***Review article***

# Mixing and formulation of low dose drugs: underlying problems and solutions

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## Abstract:

Mixing and formulation of low dose drugs can be very challenging due to problems related to segregation, content uniformity and physical stability. A careful control on these factors is necessary while manufacturing low dose drug products. Selection of excipients for the specific steps during formulation/process development is critical to develop a homogenous and segregation-free low dose formulation. Many types of equipments have been designed to facilitate mixing of low dose drugs with excipients. Apart from conventional formulation techniques (like wet granulation, dry granulation, and direct compression) various new techniques have been reported such as high shear granulation, ordered mixing and spray drying. These technological advancements have improved the manufacturing and quality of low dose drug products by achieving their predefined objective of content uniformity during mixing and formulation of low dose drugs. This article reviews current advancements related to formulation techniques of low dose drugs.

**Keywords:** Content uniformity; Homogeneity; Low dose drugs; Segregation

## Introduction

Progress in pharmaceutical research has produced very potent drugs, which require careful formulation and production in order to produce solid oral dosage forms with acceptable homogeneity and physical stability. Assuring the physical stability of a powder blend for production of tablets or capsules represents a major quality assurance consideration. The content uniformity quality control procedure for most tablets and capsules which are the subject of official monograph is by the analysis of mean drug content of 20 tablets which have been ground together. Table 1 presents low dose drugs for which content uniformity test is mandatory in Indian Pharmacopoeia 1996 edition [1]. Train (1960) realized that such an assay procedure could provide a satisfactory mean value, even though individual tablets showed large variations about the mean. The B.P. recognized the importance of the problem in 1973 and introduced a requirement of individual tablet assay for "micro dose" preparations (tablets containing less than 2 mg or 2% w/w of active drug) [2]. In addition to specific problems associated with interpretation of the data, in such assays there are also more general problems such as inability to detect batches where loss of homogeneity has occurred up until the testing provides no information concerning the point of failure nor the mechanism by which content uniformity has been lost [3]. In order to solve both specific and general problems associated with current pharmacopoeial testing, simple reproducible and informative tests are required on powder mixes prior to processing.

Latest pharmacopoeial guidelines ensure the consistency of dosage units by uniformity of dosage unit tests. The term "uniformity of dosage unit" is defined as the degree of uniformity in the amount of the active substance among dosage units. The uniformity of dosage units can be demonstrated by either content uniformity or mass variation. The content uniformity method may be applied in all cases. However the test for mass variation is applicable for selected dosage forms as given in Table 2 [4-6].

**Table 1** List of low dose drugs for oral delivery [1]

| No. | Drug | Dose | Category |
|---|---|---|---|
| 1 | Alprazolam | 250 to 500 µg three times daily | Anxiolytic |
| 2 | Amiloride hydrochloride | Initially, 5 to 10 mg daily; maximum 20 mg daily | Diuretic |
| 3 | Astemizole | For adults, 10 mg (not to be exceeded) once daily up to 7 days. For children, 5 mg (not to be exceeded) once daily up to 7 days. | Antihistaminic |
| 4 | Atropine methonitrate | 200 to 600 µg | Anticholinergic |
| 5 | Atropine sulphate | 250 µg to 2 mg daily in single or divided doses | Anticholinergic; antidote to cholinesterase inhibitors |
| 6 | Benzhexol hydrochloride | 1 mg, gradually increased to a usual maintenance dose of 5 to 15 mg daily in 3 to 4 divided doses | Antiparkinson |
| 7 | Betamethasone | 0.5 to 5 mg daily, in divided doses | Adrenocortical steroid |
| 8 | Bromhexine hydrochloride | 8 to 16 mg three to four times daily | Expectorant |
| 9 | Bromocriptine mesylate | Equivalent of 2.5 mg to 20 mg of bromocriptine daily, in divided doses | Dopamine agonist |
| 10 | Buprenorphine hydrochloride | Equivalent of up to 400 µg of buprenorphine every 6 to 8 hours | Narcotic analgesic |
| 11 | Busulphan | 2 to 4 mg daily; maintenance dose, 0.5 to 2 mg daily | Cytotoxic |
| 12 | Carbimazole | Controlling dose, 30 to 60 mg daily, in divided doses; maintenance maintenance dose, 5 to 20 mg daily | Antithyroid |
| 13 | Chlorpheniramine maleate | 4 to 16 mg daily, in divided doses | Antihistamine |
| 14 | Clonidine hydrochloride | 50 to 100 µg thrice daily increased gradually according to the needs and response of the patient; maximum daily dose 1.2 mg | Antihypertensive |
| 15 | Colchicine | Initial dose, 1 mg; subsequent doses, 500 µg every two hours | Gout suppressant |

