ISSN: 0976-3031

Available Online at http://www.recentscientific.com

CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 9, Issue, 2(F), pp. 24226-24230, February, 2018

International Journal of Recent Scientific Research

DOI: 10.24327/IJRSR

Review Article

CRYSTALLO CO-AGGLOMERATION-A REVIEW

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DOI: http://dx.doi.org/10.24327/ijrsr.2018.0902.1621

ARTICLE INFO

Article History:
Received 05th November, 2017
Received in revised form 21st December, 2017
Accepted 06th January, 2018
Published online 28th February, 2018

Key Words:

Crystallization, Agglomeration, Direct compression, Excipients, Spherical.

ABSTRACT

Modification of formulation and process parameters to improve the quality of existing dosage forms is an important branch of the pharmaceutical research. Development of crystal agglomerates as well as drug-excipient co-agglomerates to improve the flow property is one of the latest addition in this field. Spherical agglomeration is a novel technique to produce spherical crystals which are reported to have better bioavailability. Crystallo co-agglomeration is a type of spherical agglomeration technique, which enables both crystallization and agglomeration to be done simultaneously of two or more drugs to yield complex agglomerates of drug and excipients. These techniques are useful to yield directly compressible crystal/agglomerates to achieve fast dissolving tablet as well as modify the drug release for controlled release dosage form. The objective of this article is to review the status of research in this field. Different strategies used to develop drug-excipient agglomerates, their pharmaceutical applications as well as factors affecting rate processes of agglomeration are also included.

INTRODUCTION

In spite of the great advances in novel drug delivery, conventional tablet is the most popular and widely used dosage form. The unparalleled popularity of tablets both among the manufacturers and the consumers is due to its stability and ease of administration. But certain problems still complicate the manufacturing of tablets, which is a multi-step process. A long sequence of events takes place before an active ingredient could be ready to be processed as tablets. As scope of improvement exists in each of the manufacturing steps like mixing, blending, granulation, drying and compression, there are continuous efforts for simplifying the procedures as well as improving the product quality using newer strategies. In this context, making of spherical crystal agglomerates, which is one of the techniques for crystal size growth, is recently gaining prominence. Many pharmaceutical parameters for example, bulk density, flow property, compactibility, cohesiveness, dissolution rate and stability depend on the crystal habits (form, size, surface and particle size distribution) and can be modified by controlled crystallization[1-2]. Kawashima *et al* with their pioneering work had given the initial impetus on spherical crystallization technology in the pharmaceutical field [3]. Later, it was established that drug materials prepared by the spherical crystallization technique are economical for the development of the solid dosage forms [4]. However, the spherical crystallization technique cannot be used effectively for low-dose drugs and for developing agglomerates in combination of two or more drugs. Crystallo co-agglomeration, a type of spherical crystallization is free of this difficulty. In crystallo co-agglomeration, crystallization and agglomeration can simultaneously be carried out to obtain agglomerates of two or more drugs or drugs with excipients[5-8]. The objective of this article is to review the research in this field.

Crystallo co-agglomeration (CCA) technique

CCA is a novel technique, which uses the processes of crystallization and agglomeration simultaneously to be done of two or more drugs. Basically it yields complex agglomerates of drug and excipients, which are directly compressible in

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nature. The term crystallo-co-agglomeration (CCA) indicates crystallization takes place concurrently with another moiety which may be a drug or external inert material. Spherical crystallization technique has limited application to only high actives whereas CCA was can be used for both high and low dose actives. However this technique is used for other purposes too. So far it has been exploited to achieve the following objectives.

Pharmaceutical applications of crystallo co-agglomeration

Drugs with large dose can be directly compressed with excipients using crystallo co-agglomeration process. Low dose drugs can be agglomerated with excipients to give sustained release formulations with predictable dissolution pattern. The process can be used to improve number of properties: micromeritic properties (flowability, packability, compressibility) mechanical strength of particles, ,for avoiding contamination due to dust generation ,improving solubility and dissolution character of poorly soluble drugs[9-10] .However, the technique is not universally applicable. It is not suitable for poorly compressible excipients as well as low dose (potent) drugs.

