ИЗВЕСТИЯ ВЫСШИХ УЧЕБНЫХ ЗАВЕДЕНИЙ.
Т 61 (12) Серия «**ХИМИЯ И ХИМИЧЕСКАЯ ТЕХНОЛОГИЯ**» 2018

IZVESTIYA VYSSHIKH UCHEBNYKH ZAVEDENII
V 61 (12) **KHIMIYA KHIMICHESKAYA TEKHNOLOGIYA** 2018
RUSSIAN JOURNAL OF CHEMISTRY AND CHEMICAL TECHNOLOGY

DOI: 10.6060/ivkkt.20186112.5896

УДК: 621.927

ПРОМЫШЛЕННОЕ СМЕШИВАНИЕ ДИСПЕРСНЫХ МАТЕРИАЛОВ: СОВРЕМЕННАЯ ПРАКТИКА И БУДУЩАЯ ЭВОЛЮЦИЯ

C. Gatumel, H. Berthiaux, В.Е. Мизонов

Смешивание порошкообразных материалов является частью нашей повседневной жизни, но и источником озабоченности промышленности. Смешивание широко распространено во многих отраслях промышленности, но проектирование технологии смешивания и смесительного оборудования скорее принадлежит инженерному искусству, чем научно обоснованному расчету. Каждая отрасль промышленности накапливает свой опыт в этой сфере, базирующийся, главным образом, на продолжительных и трудоемких экспериментальных исследованиях, и очень часто эти результаты не могут напрямую использоваться в других отраслях, то есть проблема моделирования и расчета смешивания далека от универсальности. Поэтому очень важно выделить среди частных отраслевых задач общие межотраслевые задачи теории и практики смешивания и сосредоточить внимание исследователей и инженеров на их решении, чтобы создать общий базис для научно обоснованного проектирования технологии и оборудования для смешивания. Текущие проблемы связаны с определением однородности смесей, путями ее измерения, техникой и ошибками отбора проб, сегрегацией смесей в ходе их переработки, выбором смесителей, а также техническими предложениями по смесителям. В данной статье дан обзор этих аспектов и сделана попытка выявить некоторые перспективы из комбинированного промышленного опыта с позиций химической инженерии: применение техники онлайн мониторинга для достижения однородности смеси и управления процессом; совершенствование процедур масштабного перехода; оптимизация конструкций и режимов работы смесителей; развитие новых многофункциональных универсальных технологий непрерывного смешивания; завершение разработки актуальных стандартов для однородности дисперсных материалов на основе введения структурированной информации.

Ключевые слова: дисперсный материал, смешивание, сегрегация, конструкция смесителя, управление процессом, оптимизация, качество смешивания

INDUSTRIAL MIXING OF PARTICULATE SOLIDS: PRESENT PRACTICES AND FUTURE EVOLUTION

C. Gatumel, H. Berthiaux, V. Mizonov

Powder mixing is a part of our everyday life, but is the source of major industrial preoccupations. Mixing is widely used in many industries but until now design of mixing technology and mixing equipment belongs sooner to engineering art than to scientifically based calculation. Each branch of industry develops its own experience in the field mostly based on time and labour consuming expe-rimental research, and very often the obtained results cannot be used directly in

another branch, i.e., the problem of mixing simulation and calculation is far from universality. This is why it is very im-portant to separate from particular sectorial problems the general intersectorial problems of theory and practice of mixing and concentrate the attention of researchers and engineers on them solution to build the general basis for scientifically based design of mixing technology and equipment. Current problems are associated with the definition of the homogeneity of the mixtures, the ways of measuring it, the sampling errors and techniques, the segregability of the mixtures in the powder handling operations, mixer choice, as well as mixer conception. In this paper, we review such aspects and try to draw some perspectives from a combined industrial experience – chemical engineering approach: the development of on-line monitoring techniques to assess homogeneity and further con-trol the process; the improvement of mixer's scale up procedures, as well as the optimisation of mixer design and operation; the development of new mixing technologies, multifunctional, nearly "universal", with a special emphasis on continuous processes; the completion of the actual standards on powder homogeneity by introducing structural information.