**Table 1** List of low dose drugs for oral delivery [1] (Cont.)

| No. | Drug | Dose | Category |
|---|---|---|---|
| 16 | Cyproheptadine hydrochloride | 4 to 20 mg daily, in divided doses | Histamine H1-receptor antagonist |
| 17 | Dexamethasone | 500 μg to 10 mg daily, in divided doses | Adrenocortical steroid (anti-inflammatory) |
| 18 | Diazepam | In anxiety states, 2 mg thrice daily, in insomnia associated with anxiety, 5 to 15 mg at bedtime | Anxiolytic; sedative; anticonvulsant |
| 19 | Dienoestrol | 500 μg to 5 mg daily | Oestrogen |
| 20 | Digitoxin | 50 to 200 μg daily | Cardiac glycoside |
| 21 | Digoxin | 62.5 μg to 1.5 mg in divided doses | Cardiac glycoside |
| 22 | Dydrogesterone | 10 mg twice daily | Progestogen |
| 23 | Ergometrine maleate | 250 μg to 1 mg | Uterine stimulant |
| 24 | Ergotamine tartrate | 1 mg to 2 mg | Sympatholytic; antimigraine |
| 25 | Ethinyloestradiol | For menopausal symptoms, 10 to 20 μg daily continuously or for 21 days, repeated after 7 days, with a progestogen from day 17 to day 26 of cycle if uterus is intact. For primary amenorrhoea, 10 μg on alternate days increasing to a maximum of 50 mg daily continuously with a progestogen for the last 5 days of month | Oestrogen. (For menopausal symptoms and primary amenorrhoea) |
| 26 | Fludrocortisone acetate | 50 to 300 μg daily | Mineralocorticoid |
| 27 | Fluphenazine hydrochloride | 1 to 10 mg daily | Antipsychotic |
| 28 | Glibenclamide | 5 mg daily, adjusted according to response; maximum 15 mg daily, after food | Hypoglycaemic |
| 29 | Haloperidol | 1.5 to 20 mg daily | Antipsychotic |
| 30 | Melphalan | 2 to 4 mg daily for 4 to 6 days | Cytotoxic |
| 31 | Methadone hydrochloride | 5 to 10 mg every 6 to 8 hours | Narcotic analgesic |
| 32 | Methylergometrine maleate | 250 μg to 500 μg | Uterine stimulant |
| 33 | Nicoumalone | Initial dose, first day, 8 to 12 mg; second day, 4 to 8 mg; maintenance dose, 1 to 8 mg daily | Anticoagulant |
| 34 | Nitrazepam | 5 to 10 mg daily, at bed time | Hypnotic; sedative |
| 35 | Norethisterone | 5 to 20 mg daily, in single or divided doses | Progestogen |
| 36 | Norgestrel | 150 to 300 μg | Progestogen |
| 37 | Prednisone | 5 to 60 mg daily, in divided doses | Adrenocortical steroid |
| 38 | Prednisolone | 5 to 30 mg daily, in divided doses | Adrenocortical steroid |
| 39 | Prazosin hydrochloride | 500 μg to 1 mg two to three times daily | Antihypertensive |
| 40 | Salbutamol | 6 to 16 mg daily, in divided doses | Beta-adrenoceptor agonist |
| 41 | Thyroxine sodium | 50 to 300 μg daily | Thyromimetics |
| 42 | Timolol maleate | In hypertension, initially 5 mg twice daily or 10 mg once daily; maximum 60 mg daily. In angina, initially 5 mg 2 to 3 times daily; maintenance dose, 15 to 45 mg daily. For prophylaxis after infarction, initially 5 mg twice daily, started 1 to 4 weeks after infarction. For migraine prophylaxis, 10 to 20 mg daily | Beta-adrenoceptor antagonist |
| 43 | Triamcinolone | 2 to 24 mg daily | Corticosteroid |

**Table 2** Application of content uniformity (CU) and mass variation (MV) test for dosage forms [4-6]

| Dosage forms | Types | Subtypes | Dose and ratio of active substance | |
|---|---|---|---|---|
| | | | ≥ 25 mg and ≥ 25% | < 25 mg and < 25% |
| Tablets | Uncoated | | MV | CU |
| | Coated | Film-coated | MV | CU |
| | | Others | CU | CU |
| Capsules | Hard | | MV | CU |
| | Soft | Suspension, emulsion, gels | CU | CU |
| | | Solutions | MV | MV |
| Solids in single-dose containers | Single component | | MV | MV |
| | Multiple components | Solution freeze-dried in final container | MV | MV |
| | | Others | CU | CU |
| Solutions enclosed in single-dose containers | | | MV | MV |
| Others | | | CU | CU |

The recommendation given by product quality research institute (PQRI) regarding blend uniformity was reviewed and finally accepted by US FDA. According to this recommendation, sampling plans for process validation batches include identification of at least 10 locations in the blender to pull blend samples and identification of at least 20 locations throughout the compression or filling operation to obtain dosage units. Blend sample criteria includes relative standard deviation (RSD) ≤ 5.0% and all individuals should be within the mean ± 10% (absolute). Dosage unit criteria includes RSD of all individuals ≤ 6.0%. Each location mean should be within 90.0-110.0% of target potency, and all individuals should be within 75.0-125.0% of target potency [7]. Three factors can directly contribute to content uniformity problems [8].

1) Non uniform distribution of the drug substance throughout the powder mixture or granulation.

2) Segregation of the powder mixture or granulation during the various manufacturing processes.

3) Tablet weight variation.

The uniform mixing of potent drugs is essential for assuring content uniformity of the final product. This is vital determining factor in case of drugs having narrow therapeutic window and a small change in drug content (in µg or mg) altering the therapeutic range of drugs causing underdose or overdose. Both the situations are harmful for patients e.g. patient with congestive cardiac failure (CCF) taking digitoxin; under-dose causes therapeutic failure of drug and leads to death from CCF while overdose causes toxicity and chances of death due to development of arrhythmia.

A dry blending process for low dose drug is possible provided that the preblending and blending is carefully designed and process parameters are optimized [9]. The current article provides an overview on several formulation techniques for low dose drugs with their pros and cons in terms of homogeneity in the finished products.

## General mixing problems and their solutions

### *Segregation problem and its solution*

Segregation refers to the separation of the coarse from fine material during the flow of a powder or the vibration of a bed of powder. It is the opposite effect to mixing [10] and can occur by several different mechanisms, depending on the particles physical characteristics and the handling method [11].

#### Segregation by sifting/percolation

Sifting or percolation is the movement of smaller particles through a matrix of larger ones [11]. It may be

produced by pouring a powder from one container to the next as is done by emptying the contents of blender into another hopper or into drums [12]. This is due to the particle size differences between individual components and interparticle motion.

In general larger the ratio of particle size, the greater the tendency for particles to segregate by sifting. If particles are stationary or moving with a uniform velocity, they are not essentially locked together, almost eliminating the tendency to segregate, even for high segregating mixtures. For sifting to occur, particles in the mixture must flow at different velocities [11].