General strategies adopted for obtaining agglomerates

The methods for obtaining agglomerated crystals can be categorized on the basis of achieving super saturation. The selection of method mainly depends on the nature of the drug and excipients as well as the objective of the study. In general, drugs and excipients are dissolved separately in their respective solvents. Next, both are mixed in glass vessels with high-speed rotation (approximately 900 – 1000 rpm) to achieve uniformity. The mixture turns cloudy once the agglomerates are formed. Agglomerates are collected by filtering and kept for drying overnight at room temperature.

Some of the methods for achieving agglomerates are given below-

Spherical agglomeration method

This method employes, a quasi-saturated solution of a drug in a miscible solvent, which is poured into a poor solvent of the drug. It is essential that the good and the poor solvents are freely miscible and the binding force between the solvents is stronger than the solvent-solute interaction force with good solvent, for the crystals to precipitate immediately. Next an adequate amount of a third solvent, which is not miscible with the poor solvent but substantially wets the precipitated crystals, is added to the system by continuous stirring. The third solvent or the 'bridging liquid' collects the crystals suspended in the system by forming liquid bridges between the crystals due to the combined force of capillary pressure and interfacial tension at the interface of solid and liquid[11].

Quasi-emulsion solvent diffusion method

This method is applied when interaction between the drug and the good solvent is stronger than that of the good and poor solvent. First, concentrated drug solution is dispersed in the poor solvent, which produces quasi emulsion droplets due to an increase in interfacial tension between good and poor solvent. Next, the good solvent diffuses gradually out of the emulsion droplets into the outer poor-solvent phase. The counter-diffusion of the poor solvent into the droplet induces crystallization of the drug within the droplet due to its decreased solubility in the poor solvent. This process is known as the emulsion solvent diffusion process.

Ammonia diffusion method

This method can be applied to amphoteric drugs only. It consists of three components: ammonia water acting as good solvent as well as bridging solvent, a bad solvent and a hydrocarbon/halogenated hydrocarbon. The hydrocarbon should be miscible with the system but it should reduce the miscibility of ammonia water with the bad solvent. First, the drug which is dissolved in ammonia water is precipitated and the crystals are collected. Simultaneously as ammonia in the agglomerates diffuses to the organic solvent, its capability to act as a bridging liquid weakens and subsequently spherical agglomerates are formed [12]. Number of researchers has studied the effect of various factors on quality and quantity of agglomerates**.**

Factors Affecting Agglomeration

Physicochemical parameters specifically the drug solubility is shown to have highly significant effects on quality of agglomerates [13]. Crystallization is affected by formulation parameters like source, grade and concentration of excipients used [14]. The type of the polymer usually affects the quality of crystallization [15]. The experimental methodology like type of bridging liquid, concentration of bridging liquid, temperature, agitation speed, and mode of addition of bridging liquid also affect the quality of agglomerates [16]. Process parameters like stirring and cooling rate can affect the final yield [17].

Stages of Growth of Agglomeration

The growth of agglomerates follow a sequence of zonal divisions- namely, flocculation zone, zero growth zone, fast growth zone, and constant size zone. In the flocculation zone, the bridging liquid displaces the solvent from the surface of the particle and and loose flocs are formed by pendular bridges. In the zero growth zone, the loose floccules convert into tightly packed aggregates. The entrapped liquid seeps to the surface of the small floccules. In the zero growth zone, the squeezing out of the bridging liquid from the pores of the initial floccules for the formation of the small agglomerates is the rate-limiting step in agglomeration growth process. The fast growth zone can be observed at the point where the sufficient amount of bridging liquid has been squeezed out of the surface of the small agglomerates.[39] In the process of coalescence, the large size particles form by the random collision of the well-formed nucleus. For the collision process to be successful, slightly excess surface moisture on the nucleus is required. The constant size zone involves the arresting of agglomeration growth. Even a slight reduction of size of agglomerates is seen due to attrition, fracture, and shatter.[38]

A Review of CCA Research

In spite of its considerable potential for industrial application, the field of CCA research is still in infancy. Work had been carried out at university and institutions but the work is mainly confined to the laboratory levels. While efforts have taken to modify and diversify the processes of CCA, paracetamol, ibuprofen and some common NSAIDS have been used as

model drugs. Given below is a glimpse some important research on CCA.