Key words: particulate solids, mixing, segregation, mixer design, process control, optimization, mixing quality

Dr. **Cendrine Gatumel**
eanchem@mail.ru*

Dr., Prof. **Henri Berthiaux***
berthiau@enstimac.fr*

Centre RAPSODEE, UMR CNRS 5302, Toulouse University, IMT-Mines Albi-Carmaux, Campus Jarlard, route de Teillet, 81000 Albi, France

Области научных интересов/ Research Interests:
Математическое моделирование и экспериментальное исследование смешения твердых тел

Mathematical modeling and experimental investigation of mixing of solids

Вадим Евгеньевич Мизонов
Dr., Prof. **Vadim Mizonov**, mizonov46@mail.ru

Ивановский государственный энергетический университет, Рабфаковская, 34, Иваново, Российская Федерация, 153003
Ivanovo State Power Engineering University, Rabfakovskaya, 34, Ivanovo, 153003, Russia

Области научных интересов/ Research Interests:
Применение цепей Маркова в химической технологии
Application of Markov chains in chemical engineering

Для цитирования:
Gatumel C., Berthiaux H., Мизонов В.Е. Промышленное смешивание дисперсных материалов: современная практика и будущая эволюция. *Изв. вузов. Химия и хим. технология*. 2018. Т. 61. Вып. 12. С. 4–13
For citation:
Gatumel C., Berthiaux H., Mizonov V. Industrial mixing of particulate solids: present practices and future evolution. *Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol.* 2018. V. 61. N 12. P. 4–13

Industrial and social relevance of powder mixing

The wide majority particulate products sold in the market today are mixtures and those who are not, have probably been homogenised in particle size to avoid segregation. Mixtures are everywhere: salt for cooking also contains NaI and anti-agglomeration additives; a current pharmaceutical drug may contains several active ingredients and perhaps 10 excipients including starch, sugar and an aroma; icing sugar is made of sugar and starch; typical cement composition includes 5 to 10 components. All industrial sectors are concerned with mixtures: cosmetics, cements, agro-food, pharmaceutics, plastics, pigments, chemical specialties, wooden products, etc.

Industrial efforts are concentrated on obtaining a product at lower running and environmental costs, able to meet end-users needs, which are principally based on its composition and visual aspect. Consumers generally all consider that the product they have bought has exactly the same composition as the one announced in the package, whatever the scale. This may be the fact of marketing efforts, but not only: our trust in mixtures is close to a sort of social faith, although not all the mixtures are socially equal

regarding homogeneity. Consider salted peanuts for example: if it contains too much salt, it will be said "these salted peanuts does not fit my consumer's hopes". Consider a drug: if it does not contain enough active ingredient (API) to provoke a therapeutic effect, one will judge "the patient does not fit the treatment".

A mixing step inside a process is always a crucial operation, in which functional properties or quality attributes are to be fixed, and sometimes controlled. Engineers working with powders are currently faced with problems associated with mixture quality. They have to integrate more or less advanced statistics to understand sampling, cope with different standards and practices, but also with a wide range of available technologies. If one wants to improve its mixing practice, the following questions will be addressed:

What is mixture homogeneity? How can we measure it? Do we have standards? Do they really suffice to describe our problem?

Is the mixture robust? How can we avoid segregation? Do the following process steps will destroyed the quality of the mixture?

What type of mixer can we elect? Is there a "universal mixer"?

Do we require a specific study to validate the process? How long will it take?

It is therefore not surprising that, most of the time, the general tendency in the industry is to avoid any change, and to concentrate on the way to validate the actual mixing process with respect to quality insurance and traceability needs. Therefore, sampling is performed always in the conditions through which the process will be validated, operating conditions seems to be fixed forever and technological innovation remains somewhat unexpected.

The objective of this paper is first to review the actual practices concerning powder mixing processes, basically to what concerns the above questions. Then, we will discuss on future improvements of mixing processes and mixing understanding, as significant evolutions are profiling at more or less short terms.

Present practices and needs

Homogeneity definition and sampling practice

First of all, the quality of a powder mixture cannot be defined if there is no precision on the scale at which the mixture is observed. If this scale is the entire production, the whole batch, mixture quality is irrelevant. Conversely, if it is a single particle of a binary mixture, mixture quality will be zero. Normally, this scale of scrutiny corresponds to the size at which quality attributes pare to be attained, or in other words, under which defects have no importance on the functional properties. For drugs, it will be that of the unit dose a patient may take something between 10 mg and 5 g in typical human recipes, and perhaps 10 g to 500 g for cows or pigs. There is no sense to investigate the distribution of the API inside a tablet, unless it is a scored tablet. For salted peanuts, depending on the consumer's sampling ability, it may be between 1 to 5 peanuts. According to our own experience, industrialists that are suspecting to have problems in the mixing step are hardly able to define this scale of scrutiny.