**Segregation by dusting/particle entrainment**

Segregation may also take place during pouring of a powder; particularly of there is considerable free falling of the particles. In this case the fine particles become airborne and separate form the bulk of the powder [12]. This problem is particularly acute with pyramidal bins, as airborne fines that settle toward the walls eventually slide to the valleys (corners) of the bin [13].

**Segregation by nature of flow of mixture**

Segregation may also take place inside the blender when the powder bed does not exhibit mass flow characteristics, i.e. the powder does not flow from a hopper or mixer in the order in which it is situated in the container. In this case, the large particles move as the powder structure breaks down because of their larger mass, leaving the smaller structured particles behind [12].

## Solution of segregation problems [10, 11, 13, 14]

1) Selection of particular size fractions to get drug and excipients of the same narrow particle size range.

2) Milling/size reduction of components to reduce the particle size range followed by sieving to remove fines or lumps.

3) Controlled crystallization during production of the drug/excipients to give components of particular crystal shape or size range.

4) Selection of excipients with density similar to the active component (s).

5) Granulation of the powder mix for even distribution of large number of different particles in each granule.

6) Reduction of vibration or movement of powder mass after mixing.

7) Use of filling machine hoppers designed so that powder residence time is minimized.

8) Use of multi-operation equipments to minimize transfer of mix, e.g. a fluidized-bed drier or a high speed mixer or granulator for mixing and granulating.

9) Mixing by serial dilution method or ordered mixing.

10) Selection of correct equipment e.g., use of nauta mixer or ribbon blender rather than tumbling mixer. Traditional mass-flow bin can be replaced with mass-flow insert inside an existing bin in which insert consists of a hopper with in a hopper to provide uniform velocity profile in the bin that will minimize segregation.

11) Avoiding slopping surfaces in machinery.

12) Minimizing transfer steps, drop height, and controlling fluidization of powder.

## Formulation techniques used for low dose unit dosage forms

### *Granulation techniques*

**Wet granulation technique**

The drug is dissolved in water or another solvent, and blended with excipients including a binder, for example povidone, to form a wet mass containing 5-20% by weight of solution to total weight of granulation mix, which is then dried off in a separate step. The binder causes particles of excipient to lumps together, and as the mass dries these clumps (“granules”) either contain or are coated with the drug. This is effective but cumbersome since the drying step requires special equipment, and generally involves high temperatures which may degrade labile drugs. Also, the use of the binder requires the further inclusion of a disintegrant such as sodium starch glycolate or starch to help the tablet, which is cohesive, to disperse in the stomach [15].

Desogestrel tablets (60 µg) were prepared by wet granulation using hydroxypropylcellulose as granulating agent in a Gral 10 granulator. Decomposition of desogestrel at 40°C for two months at relative humidities of 10 and 95% was observed 0 and 1% respectively [15].

If the drug is unstable in water (like mestranol) then wet granulation process approach using organic solvents such as chloroform can be employed. Disadvantages of the process includes environmentally unsafe, considerable manufacturing expenses, in that appropriate solvent scrubbing and/or explosion proof equipment must be acquired at substantial capital expenditure.

**Modified wet granulation techniques**

This method utilizes an aqueous medium (water medium, with added water-miscible solvents such as isopropanol or ethanol if needed) which contains the active ingredient(s), a quantity of one or more surfactants sufficient to dissolve or suspend active ingredients uniformly throughout the medium and other manufacturing additives such as granulating-binding agents, pharmaceutical fillers, tabletting lubricants etc. This technique prevents migration of drugs through the carrier upon drying. Estradiol tablets (2 mg) were prepared by modified wet granulation using sodium lauryl sulfate, as surfactant and 1% povidone solution in water [16].

Modified wet granulation process was used for formulations of (2R)-(1 alpha, 5 alpha, 6 alpha)-N-[3-azabicyclo [3.1.0] hexyl-6-(aminomethyl)-yl] -2-hydroxy-2-cyclopentyl-2-phenyl acetamide hydrochloride. The process includes blending excipients, granulating blend with solution of drug in a rapid mixer granulator, drying and sizing of granules, blending granulate with other necessary excipients like lubricant and processing into a dosage form. Another process includes preparing a bed of excipients, wetting bed with solvent, granulating bed with solution of drug by spraying an atomized solution of the drug, drying and sizing of granules, blending granulate with other necessary excipients like lubricant and processing into a dosage form. [17].

**Fluid bed granulation technique**

Fluid bed granulation has been used to achieve content uniformity of low dose (1 µg-10 mg) tablets. In this process, the micronised drug is blended as a powder with other excipients, then loaded into a fluid bed granulator and the powders are agglomerated by spraying on a solution of a binder; drying takes place concomitantly. The process does not require a separate drying step, but it does require the use of micronised drug and also incorporates a separate blending step prior to granulation. It also requires specialised equipment and precise optimization of the process parameters. This process overcomes the problem of mixing cohesive materials, which tends to occur during conventional granulation of microdose products and eliminates the adverse effects caused by differential solubility and hydrophobicity of the components.

Tablets containing micronized salicylic acid (which is hydrophobic and has a low aqueous solubility) were prepared using spray dried lactose as carrier material by interactive mixing in revolve cube mixer and granulating with polyvinylpyrrolidone. The content of tablets fell within ± 15% of the mean and coefficient of variation was < 5% (99% confidence) for all batches [18].

Tablets of 2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethylphenyl]-thiazol-5-ylcarbonyl)amino] methyl} phenoxy]propionic acid (10 µg) were prepared by fluid bed coating and preferred content uniformity % RSD = 2.5 (< 3%RSD) was achieved [19].

