles to be compressed consist of one or more active ingredients with or without auxiliary substances such as diluents, binders, disintegrating agents, glidants, lubricants, substances capable of modifying the behavior of the active ingredients in the digestive tract, authorized colouring matter and flavouringagents[6]. Low dose drugs are substances that are highly potent requiring only very small quantities to produce the required therapeutic activity, i.e. they contain very small quantities of active ingredients. Drug with active ingredient less than 50mg is considered low dose drug[7]. E.g. Chlorpheniramine 4mg, Phenobarbitone 30mg, Glibenclamide 5mg, Folic acid 5mg, Salbutamol 2mg, 4mg, Digoxin 0.25mg, misoprostol 0.2mg etc.

Particle size of drugs was reported to have effects on content uniformity (variation in distribution) of low dose drug[2]. In pharmaceutical industry, homogeneity of granules is critical for good quality control and fulfilling the strict content uniformity criteria from regulatory agencies (eg FDA) for tablets and granulated formulations[8].

Therefore, the aim of the study was to investigate the influence of the method of incorporation of low dose drugs on its distribution in granules prepared from different diluents. Folic acid and salbutamol sulphate powders were selected because they are insoluble and soluble low dose drugs respectively.

MATERIALS AND METHODS

Folic acid powder (Sigma, UK), Salbutamol sulphate (Sigma, UK), Maize starch BP (BDH, UK), Lactose (BDH, UK), kaffir potato starch, sweet potato starch and Irish potato starch were extracted from the tubers of the respective plants.

Two methods of incorporation of API, the conventional mixing of excipients (mainly diluents) and API as well as dissolving API in binder solution were used, Two local starches were extracted and characterized as described earlier[9]. A 20% w/v binder solution was prepared using maize starch BP and water as the vehicle. A 2g weight of folic acid or salbutamol sulphate powder was weighed and thoroughly mixed with 63g of lactose, maize starch, potato starch, kaffir potato starch sweet potato starch or binary mixture of lactose and each of the starches. The mixture in the first instance was massed with the prepared binder solution for 5 mins. The damp mass was forced through a 1.6 mm aperture sieve and the resulting granules were dried in a hot

air oven (Venticell, Germany) set at 40°C for 30 mins. The dried granules were passed through a 1.4 mm screen.
A 100g weight of each of the granules was poured in an already arranged set of sieve on a mechanical shaker (Shen, China). The sieves were allowed to vibrate for 10 mins, each fraction was analysed for the content of folic acid or salbutamol sulphate using UV spectrophotometer (Beckman and Coulter, DU 520 series, England).

Two gram of folic acid or salbutamol sulphate powder was dissolved in the earlier prepared binder solution. The resulting mixture was used to mass the various diluents and wet mass was processed as described above.

Statistical analysis
SPSS a statistical software program version 16 was used to compare means and the analysis of variance. $P<0.05$ was considered significant.

RESULTS AND DISCUSSION

Salbutamol or folic acid was incorporated into the granules by either mixing the drug and the diluents then adding the binder solution or the drug dissolved in the binder solution and then wetted the diluents. The influence of the method of incorporation of drug on distribution of salbutamol sulphate and folic acid are presented on tables 1 and 2 respectively. Particle shape, size, size distribution, density, moisture content, type and capacity of mixer as well as massing time are factors that influence the distribution of drugs in granules.

For salbutamol sulphate, when maize starch, kaffir potato starch, sweet potato starch or Irish potato starch was used as diluent, higher concentration of salbutamol sulphate was observed in granules of lower particle size. However when lactose a water soluble diluent was used, the higher concentration tilted towards the larger granules. This was as a result of a phenomenon called snow balling action. During massing,the wetter surface of water soluble diluent (lactose) granules is preferentially picked up by snow balling action, and thereby increasing its concentration in the larger and wetter granules[7].

Table 1: Effects of method of incorporation of API on distribution of Salbutamol sulphate in various diluents.

	mixed			dissolved		
Granule Size	90	250	750	90	250	750
Maize	92.13±0.35	105.33±1.06	99.40±0.80	92.57±0.61	106.40±1.01	100.37±0.75
Kaffir	95.50±0.82	103.20±1.48	99.60±0.62	96.60±0.10	104.47±0.15	100.43±0.61
Sweet	91.30±0.46	104.60±2.59	99.47±1.50	92.13±0.25	106.37±0.55	100.70±0.46
Irish	94.87±1.46	103.03±1.60	99.93±0.67	96.03±0.21	104.67±0.40	100.53±0.86
Lactose	73.27±1.80	96.40±0.70	104.40±0.62	81.00±1.25	98.13±0.35	103.17±0.35
MS:L	84.83±4.92	100.60±2.57	102.30±0.95	83.90±0.60	101.00±0.79	103.16±0.42
Kaffir:L	83.28±0.50	100.43±0.93	101.73±0.25	84.27±0.21	101.10±0.46	102.13±0.31
Sweet:L	81.42±0.23	102.38±1.30	102.55±0.41	82.23±0.40	102.20±0.36	102.53±0.15
Irish:L	84.42±0.85	100.80±0.95	102.22±0.28	84.27±0.47	101.17±0.42	101.03±0.72