Then, one may identify what is the component for which the mixture has to be qualified. This key component is logically the active ingredient, of therapeutic effect, for drugs. For current salt, it may be NaI. For many applications, it is an ingredient of small dosage, just because this makes its presence critical in the "unit dose". In the case of multiple key components, the analysis must be repeated for each "key" independently, which also makes the role of product formulation essential.

Let a mixture be composed of N unit doses, therefore corresponding to one batch in a discontinuous process, or a definite period of time in continuous operation. Mixture homogeneity is usually expressed through its segregation intensity by the variance or standard deviation σ in the composition x_i of key component for each dose, with respect to the mean content μ:

$$\sigma^2 = \frac{1}{N}\sum_{i=1}^{N}(x_i - \mu)^2 \qquad (1)$$

When compared to the size and filling of an industrial mixer, this one may contain from several hundreds of thousands to one or two millions times the unit dose. Until now, and probably for several additional years, it is not feasible to access to the exact value of the variance at full scale, so that sampling procedures are therefore employed to approach this criterion by taking n samples out of the N possible. This leads to define:

$$s^2 = \frac{1}{n}\sum_{i=1}^{n}(x_i - x_m)^2 \qquad (2)$$

In the above, x_m is the mean content of active ingredient in the samples. Finally, because a standard deviation only has a real significance if it is reported to the mean value, the coefficient of variation is employed:

$$CV = \frac{s}{x_m} \qquad (3)$$

In the whole pharmaceutical industry and in some parts of the food industry, homogeneity stand-

ards are all concerned with the above coefficient of variation. A CV value below 6% is required to qualify the process, otherwise the mixture is disregarded, and even so destroyed in the case of drugs. To avoid from this risk, much smaller CV values are requested during process qualification procedures. Typical acceptable values are below 2 or 1.5%, which means that mixers have to be extremely efficient, or in other word "optimised", to cope with this strong constraint. A part from these industries that are close to consumer's health problems, all the rest of the industries have in practice no "blocking" standard, and even so no standard at all, concerning homogeneity of their mixtures.

But getting back to sampling, the main problem is how to assess that s and σ are close enough to stay with the approximate value, with the ambiguity that a bad mixture will need much more effort to be detected than a good one? First a sampling "philosophy" must be developed into three points:

- Sample where it makes sense. In most cases, samples are taken inside the mixer, while the mixture has to be further discharged from the vessel to continue the process. Studies concerning the reliability of in-situ sampling protocols, through thieve probes for example, have demonstrated their inadequacy to describe the state of a mixture (Berman et al. [1]; Muzzio et al. [2]). For instance, one may always consider to sample at the outlet of a continuous mixer or during the discharge of a batch one. A 1D sampling protocol operating in a powder flow is incomparably more efficient (see fig. 1).

- Sample randomly, preferentially with random table of numbers, to avoid preferential sampling. In many industries, this rule is mostly violated by sampling through a never changing "map" of the mixer. Even if this guarantees that the whole apparatus volume will be under analysis, it may lead to pass over some possible singular zones.

- Sample at the scale of scrutiny. If samples are smaller, the homogeneity of the mixture will be under-estimated but in many cases, sampling is performed by taking a single sample of 5-10 times the unit mass, this sample being further divided into smaller ones, thus leading to non-random sampling.