**Carrier granulation technique**

This functions by spraying a solution of binder such as povidone in water onto relatively large excipient particles such as hydrous lactose and then spraying small dry drug substance particles onto that, thus coating the excipient with drug particles which are stuck on by the binder. The quantity of solution used was 3.3-3.5% by weight of solution to total granulation mix. The method was applied to a formulation containing 4-5% drug by weight. This method also requires drying; the drug particle size needs to be very small, which often requires an extra milling step and the very fine drug powder may not flow at all well; and the formula still requires a disintegrant [20].

**Spray drying using viscosity increasing excipients**

This technique utilizes a viscous aqueous based spray solution (like starch, pre gelatinized starch, hydroxypropyl methylcellulose, methyl cellulose, povidone) to provide a uniform distribution of a small amount of drug in a large amount of granulation. After the water evaporates, drug is bound to the granulation reducing the potential for downstream segregation. The excipient providing viscosity to the aqueous solution act as "glue" and bind to the drug to the granulation after the water evaporates away. Preferably weight ratio of the viscosity increasing excipient to the pharmaceutical compound is from 12:1 to 60:1.

In this technique first paste of the viscosity enhancing excipient is prepared, drug is added to a portion of this paste to make a slurry (lumps may be present) and slurry is milled once or multiple times until it is a uniform suspension. Mill is then purged with the remaining paste to incorporate residual drug in the mill. Milled suspension and purge are then added to the spray solution tank for spraying onto the granulation using a fluid bed drier [21].

Dexamethaone tablets (0.25 mg) were prepared using starch as viscosity increasing excipient. The resulting dexamethasone tablets were uniform in potency and content uniformity testing gave an average of 101.2% claim with an RSD of 0.8% [21].

**High shear granulation technique**

In high shear mixer, powder is pinched between a moving and a static surface as in a comil or between two moving surfaces as in a pair of pressurized rolls. The speed of rotation is slow but the powder is subjected to very high shear that will breakdown most aggregates. It is commonly preceded by a convective or tumbler mixer to give a general bulk quality before the conditioning of the mixture on a microscale in the high shear mixer. In some cases the pressure exerted on the powder in the pinch zone is sufficient to consolidate it into a flake form. High shear mixers tend to have a limited throughput rate and are reserved for those mixtures requiring homogeneity on a microscale [22].

This process leads to the optimal mixing of the constituents of a pharmaceutical formulation, the process is well-contained and the available modern equipment enables full in-process control [23].

Tablets containing 1 µg or 0.1 µg of 2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethyl phenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid were prepared by high shear granulation process. RSD of 1 µg and 0.1 µg tablets were observed at 2.1% and 1.5%, respectively [19].

Mefenamic acid (water insoluble) formulations were prepared by wet granulation using high shear mixing to study process parameters like amount of water added, impeller rotation speed, and kneading time. Result showed that increasing amount of water and kneading time led to an increase in particle diameter of granules and a decrease in mean pore diameter while increasing impellor speed led to a decrease in mean pore diameter but no effect on particle diameter [24].

**Low shear granulation technique**

Some micronised steroids such as desogestrel present in a low amount, the granulation process leads to a better content uniformity if the actual granulation step, i.e. wetting with binder liquid, while applying agitation, is conducted with substantially lower shear than normally applied in the current high-shear mixers. It was found that in a high shear mixer in a normal fashion, the content uniformity cannot be steered to RSD of below 3% and the demixing potential (DP) typically is 30-40%. When following the process of low shear granulation, an excellent DP of well below 10% and consequently favorable content uniformity was obtained.

This technique consists of a mixing step bringing into association the active substance and a suitable filler to form a mixture; a granulating step in which the mixture is granulated to form agglomerates or granules by wetting the mixture with a binder liquid, the wetting being conducted under agitation i.e. at low shear; post-mixing and compression for tableting or fill in capsules.

Desogestrel and ethinyl estradiol tablets were prepared by low shear granulation. DP for content desogestrel and content ethinyl estradiol was at observed

12% and 11%, respectively. Similarly desogestrel tablets (0.0075 mg) were prepared by low shear granulation technique. DP and tablet content uniformity in RSD were observed at 12% and 2.8%, respectively [23].

**Novel foam granulation technique**

In this technique foam of aqueous binder solution is prepared. Drug is dissolved in binder solution and wet granulations of drug while polymer with other necessary excipients is prepared using foamed aqueous binder solution in a high shear granulator. The granules are then compressed to form tablets. The foamed binders (like hypromellose 2910 USP, methyl cellulose USP) have a shaving cream which breaks quickly and disperses uniformly within the high-shear granulator. Formulation of propranolol HCl tablets (0.125, 0.25, 0.5, 1%) was achieved using hypromellose 2910 USP (1, 3 5, and 10% concentration) using foam granulation technique. Content uniformity testing of granulation and tablets showed a %RSD results range of 0.31 to 3.8% and 0.39 to 2.85% respectively [25].

**Fluid bed granulation with jet pulverization**

In this process formulations are produced by uniformly mixing drug combinations (e.g. one insulin sensitizer and an active drug (having a ratio of median size thereof to the median size of insulin sensitizer of 0.5 to 10) with additives or uniformly mixing after granulation and then compression molding. Mixing is performed using V-type mixer and granulation is performed using a high speed granulator, a fluid bed granulator-dryer. Desired ratio of median size of an active constituent with a large median size may be achieved by pulverizing it with an excipient like microcrystalline cellulose using jet mill, cutter mill or hammer mill.

Formulation of metformin hydrochloride and pioglitazone hydrochloride was prepared by mixing pioglitazone hydrochloride (median size 13 μm) with microcrystalline cellulose into a mixer, pulverizing mixture in a jet mill pulverizer to give a pulverized product (median size 3.6 μm) of a pioglitazone hydrochloride/ microcrystalline cellulose mixture. This pulverized product, metformin hydrochloride and microcrystalline cellulose was casted into fluidized granulating dryer for granulation and then tableting. Coefficients of variation (%) of pioglitazone hydrochloride and metformin hydrochloride were observed at 0.6 and 0.5, respectively [26].