Preparation of the ibuprofen agglomerates using talc as the main excipient using spherical crystallization technique to formulate crystals of ascorbic acid for direct tableting and evaluation of their compatibility.[5]

Development of a new method for characterization of the release of drugs from single agglomerates.[13]

Development of directly compressible naproxen –disintegrant agglomerates using CCA technique. The growth of particle size and spherical shape of the agglomerates resulted in formation of products with good flow and packing properties. The properties of agglomerated crystals, such as flowability, compactibility and dissolution rate were profoundly improved over that of conventional granules[18].

Study of preparation of deformable agglomerates of talc with poorly compressible bromhexine hydrochloride. The agglomerates obtained were found to have good mechanical, compression, and drug release kinetics[19].

Development of agglomerates of nabumetone and mefenamic acid to improve micromeritics and solubility of the drugs using spherical agglomeration technique[20].

Investigation of the spherical crystallization using the drug celecoxib[21]. Study of optimization of crystallization conditions using ibuprofen- eudragit S100 combination[22].

Study of the static compression behavior and tabletabilities of spherically agglomerated crystals produced by the spherical crystallization technique with a two – solvent system[23].

Preparation of spherical crystals of mefenamic acid using ammonium diffusion technique and the physical properties of the spherical crystals were compared with those of mefenamic acid powder. The crystals demonstrated good flow and compressibility and had more wet tability than the drug powder[24].

Study of the drugs of poor water solubility and compressibility. The poorly soluble Flurbiprofen conventional drug crystals were converted into spherical crystal agglomerates via the spherical crystallization technique using acetone-water-hexane solvent system. These were characterized for micromeritic properties (particle size and shape, flowability), packability (bulk density), wet tability (contact angle) and compressibility. The study revealed that spherical agglomerates exhibited improved flow ability, wet tability and compaction behavior.[14] Ibuprofen and rifampicin are high dose drugs and are known to have compression related problems. Preparation of directly compressible tablets of rifampicin and ibuprofen. These drugs were modified to directly compressible forms by granulation and spherical crystallization technique.[17]

Working of improvement in flow ability and compressibility of ampicilin trihydrate by spherical crystallization. Spherical crystallization was carried out by ammonia diffusion method to achieve agglomerates of primary crystals of the drug [25].

Spherical agglomerates of steroid KSR-592, consisting of fine primary drug crystals suitable for dry powder inhalation were also prepared [26].

Working on the CCA technique which could be successfully employed as an alternative to conventional wet granulation by an integrated approach of principal component analysis and Box–Behnken experimental design to prepare and evaluate agglomerated crystals by crystallo-co-agglomeration [27]

Development of the process by using quasi-emulsion solvent technique itraconazole can be made into spherical crystal agglomerates using soluplus and PEG to enhance its solubility and hence its increase in bioavailability is seen .[28]

The method by which crystal modification of Phenytoin with PEG the bioavailability, dissolution rate and mechanical strength can be improved[29].

The development of a method by utilizing acetone-acetonitrile system spherical agglomerates of Fluvastatin sodium was prepared in presence of Eudragit RS100 and RL100 as release retardant polymers which was designed and evaluated to produce ready to compress sustained release spherical agglomerates [30].

Spherical agglomerates of acetylsalicylic acid by a system of good and poor solvents as well as bridging liquid in which alcohol, water and carbon tetrachloride were used as the good solvent, poor one, and bridging liquid, respectively after which they were subjected to a tableting process[31] about the effects of polyethylene glycol on the size of agglomerated crystals of phenytoin prepared by the spherical crystallization technique [32].

Development of spherical agglomerates of valsartan by crystallo-co-agglomeration technique by using alcohol-chloroform-water system as a crystallizing medium. PVP K30, PEG 4000 and sodium alginate were used as carriers. . FTIR and DSC studies showed that valsartan particles, crystallized in the presence of PVP K30, PEG 4000 and sodium alginate showed compatibility with carriers[33].