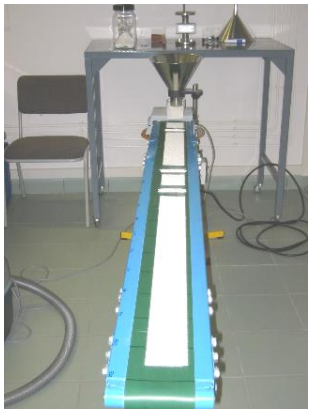

Fig. 1. Two 1D sampling procedures developed at lab-scale for a Turbula® batch mixer and at pilot-scale continuous mixer Gericke GCM500®
Рис. 1. Две одномерных процедуры отбора проб для лабораторного смесителя периодического действия Turbula® и для пилотного непрерывного смесителя Gericke GCM500

Then, a sampling technique must be defined and set to the specific problem, with probably a certain risk to assume. Since the Barr case (US vs Barr lab Inc. [3]), in which a pharmaceutical firm has been condemned by the US administration, the whole sector has employed many efforts to qualify its mixing processes. As an example, three criteria must be passed for putting a drug in the market otherwise the production is destroyed, which of course means a certain cost:

- The mean of the samples x_m. Even if there is always a sampling error, an important difference with the "true" mean μ can be indicative of a bad mixture. A typical criteria attached to this is: $\mu - 7.5\% \mu < x_m < \mu + 7.5\%\mu$;

- The individual values. A unit dose must contain the theoretical composition in key component with a certain tolerance. In practice: $\mu - 15\% \mu < x_i < \mu + 15\%\mu$. So in a tablet containing 1 g of paracetamol, one may expect to have between 850 mg and 1150 mg of the active;

- The coefficient of variation. It must be inferior to 6% during processing. As stated above, in process development, CV's of around 1 or 2% are the objectives to reach, also for limiting the risk of homogeneity loss during scale up.

Up to a certain extent, the above rules not only comment on the value of the CV, but also try to quantify indirectly the sampling procedure by comparing x_m to μ. It also introduces information of a

higher rank with the criteria on the “individual” compositions, as a very small variance can be obtained by compensation of overdosed and underdosed samples.

In parallel to the existence of these criteria for batch release, one may also be faced with the real practice. As stated above, sampling must be done at the scale of scrutiny, e.g. that of a tablet. If this can be done easily at the end of the process, it is not always feasible at that precise scale for the previous steps, including the mixing one, mainly because of sampler size and process accessibility (also resulting in higher sampling errors). In many cases, qualifying a mixing process is still doing everything, including “adapting” the sampling protocol, to prove that the mixture is good rather than stating whether it is good or bad.

Robustness of mixtures (segregability)

The processing steps, such as conveying, storage, that follow the mixing operation may cause severe de-mixing of the initial mixture. This also holds true for mixtures in which end-users have to sample themselves (such as salted peanuts or washing powder). It is therefore important to quantify whether a mixture will be sensible to this phenomena, or at the contrary will be robust enough. The industry is very much aware of this problem, in particular because each production steps have to be qualified in a process. Factors affecting segregation are basically:

- A difference in particle size, for which percolation of the small particles can take place. This has been widely commented in the literature so far and is likely to appear even during storage, because of unavoidable vibrations.

- A difference in particle density, especially for fluidised or pneumatic conveying systems.

- A difference in particle shape, spherical particles inducing much more segregation than irregular ones (Massol-Chaudeur et al. [4]).

- The lack of poly-dispersity of the particulate system with respect to the above properties. Indeed, it is much better to have multicomponent mixtures of very different particle sizes than a simple binary mixture of two particle sizes to avoid segregation. This is also the case for a single product of very wide particle size spectra.

Some few segregation tests have been developed by the industry and/or by universities (Popplewell et al. [5]; Harris and Hildon [6]; Schneider [7]). They all consist in placing a mixture in a critical step with regards to segregation, like during pouring a heap (see fig. 2), vibrating a sample, and measuring the homogeneity of the segregated mixture. Of course, the sampling aspects explained above still holds, but there is also the problem of examining the homogeneity of a poor mixture, which will require a higher number of samples than for a good one for the same precision in the analysis.