***Compression techniques***

**Direct compression technique**

The simplest way of manufacturing tablets is to blend all the ingredients as dry powders and tablet them. This is rarely successful for low-dose drugs; common problems being segregation of the powder blend during tabletting [27], fluidity, compressibility and maintenance of content uniformity. Proper selection of excipients in the formulation of low dose drugs could be employed to alleviate these problems in dosage forms prepared by direct compression technique.

Diazepam tablets (5 mg) were prepared by direct compression technique utilizing Emcompress® (Dicalcium phosphate dihydrate) as direct compressible vehicle. The Diazepam and Emcompress® at 1:1.5 ratio have imparted good tabletting properties and uniformity of mixing was satisfactory (S.D. of ± 2.46%) due to the compatibility of particle size of diazepam and Emcompress® [28]. Fluoxetine tablets (7.5 mg and 15 mg) at low hardness (less than 5 kilopascal) were prepared by direct compression utilizing dicalcium phosphate dihydrate as diluents and microcrystalline cellulose as disintegrant at a ratio of 5:1 [29].

Experimental batches were prepared by mixing the active drug (0.07% w/w) with lactose anhydrous, Starch 1500® and microcrystalline cellulose and finally compressing after addition of other excipients. Content uniformity of final powder blend with lactose anhydrous, starch and microcrystalline cellulose were observed at 82.20 ± 4.61, 90.65 ± 3.89 and 98.52 ± 3.98, respectively. Mean drug content (%) ± RSD tablets were observed at 92.43 ± 1.42, 96.00 ± 1.25 and 99.59 ± 3.19 using lactose anhydrous, starch and microcrystalline cellulose, respectively [2].

**Modified direct compression technique**

Dose uniformity in formulations of highly potent drugs (50 μg to 1000 μg) may be achieved by dissolving

the drug in a solvent (like ethanol, methanol, acetone, tetrahydrofuran etc); distributing a solution of the active ingredient over a directly compressible tableting vehicle (like dicalcium phosphate dihydrate, compressible sucrose, lactose, mannitol, microcrystalline cellulose, modified starches) with subsequent evaporation of the solvent; adding lubricant and other excipients if desired, followed by tableting.

Formulation of (2S, 12bS)-1',3'-dimethylspiro-(1,3,4,6,7,12b-hexahydrobenzo[b]furo[2,3-a]quinolizin)-2,4'-(5,'6'-dihydro-1'H-pyrimidine-2'(3'H)-one) tablets 50 µg was achieved by this technique utilizing microcrystalline cellulose, as directly compressible excipient and anhydrous ethanol as solvent. Uniformity test showed satisfactory content uniformity (mean RSD=0.9781%) [30].

**Dry blend compression of potent drugs with low solubility using directly compressible agglomerated excipients**

Estradiol and a number of other low-dose potent drugs precipitate in a variety of polymorphs and/or crystal habits. The changes in the crystal structure on drying during wet granulation can affect the bioavailability of the drug [31]. This problem can be solved by utilizing dry blend compression using directly compressible agglomerated excipients.

The dry preparation makes use of excipients that have been prepared by agglomeration methods other than by spray drying (like granular mannitol, agglomerated maltodextrin, corn syrup solids, mixtures of these agents with added conventional direct compression excipients). Drug is located in crevices of the agglomerate which indicates a different mechanism of attachment. This technique is an important alternative to wet granulation, thus eliminating recrystallization and the issue of polymorphism and bioavailability.

Formulation of estradiol 2 mg tablets using agglomerated mannitol as directly compressible agglomerated excipient and formulation of medroxy-progesterone tablets using combination of agglomerated mannitol & maltodextrin was achieved [32].

**Active layering and direct compression of sugar spheres**

In this process layering of sugar spheres (250-355 µm) is achieved by spraying drug contained in aqueous solution of binder followed by drying in a fluidized bed apparatus. The layered sugar spheres are then compressed into tablets after addition of lubricant. Layered sugar spheres show a much smoother surface which contributes to sphericity. The narrow distribution range of sugar sphere size, regular fluidization and solution spraying contribute towards uniformity of layering and this layering uniformity leads to a homogenous distribution of drug.

Formulation of acetaminophen (0.4% w/w) was prepared by active layering of sugar spheres using PEG 6000 as binder and compressing after addition of magnesium stearate as lubricant. Content uniformity data showed mean content value of 2.04 ± 0.05 mg [33]. Similarly extended release tablets of ketoprofen with increased homogeneity were prepared by directly compressing dried micro granules obtained by coating neutral sugar spheres/quasispheres (after moistening with binder solution) with polymer material (for extended release like xanthan gum base, carbopol) by manual powdering in rotating coating pan (to increase the amount of polymer bound on sugar spheres and prevention of viscosity problems), drying and layering of this functionalized excipient by spraying solution containing drug and a binding agent [34].

***Ordered mixing/Interactive mixing technique***

Ordered mixing comes to yield the perfect mixture and may be obtained in a number of ways like mechanical means, adhesion, and coating. The major difference between the mechanical, the adhesional and coated ordered mixing is the degree of force holding the ingredients in each type of the ordered units together. Ordered mixing is not only beneficial in approaching a perfect mixture, but it minimizes the possibility of segregation of a mixture by holding the ingredient ratio constant via the intact ordered units [12].

Physicochemical properties of excipients significantly affect adsorption of small drug particles. Excipients with larger particle size, better flow ability and higher brasivity can help to break down agglomerates formed by very fine drug particles, adsorb individual drug particles onto the surface of large excipients, and improve homogeneity [35].

Fentanyl tablets (100 μg, 200 μg, and 400 μg) were prepared by ordered mixing using adhesion method in which coarse mannitol particles were covered with fentanyl citrate by dry mixing to form an interactive mixture which then mixed with other ingredients and compressed into tablets. The average content was observed at 95-96% and uniformity of content (minimum-maximum) was observed at 88.2-101.4% [36].