Preparation of directly compressible agglomerates of Meloxicam-Paracetamol containing desired ratio of drugs using a crystallo – co- agglomeration technique which proved that it can be used to design immediate release Meloxicam-paracetamol agglomerates with varying concentration of polymer[34].

Combined crystallization and agglomeration were used to directly generate spherical crystals with improved micromeretic properties, thus obviating need for further processing by granulation and agglomeration to make spherical crystals of mebendazole to improve processability[35].

Evaluation Parameters of Agglomerates

Yield: Yield of the agglomerates is the most crucial of all the evaluation parameters. Active ingredients are expensive and if the yield of the drug agglomerates complex is below 80-90%, (depending upon cost) the process may become commercially unviable. So far the yield reported by various researchers in range between 90 to 98 %.

Drug content

This represents the percentage of drug in the drug-agglomerates complex. In simple terms it is the percentage purity. Data obtained from CCA studies vary widely regarding this aspect. Some of the researchers had reported that the drug content

between 51 to 58% was optimum. The increase in bulk due to incorporation of excipients in the drug-agglomerate complex is thought to be advantageous for the formulation of potent drugs. However, it could be a problem where the dose is high.

Micromeritic properties

This property is the most important in terms of compressibility. During the compression particles are deformed or broken under pressure. Resistance to the pressure is intrinsic property of the crystals. Hence micromeritics of drug-agglomerates is an evaluation parameter.

Surface topography

Surface character of the drug-agglomerate becomes important in terms of binding, finish and glossiness. Increased compression pressure makes smoother tablet surface , which increases the acceptability. A change in surface roughness was thought to be the most likely reason [40]. Hence surface topography is an important evaluation parameter.

Drug-excipient interaction

From formulation viewpoint, drug-excipient interactions may be categorized in two types; (1) planned or intentional interactions and (2) accidental interactions. Drug-excipient interactions may affect the stability of the formulation. They may lead to either enhanced or reduced stability. It is desirable the pharmacological property of drug in the agglomerates remain unaffected. Whether or not the nature of the drug is influenced by CCA process is ascertained by infrared spectroscopy as well as differential scanning colorimetry.

Compressibility

Compressibility is a measure of the relative volume change of a fluid or solid as a response to pressure change. The shape and size of crystals in physical mixture decide the compressibility of the tablet. It reflects packing characteristics of particles and also depends on the porosity of material. In the CCA, drug and excipient are made into coherent mass due to the natural affinity for each other and this process ensures higher homogeneity than any form of physical mixture. The agglomerates, when tableted, result in more uniform packing and less weight variation. Hence compressibility is an important evaluation parameter for drug-excipient agglomerates.

In vitro dissolution study

It is the most important parameter. Tablets need to dissolve in the dissolution media to release the active ingredient. The rate and extent of drug release in a dissolution media is often related to bioavailability. Usually drug release is studied by U.V. spectrophotometers at a suitable wavelength and also by HPLC.

CONCLUSION

This field of CCA research is still in infancy. However, it is likely to have a strong impact on formulation development as it has the potential to be used in controlled release/fast release/directly compressible purposes too. Smart choices of polymers and diluents can extend the release of drug or can improve dissolution of poorly soluble drugs.

Number of Indian workers has shown interest in the CCA technique. But so far mostly work was confined to some anti-inflammatory molecules. The main difficulty encountered is cost. Hence only cheap and easily available active ingredients have been subjected to this research so far.

Two approaches have been used so far-

- Drug-drug co-agglomerates
- Drug- excipient co-agglomerates

The studies on the mechanism and factors are rare. However the groups have studied various dug molecules which have succeeded in minimizing the steps of production ensuring better distribution. But these agglomerates itself will introduce a few step, increase the cost and also decrease the flexibility.

So, the survivability of the experiments will depend upon the ultimate cost against the benefit offered. Cost of production of agglomerate and cost of tablet is likely to be more , but the benefit should over-weigh this cost – balance. Greater support from industry as well as academia is needed to develop this branch of formulation research.

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