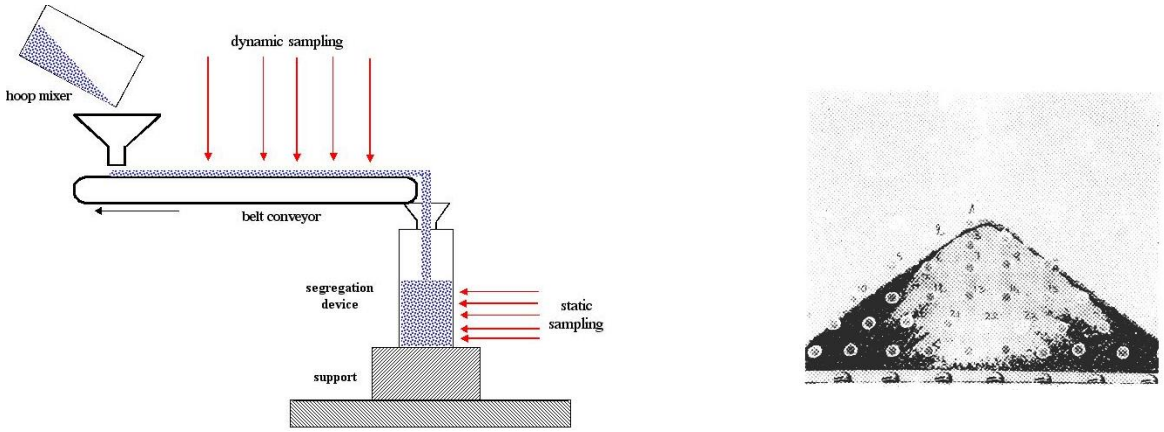

Fig. 2. Test rig developed by Massol-Chaudeur et al. (2003)[4] for evaluating segregation of powder mixtures
Рис. 2. Тестовое приспособление, разработанное Massol-Chaudeur с соавторами (2003)[4], для оценки сегрегации смеси порошков

Formulation of mixtures practically does not take physical characteristics of the products into account, which means that segregability is even not suspected *a priori* as the mixer is supposed to do the job! Paradoxically, one will preferably consider spherical particles because of their ability of being analysed or their advantageous flow properties for preventing from silo arching. Unfortunately, they can be the source of very serious out of specification problems if care is not taken in the handling operations.

Powder mixers

If somebody needs a distillation column, nearly half a day will be necessary to make a full choice on its dimensions and characteristics, and probably another one for consulting vendors and buy the vessel. If somebody needs a powder mixer, the time elapsed up to the final decision will probably be several months. At least two reasons for that:

- The range of technologies available is incredibly wide. The shape of a tumbler mixer may be a

cylinder, a sphere, a cube, a double-cone, a double cylinder, the axis of rotation may differ from the axis of symmetry, inserts can be included, etc. Convective mixers all differ from each other by the shape of the stirrer that may be a ribbon, paddles mounted on a shaft, blades mounted on a frame, multiple screws, planetary motion with various axis of rotation all this being combined with different possible shapes of the mixing vessel. In addition, one may consider fluidised bed mixers, static mixers, silo mixers, up to the unsaid category of the home-made mixers. They will all give very different results for a single formulation.

- The range of possible products is even so wider. The absence of tabulated data concerning the mixtures makes that there is practically no way to determine a priori what will be the best mixer. This makes costly pilot scale tests necessary to choose an apparatus, with the issue that it will probably be used for different mixtures. Of course, guidelines are available to state whether a type of mixer will be more indicated than another type, but they are far from being complete and are lacking of quantization.

As a consequence, "dimensioning" a mixer (as one may do the same for a distillation column) to address a specific mixing problem is not feasible today. It is still preferable for an equipment vendor to present a wide range of mixers, because he is sure that at least one mixer will respond to the demand.

Nowadays, the large majority of operational mixers are batch mixers. This fact is much more the result of traditions, mixer availability, or ignorance, than the result of process optimisation. This has been pointed out by Pernenkil and Cooney [8] in their very complete review on continuous powder mixing, some thirty years after the first one written by Williams [9]. They also emphasised the absence of reported work concerning continuous mixing of pharmaceutical powders. In fact, to our knowledge, the effective use of continuous mixers in pharmaceutical plants is still restricted to less than ten examples throughout the world. And in terms of technologies, while more chaotic mixers such as the Nautamixer® or the Turbula® are generalizing at the R&D stages, production is still made of plough blenders and basic tumblers as remarked by Bridgwater [10].