Mixing of tetracycline (0.25% w/w) with spray dried lactose and fine grade of crystalline lactose was conducted. At this concentration both ordered and random mixing took place. Mixture quality was better (coefficient of variation = 1%) using a fine grade of crystalline lactose than with spray dried lactose (coefficient of variation = 4%) [37].

A 0.1% ordered mixture of cohesive salicylic acid and spray dried lactose excipient was stable when fluidized and no significant loss of salicylic acid occurred during fluid bed granulation. All batches of 100 and 350 mg tablets produced had a content coefficient of variation ≤ 4.6%, a weight coefficient of variation ≤ 1.5% [38]. Resemblance to an ideal ordered state in binary mixtures of sodium salicylate and mannitol was found with 0.15% drug proportion and the smallest particles [39].

### *Miscellaneous techniques*

#### Low steroid dose dry pharmaceutical preparation by dry mixing

Low dose steroid drugs can be prepared by dry mixing of drugs with excipients having a demixing potential of less than 10% and a binding affinity of greater than 80% (like spray-dried polyalcohols, granulated alpha-lactose monohydrate, and mixtures of these) followed by adding further excipients for direct compression and compressing the admixture into tablets or filling in capsules. This process results into good properties with regard to robustness and ruggedness, while the resulting dry mixtures are very homogenous with regard to content uniformity even with very potent steroids.

A dry mix sample containing micronized ethinyl estradiol and spray dried lactose was made by mixing lactose with ethinyl estradiol for 2.5 mins. and good content uniformity (± 0.5%) was observed. Similarly ethinyl estradiol and 3-ketodesogestrel tablets, ethinyl estradiol and desogestrel tablets, desogestrel tablets, digoxin tablets were prepared using a dry mix process [40].

#### Dry blending with jet milling

Microparticles of active drug were blended with excipients and jet milling was used to deagglomerate microparticle aggregates formed during or subsequent to production of microparticles, by bombarding the feed particles with high velocity air or other gases. By proper selection of jet milling conditions, deagglomeration of microparticles were achieved without altering the size and morphology of particles. Typical jet mills used in process could include spiral jet mills, loop jet mills, fluidized bed jet mills, with or without internal air classifiers and blenders could be V-blenders, slant-cone blenders, dynamic continuous blenders, orbital screw blenders, planetary blenders, forberg blenders, horizontal double-arm blenders, horizontal high intensity mixers, vertical high intensity mixers, tumble blenders to attain satisfactory blend uniformity [41].

#### Homogeneous preformulations containing high concentrations of steroids, for producing low-dose solid and semi-solid pharmaceutical preparations

The technique of making the homogeneous steroid-containing preformulation includes the dissolving steroid(s) in a solvent (ethanol or a mixture of ethanol and water) to form a dispersant and dispersing an adjuvant consisting of adjuvant particles in the dispersant in a mass ratio of adjuvant to the steroid(s) of 1:1 to 1000:1 to form a suspension. Then, a spray-mist of the suspension is used so as to evaporate and remove the solvent from the suspension and thus to form a dried

particulate comprising a plurality of steroid-containing particles. The steroidal preformulations thus produced are mixed dry in a suitable mixture together with other direct-tablet adjuvants and then filled into hard gelatin capsules or in the form of an oily suspension in soft gelatin capsules, or tableted in the usual way. The tablets are made into lozenges or coated in aqueous or organic fashion, together with the usual, known adjuvants.

The process parameters to be controlled include particle size distribution of the active ingredient, solid concentration of the suspension, droplet size distribution in the spray mist, air inlet temperature, air outlet temperature, temperature for inflow of the suspension, spray pressure, nozzle size, drying air etc.

Preformulation of tablets containing 250 µg of sulfamate steroid was achieved using ethanol solvent, adding lactose monohydrate and then drying using drier with a dual-substance nozzle in the parallel flow process. The relative standard deviation was observed 1.28%. Similarly preformulation of desogestrel and ethinyl estradiol was done with satisfactory results [42].

**Process for preparing solid unit dosage forms of ultra-low dose drugs using spray drying**

In this technique active material is dissolved in a volatile solvent (methylene chloride, ethyl acetate, ethanol, methanol, fluorinated hydrocarbon (Freon)) and mixtures of these to form a very dilute solution of the active material. This solution is atomized and sprayed, in the form of a fine spray or mist of droplets of substantially uniform size, in a small amount, supplied over an extended period of time, onto fine, inert, excipient particles (insoluble in the solvent) that are undergoing continuous agitation (in an inclined rotating tumbler pan to ensure even distribution of the drug solution on the excipient particles) in a surrounding gaseous medium (to facilitate evaporation of the solvent) so that the droplets are substantially uniformly deposited on the excipient particles. The solvent is continuously and slowly evaporated into the surrounding gaseous medium and thereby a large number of very small solid particles of the active material become deposited uniformly on the excipient particles, without the occurrence of substantial agglomeration of the excipient particles or build-up of significant wetness in the excipient powder. Upon completion of the spraying and evaporation, the excipient particles having the very small amount of the active material deposited thereon are formed into individual solid unit dosage forms, such as tablets. Process parameters to be controlled include spraying rate of drug solution, total spraying time etc.

This technique is very useful to reduce particle size when milling cannot be used because drug particles are not monodispersed or in the case of heat labile drugs which on micronization are soften/melt and then agglomerated during micronization. Examples of known drugs advantageous for use in this technique include various prostaglandins, oxytocin and other peptides, vasopressin, vitamin $B_{12}$, VIP analogs, LHRH analogs etc [43].

**Manufacturing a low dose pharmaceutical composition having uniform drug distribution and potency utilizing silicon dioxide**

The process includes use of silicon dioxide (concentration 0.1 to 2%) for reducing the loss of active ingredients that adhere to the metal surfaces of equipment during the manufacturing process of a pharmaceutical composition or medicament. The addition of other glidant such as talcum or addition of a manual brushing step did not resolve the problem.