Key: MS = maize starch, L = lactose

According to Jaiyeoba and Spring[10], the snow balling phenomenon is not expected in insoluble diluent (starch) because starch would allow much of the binder solution to the “trapped” in the

intra-particulate voids. Moreover, addition of binder solution to drug mix of powders makes the first portion to touch the binder to become excessively wet thereby soluble drug or diluent would dissolve in binder. The binder that is distributed from the over-wetted portion contains more of the dissolve solutes and the drug areas were massed with dissolved solutes. It is a known fact that larger granules are formed from the wettest granule[11]. There was no significant difference between the starches ($p > 0.05$) but significant difference was observed between all the starches and lactose ($p < 0.05$).

Table 2: Effects of method of incorporation of API on distribution of Folic acid in various diluents

	mix			dissolve		
Granule Size	90	250	750	90	250	750
Maize	92.13±0.35	105.33±1.06	99.40±0.80	84.97±1.38	88.37±0.95	92.67±0.85
Kaffir	95.50±0.82	103.20±1.48	99.60±0.62	85.27±0.86	92.10±0.40	94.70±0.26
Sweet	91.30±0.46	104.60±2.59	99.47±1.50	83.27±1.04	89.47±2.85	92.40±0.26
Irish	94.87±1.46	103.03±1.60	99.93±0.67	84.53±0.99	90.20±0.50	92.30±3.76
Lactose	73.27±1.80	96.40±0.70	104.40±0.62	100.23±1.42	96.30±0.46	91.00±0.66
MS:L	84.83±4.92	100.60±2.57	102.30±0.95	98.47±1.19	92.30±0.53	85.07±0.35
Kaffir:L	83.28±0.50	100.43±0.93	101.73±0.25	98.13±0.50	92.27±0.42	83.43±0.71
Sweet:L	81.42±0.23	102.38±1.30	102.55±0.41	98.27±0.40	93.03±0.72	88.57±0.91
Irish:L	84.42±0.85	100.80±0.95	102.22±0.28	99.13±1.10	94.30±0.92	87.73±0.57

Key: MS = maize starch, L = lactose

For the binary mixtures of each of the starches and lactose, the concentration of salbutamol sulphate were within the intermediates but more to the larger granules than the smaller ones as shown on table 1. There was significant difference between the distribution of salbutamol sulphate in binary mixture and only individual starch alone ($p < 0.05$).

For the folic acid, the distribution of the drug in various starches showed similar pattern with higher concentration of folic acid observed in larger granules. When lactose was employed as a diluent the concentration of folic acid was observed to be highest in the smaller granules.

Onemay expect that since folic acid is not a water soluble drug, the distribution might be uniform considering the fact that the diluents (starch) were also not soluble in water. Jaiyeoba and Spring[10], reported that the inter-particulate capillaries present in starch powder could trap some binder solution in the pores and would not take part in granule formation. The lower content of folic acid in larger granule of lactose might be as a result of soluble diluent (lactose) in solution which formed the wettest portion. The wettest portions also have higher binder solute and these solutes dilute the concentration of folic acid inthe wettest portion and consequently cause low concentration in the larger granules[8].

When binary mixtures were used a near uniform distribution of folic acid was observed. Significant difference was observed between lactose and all the starches ($p<0.05$). Similarly there was significant difference between distribution of folic acid in maize starch and kaffir potato starch or Irish potato starch. However the difference was not observed between maize starch and sweet potato starches ($p > 0.05$).

When salbutamol sulphate was dissolved in binder solution and used to wet diluents, increased distribution was observed while in case of folic acid there was decrease distribution in the

granules. This might be as a result of salbutamol sulphate being soluble spread well in the binder solution and hence distributed better than folic acid which was insoluble, moreover, folic acid powder is known to be unstable in water [12]. When lactose was used the distribution was significantly higher in larger granules.

CONCLUSION

Solubility of the API in the binder solution is an important parameter in the distribution of the drug in granules. For folic acid powder, mixing the powder with diluent prior to massing is most appropriate because of instability and insolubility.

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