Short-term evolutions

on-line measurement for assessing homogeneity

The problems associated with sampling, as evoked above, have led the industries to develop ways of "passing" controls, rather than trying to evaluate the mixture homogeneity. In other words, the mean has become the objective. This danger has been pointed out by the FDA in the pharmaceutical sector at the beginning of the century, and motivated the Process Analytical Technologies (PAT) initiative to help the sector in developing ways of controlling mixture's homogeneity. Basically, the idea is to develop and industrialise, either on-line techniques or in-situ techniques for measuring powder blend homogeneity during processing, and use this directly for product validation. For this, electrical methods -such as capacitance- can be used (Ehrhardt et al. [11]), but also image analysis (Muerza et al. [12], Berthiaux et al. [13], Ammarcha et al. [14]), NIR spectroscopy (Hailey et al. [15]; Koller et al. [16]; Martinez et al. [17]; Vanarase et al. [18]), FT-Raman (Vergote et al. [19], De Beer et al. [20]), Laser Induced Fluorescence (Lai et al. [21]), NIR chemical imaging, etc. Of course, because of mixtures variety, there is not a single technique able to treat all the cases, and not all the methods cited have the same running price. But apart from this, the main difficulties to cope with are:

- Data treatment and interpretation. The result of a measure is the response of a particulate system from its physical or chemical properties, and is not directly the composition of a sample. This means that the relation between the property measured and the composition must be worked out extensively as a preliminary, and in particular, the range of validity and the sensibility of such a relation. Indeed, it may happen that the value of a measurement can correspond to different compositions. If there is no doubt on the relation between the measurement and the composition, it becomes possible to follow mixture's homogeneity through the standard deviation of the property measured, or to focus on the signal's deviation without need to re-calculate the composition.

- Time-stability of the measuring technique. Once a method has been set, the aim is to insert it in a production line. This means, under industrial conditions: with dust, vibrations, temperature changes, moisture, and time. It is therefore essential to define and run validation protocols during processing, and maybe to estimate and correct from the signal's deviation.

- Sampling problems may still remain. This is yet true because some of the methods cited above need to capture a sample for further destructive analysis. But also, and even if much more samples may be analysed, because not all the possible samples will be considered. Non-random sampling will still be a danger in proper estimation, together with sampling under or over the scale of scrutiny.

The industrialisation of such techniques has been slow during the last 10 years, and is expected to experience a significant increase within the 10 years to come, partly because some regulatory agencies -like the FDA- are actively pushing towards continuous processes (Ierapetritou et al. [22]).

Improving mixer's scale-up and design

The development of validation methods to control mixing processes will undoubtedly serve as a detonator for increasing process performance. This may be traduced by:

- Improvement of general mixer design by the elimination of dead zones, premix in the feeding section by static mixers, better discharge systems to prevent from segregation, fully adjustable gate valves at the outlet of continuous vessels, etc.

- Improvement in stirrer design for convective mixers. Much can be done to that respect if a scientific basis is considered to compare stirrers (Marikh et al. [23]). We can suggest the use of the centred variance of Residence Time Distribution (RTD) for continuous mixers (Marikh [24]), as a way to quantify the agitation that takes place in the bulk. Later on, it was shown by Mizonov et al. [25] that the crosswise non-homogeneity of particle flow field had a strong influence on RTD and its characteristics.

- Improvement in scale-up procedures. The use of fully empirical correlations between dimensionless groups may be replaced by a systems dimensional analysis procedure using accessible values as suggested by André et al. [26]. For example, it is possible to consider the engine torque, as an indirect measure of powder viscosity and draw correlations that take into account a characteristic speed (Legoix et al. [27]; Legoix et al. [28]).

- Lower power consumption mixers. While such apparatuses are not big energy consumers, if they can be compared with grinding machines for example, new mixers on the market are yet of very low specific power demand (nearly between 1 to 2 Watts per kilogram).

All this will probably drive the manufacturers of equipment to have less, but better mixers than now, thus reducing the range of available technologies.

Of course, all these changes will be enhanced by advanced mechanical engineering techniques, in the conception of the surfaces, of the seals. It is also hoped that other product specification will be integrated in the analysis, such as particle friability, as no muesli consumer would like to have dust in its bowl, even if it is perfectly mixed!

Continuous processes

The predominance of batch mixing processes on continuous ones is so important, that it makes no doubt that the latter will gain place against the former in a near future. Replacing an old batch mixer by a continuous one would result in a significant increase of productivity in many cases. This is currently due to:

- Lower size of the mixing vessel for a same production level.

- Less segregation risk due to the absence of handling operations, such as filling and emptying.

- Lower running costs.

- Better definition of mixture homogeneity, at the outlet of the apparatus.