In this process silicon dioxide is blended with excipient, carrier or diluent in a high shear granulator to produce a blended mixture, and then active ingredient is added to the granulator and blended for an additional period of time to form an active blend. The active blend is transferred from the granulator to a blender like twin shell “V” or bin blender. Other excipients, lubricants, carriers or diluents to the active blend are added if required and blended for a suitable period of time to form a pharmaceutical composition having uniform distribution of the active ingredient and uniform potency. The resultant blended composition may then be processed further into a desired unit dosage form.

This process provides efficient mixing and a more uniform distribution of the active ingredient without

significant degradation of the active ingredient. Loss of lasofoxifene due to adherence to metal surface of the blender can be minimized by means of silicon dioxide [44].

**Spray-on liquid drug carrier**

The model drug is dissolved in a non-volatile solvent, propylene carbonate and sprayed onto a compressible sugar at a loading of around 0.01% by weight of drug to total solid, to give a final unit dose of 35 μg. The solvent, being non-volatile, remains in the blend. It is added at around 5% by weight of the total formulation. Lower ratios of solvent to solid resulted in decreased ability to disintegrate and dissolve. The result, somewhat sticky powder, showed some difficulties in automated encapsulation machines and would be likely to give significant problems in tabletting [45].

Formulation of rasagiline (1.6 mg) were prepared by wet granulation. The dry granulate was milled in an oscillating granulator to reduce particle size of drug less than 250 μm. A lubricated blend was then prepared using a tumbler blender. The mixture was then pressed into tablets. Content uniformity of tablets ranged from 98.6 to 100.6% and RSD was lower than 2.0%. [46]. Similarly formulation of metformin/glibenclamide includes mixing step using tumbling mixer to achieve content uniformity [47].

Formulations of entecavir (0.01-10 mg active drug) were prepared by dissolving drug and adhesive (povidone, methyl cellulose, guar gum, gelatin etc) in a solvent (water or water having a acidic and basic pH to increase solubility of drug) at temperature 25-80 °C and spraying this solution onto a carrier (lactose, microcrystalline cellulose, dextrose, mannitol, sorbitol, calcium phosphate, etc.) in motion by mechanical means in fluid bed drier or air stream agitation, drying, adding dried coated carrier with other necessary excipients to produce capsule or compressed tablets [48].

In spray drying technique, during handling of a mixture, demixing of active drug from carrier may occur due to difference in densities. This demixing can be prevented by adding an excipient having high specific surface area and a high electrostatic charge like silicon dioxide. This excipient is added to the carrier excipients before spraying the active drug solution. Formulations of warfarin sodium tablets (1, 2, 2.5, 3, 4, 5, 6, 7.5, 10 mg) were done by spray drying technique using silicon dioxide to prevent demixing of components with satisfactory content uniformity [49].

Micronized fentanyl citrate (1-10 μm) have self aggregating properties which can be prevented by blending drug with hydrated dextrose to yield a matrix wherein drug particles are uniformly distributed over the surface of dextrose particles. The adsorption energy of the drug over excipient enables particle to break self aggregation. Oral transmucosal lozenzes of fentanyl citrate (200, 400, 1600 μg) were prepared using dextrose to prevent aggregation of drug particles with content uniformity in average of 100.8, 100.7, 98.4%, respectively, with %RSD of less than 3% [50].

Formulations of [R-(Z)]-α-(methoxy-imino)-α-(1-azabicyclo [2,2,2]Oct-3-yl)acetonitrile monohydrochloride tablets (drug 5, 12.5, 25, 50, 75 μg per unit dose) were achieved by dissolving drug in water and adding to lactose monohydrate (directly compressible vehicle) in a high shear granulator, blending with magnesium stearate as lubricant and colloidal silica as glidant and compressing to tablet with satisfactory content uniformity [20].

**Table 3** List of formulation techniques used for low dose dosage forms

| No. | Name of technique | Problem solved/advantages of techniques | Example of drug(s) | Major excipients used | References |
|---|---|---|---|---|---|
| 1 | Wet granulation | Improvement of cohesiveness and compressibility of powders. Good distribution and uniform content of micronised or finely milled low dosage drugs. Reduction of a grate deal of dust and air borne contamination. Prevention of segregation of components | Desogestrel, Ethinyl estradiol | Calcium phosphate(di- and tribasic), Gelatin, Calcium sulfate dihydrate, Water soluble modified starches, Poly vinyl pyrrolidone, Sugars, Lactose | [15] |
| 2 | Modified wet granulation | Useful for drugs insoluble in water. Prevent migration of drugs through the carrier upon drying | Estradiol, Estrone Ethinyl estradiol, Methyl testosterone, Compound 2 | Lactose 316, Nonoxyl, MCC, Croscarmelose sodium, Polysorbate 60, Polyoxyl 20 cetostearyl ester | [16,17] |
| 3. | Fluid bed granulation | Rapid granulation and drying of a batch. Granulation prevents adhesion unit and constituent segregation occurring during compression. Eliminates the adverse effects caused by differential solubility and hydrophobicity of the components | Micronized salicylic acid, Compound 1 | Poly vinyl pyrrolidone, Lactose monohydrate, MCC (Avicel PH 102) | [18] |
| 4 | Spray drying using viscosity increasing excipients | Prevention of segregation. | Dexamethasone | Starch, Povidone, Pre gelatinized starch, Hydroxypropylmethyl-cellulose, Methylcellulose | [21] |
| 5 | High shear granulation | Improvement in content uniformity. Full in process control | Compound 1 | Sodium citrate, dehydrate, Croscamellose sodium, MCC | [19] |
| 6 | Low shear granulation | Prevention of segregation of components. Reduction of a great deal of dust and airborne contamination | Desogestrel, Ethinyl estradiol | PEG 400, Corn starch, HPC, Lactose 200M | [23] |
| 7 | Novel foam granulation | Improvement in content uniformity | Propranolol HCl | Hypromellose 2910, Methyl cellulose | [25] |
| 8 | Fluid bed granulation with jet pulverization | Improvement in content uniformity | Metformin hydrochloride, Pioglitazone hydrochloride | MCC | [26] |
| 9. | Direct compression | Fluidity, compressibility and maintenance of content uniformity. Material handling is minimized | Diazepam, Fluoxetine | MCC, Microfine cellulose, Spray dried lactose, Compressible sugars, Sucrose-Dextran coprecipitate, Dicalcium phosphate dihydrate (Em compress) | [27,29] |
| 10 | Modified direct compression | Especially useful for formulating of drugs in which the unit dose is about 50 mg to 1000 mg. Unit operations are minimum | Compound x | Dicalcium phosphate dihydrate, Lactose, Compressible sucrose, MCC, Modified starches, Mannitol, Ethanol, Methanol, Acetone, Tetrahydrofuran | [30] |
| 11 | Method of dry blend compression of potent drugs with low solubility using directly compressible agglomerated excipients | Eliminate recrystallization and the issue of polymorphism and bioavailability observed during wet granulation | Estradiol | Granular mannitol, Agglomerated maltodextrin, Corn syrup solids | [16] |