In a pharmaceutical context, for which continuous processes in general have a clear future, we may add and emphasize:

- The possibility to include an on-line analysis set-up at the outlet of the mixer for measuring the quality of the mixtures, but also to proceed to process control. This point is exactly in the direct line of the PAT recommendations.

- The fact that practically all the final steps, such as tabletting and conditioning, in a drug fabrication scheme are yet continuous operations.

- The reduction of scale-up problems during process development. The validation of an industrial "batch" during process development must actually be done at a scale of 1/10 the real batch capacity. This means that if one wants to produce 100 kg at industrial scale in a batch mixer, the validation can be done with a mixer containing 10 kg of mixture. In continuous mixing, this may be traduced by 1 hour of full scale test to represent 10 hours of industrial production, with no risk of error during scale-up.

It is worth noting that this shift is now clearly supported by the FDA since five years (Ierapetritou [22], Roche [29]).

Longer-term evolutions

Process control

With the diffusion of on-line and in-situ techniques, as well as real-time interpretation of the data in terms of mixture specification (homogeneity in the present case), it will be soon possible to assess product control in many cases. However, only half of the road is done if one stops at this point, as it will still be necessary to consider long pilot tries to determine the operating conditions with a certain precision. What remains to be explored is the development of process control through automatic adjustment of process variables. This has been done for loss-in-weight feeders for example and is clearly a subject for today's chemical engineering research branch dedicated to powder technology (Christofides et al. [30]; Ramachandran et al. [31]; Zhao [32]).

The major gap between industrial application and research deals with the establishment of models to create the link between the data measured and the way the process controller software will have to act on process variables, such as stirrer rotational speed, outlet gate valve opening, mixing time. Basically, two types of models can be derived:

- Purely empirical models in which the effect of process variables has been qualified, and a "blind" algorithm helps to find out an acceptable condition.

- Semi-empirical models, in which a relationship between the measure and the process variables has been derived, or in other word, for which the effect of agitation on product homogeneity is known. For continuous mixers, this can be done through the help of RTD models, or Markov chain models (Berthiaux and Mizonov [39]), for which there generally exist a single parameter to adjust.

Of course the first model type can be developed in a shorter time than the second, but is less robust and predictive, as it will be valid for a given mixer and for a specific range of operating conditions. Also, RTD-Markov-based models can be integrated earlier in the conception stage of better stirrers.

Towards the universal mixer?

The birth of mixing process control and the major improvement in mixer's conception (scale-up and design) will probably lead to reduce the range of available technologies. The mixers will have to face, at least:

- An increase of the number of adjustable process variables in a single mixer: two stirrer motion to combine, adjustable outlet gate valve, interchangeable stirrer shapes, blades that can be orientated from a computer, so that a single apparatus may be used for a wider range of mixtures, through an efficient process control system.

- An increase of mixer's multi-functionality: they may be able to operate under vacuum, under pressure, at high temperature, at low temperature, for drying, for agglomeration, for coating, for pastes, for fluids.

- An increase of mixer instrumentation, including in-situ sensors such as NIR, accompanied by an increase of mixer control - command systems.

By the end, much less pilot trials will be necessary to choose a mixer. Perhaps the universal powder mixer, the one that can be chosen as a distillation column, is not for tomorrow. But it is probable that the equipment vendors will develop up to 3 or 4 mixers, each being directed towards specific mixing problems, also because the complexity of mixtures has increased so dramatically.

Evolution of standards to take into account new definitions of homogeneity

Industrial standards on the homogeneity of powder mixtures are basically concerned with the intensity of segregation σ (see section 1.1.). However, two mixtures of the same variances can be very different in their structure and lead to unexpected end-used properties. This is related to the concept of scale of segregation, that has been first pointed out by Danckwerts [33]) and practically have never been applied for mixture quality assessment and norms. The tools are not well developed yet for powders, but have been listed by Gyenis some time ago [34]: phase portraits (attractors), autocorrelation functions, spatial variance. We may also add tools for detecting defaults, such as Principal Component Analysis. It is therefore probable that standards concerned with structure and texture of mixtures will be used in the industry within some time. But in the meantime, one can also foresee:

- The surge, through quality certifications, of homogeneity criteria in a wider range of industrial sectors than today (basically pharmaceutical and food industry). This will need a specification of the scale of scrutiny of the mixture as a preliminary step that can only be derived from a deep analysis in the determination of quality attributes.