**Table 3** List of formulation techniques used for low dose dosage forms (Cont.)

| No. | Name of technique | Problem solved/advantages of techniques | Example of drug(s) | Major excipients used | References |
|---|---|---|---|---|---|
| 12 | Active layering and direct compression of sugar spheres | Increase reproducity in tablet weight and hardness.<br>Prevention of segregation.<br>Improvement in content uniformity | Acetamenophen,<br>Ketoprofen | Sugar spheres, PEG 6000, Xanthan gum base, Carbopol | [33,34] |
| 13 | Ordered mixing / interactive mixing | Prevention of segregation.<br>Promote excellent homogeneity in mixtures.<br>Improvement in content uniformity | Fentanyl citrate,<br>Sodium salicylate, Digitoxin | Coarse mannitol, PVP, Magnesium stearate, Silicified MCC | [35,36] |
| 14 | Low steroid dose dry pharmaceutical preparation by dry mixing | Minimize demixing.<br>Suitable for drugs which are sensitive to moisture or are unable to withstand the elevated drying temperatures associated with wet-granulation methods | Ethinyl estradiol,<br>3-ketodesogestrel,<br>DMP 543, Digoxin | Spray-dried polyalcohols, Spray-dried lactose, Cellactose( 75% lactose and 25% cellulose), Spray-dried mannitol, Sorbitol, Cellulose, Xylitol, Dextrose, Fructose | [9,40] |
| 15 | Dry blending with jet milling | Elimination of need of complicated wet deagglomeration process.<br>Increase stability of formulation by lowering moisture and solvent levels in microparticles.<br>Improvement in content uniformity | Alprazolam, Ziprasidone | Tween 80 | [41] |
| 16 | Homogeneous preformulations containing high concentrations of steroids, for producing low-dose solid and semi-solid pharmaceutical preparations | Good stability of the active ingredient distribution in the pharmaceutical preparation.<br>Nonhomogeneities and demixing or sizing effects during the subsequent mixing process are avoided.<br>Applicable to thermally unstable steroids like sulfamates.<br>Stable to demixing and nonhomogeneities.<br>No clumping and changes in activity of active ingredients | Desogestrel, Ethinyl estradiol, Sulfamate steroid | Lactose monohydrate, Ethanol | [42] |
| 17 | Spray drying | Improvement in content uniformity.<br>Applicable for heat labile drugs | Compound 1 | Povidone, Lactose Monohydrate, MCC | [19,43] |
| 18 | Manufacturing a low dose pharmaceutical composition having uniform drug distribution and potency utilizing silicon dioxide | Reduce the loss of active ingredients that adhere to the metal surfaces of equipment during the manufacturing | Lasofoxifene | Silicon Dioxide, Lactose, MCC, Croscarmellose sodium. | [44] |

**Abbreviations:** Compound x = (2S, 12bS)-1',3'-dimethylspiro-(1,3,4,6,7,12b-hexahydrobenzo[b]furo[2,3-a]quinolizin)-2,4'-(5',6'-dihydro-1'H-pyrimidine-2'(3'H)-one). Compound 1 = 2-methyl-2-[4-{[(4-methyl-2-[4-trifluoromethyl phenyl]-thiazol-5-ylcarbonyl)amino]methyl}phenoxy]propionic acid. Compound 2 = (2R)-(1 alpha, 5 alpha, 6 alpha)-N-[3-azabicyclo [3.1.0] hexyl-6-(aminomethyl)-yl] -2-hydroxy-2-cyclopentyl-2-phenyl acetamide hydrochloride. DMP 543 = 10,10-bis(2-fluoro-4-pyridinylmethyl)-9(10H)-anthracenone. MCC = Microcrystalline cellulose.

## Conclusions

Mixing and formulation of low dose drugs are sophisticated work and involves lot of problems related to segregation, content uniformity and physical stability which can be controlled by right selection of material, method and machine. New and novel excipients have improved the science of low dose drug formulation. Advancement in processing parameters by optimizing various processes related parameters has put a stringent control on factors leading to segregation in powder mixtures. Processing and transfer steps are minimized to increase homogeneity in formulations. A summary of recent formulation techniques for low dose drugs have been provided in Table 3. Low dose drug formulations require micronisation to increase the number of particles of drugs which could be blended with other excipients to increase homogeneity in the formulation as well as final dosage form. The formulations are designed by various techniques to obtain granules, agglomerates or ordered mixtures so as to avoid segregation and handling issues.

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