- The uniformity of such criteria in the whole industry, through the impulse of identified experts groups.

Concluding remarks: some outcomes for chemical engineering research

In this paper, we have tried to imagine an industrial perspective for powder mixing processes, from the viewpoint of Chemical Engineering Researchers that are faced almost every day with industrial problems of this kind. Our views may be partial, as we are not directly concerned with all aspects of industrial production. However, most of the ideas raised in these lines are in good concordance with the perspectives from Ennis [35], Bell [36] or more recently Jacob [37]. It is worth noting that the latter emphasized the role of education in powder technology as the most challenging perspective.

To what concerns research, as far as we are concerned and as a conclusion of this paper, three major scientific items have to be developed: Models and scales to bridge

Since more than 20 years, a major effort has been employed for the development of Discrete Element Models (DEM), based on particle-particle interactions. Such models are now able to routinely simulate the motion of particles in a mixer but with serious limitations, all having an impact on the calculation time: the number of particles to handle that are in the range 10^5-10^6; the consideration of non – spherical particles that complicates the calculation of the contacts; the motion of a stirrer inside the particle bed; the consideration of complex particle-particle interactions, as for cohesive powders. Even if new computational techniques or new computers are created to attenuate the above limitations, even if all chemical en-

gineers becomes experts in the manipulation of such codes, it is not plausible that those may be used solely for real-time process control. On another hand, Population Balance Models (PBM), such as Residence Time Distribution models or Markov chain models that are tools belonging to a systems approach, are generally lacking of valuable physical "inputs". Most of the time, their validity is ensured by fitting several adjustable parameters to the experiments, which results in a lack of prediction and finally makes them "pure" mathematical models. We may now definitely assume that a model has a range of efficiency that is dependent on the scale at which its smallest elements are operating. It is time to work out relationships between DEM and PBM, to find out the critical parameters of a PBM that may be used for process control. In addition, same bridges may be built between the molecular level and the particle level, or as between the plant level and its environment. Major challenges in modelling are probably more in the establishment of model links that in the development of models on their own.

Dimensional analysis: towards a systems approach

The difficulties in defining the physical properties of particulate systems, for their flow calculation for example, have blocked the dimensional analysis of powder mixing problems. If one wants to adapt the methodology developed for the liquids, it will promptly stop at the definition of viscosity. For complex systems (as for pastes, emulsions, gels), a major line of investigation in today's chemical engineering is what has been called "systemic rheology" at the beginning of the century (Choplin [38]). The idea is to replace physical unknown values, because of the complexity of the products, by direct measurement of their effect. For example, viscosity can be replaced by torque in many cases, and give rise to a Reynolds number in which torque appears. Researchers working with powders may try to develop similar tools to derive general correlations of interest for mixer's scale-up and power consumption predictability.

Agitation vs product homogeneity

In most cases, powder mixing problems are reduced to mixture homogeneity problems for a given mixer. The fact is that very little attention has been paid to what concerns the optimisation of mixers, from the viewpoint of both fundamental design and operation of the equipment. Undoubtedly, more science has to be put in the conception stage, in particular through models able to quantify the stirring action of the mixer. This must be done for batch processes, and particularly for continuous processes for which the margin of use is incomparably wider. Chemical Engineering may help for this, as it may help to create the link with product homogeneity. Basically, this link is at the level of the chemometrics to develop for process monitoring and control, as we have emphasised in the different sections of this paper.

All this may of course be achieved, through clear industrial – university partnerships, preferably involving a panel of industrialists from various sectors. Even if constraints or traditions are quite different from one type of industry to another, mixing problems are remaining the same.

Acknowledgement

This work was supported by the Russian Foundation for Basic Research (project 18-08-00028 A).

REFERENCES

ЛИТЕРАТУРА

1. **Berman J., Schoeneman A., Shelton J.T.** Unit dose sampling: a tale of two thieves. *Drug Develop. Indust. Pharm*. 2002. V. 22. N 11. P. 1121-1132.
2. **Muzzio F.J., Robinson P., Wightman C., Brone D.** Sampling practices in powder blending. *Internat. J. Pharmaceut*. 2001. V. 155. P. 223-242.
3. United States versus Barr Laboratories Inc., Food and Drug Law Reports, 4 : 4, 2003.
4. **Massol-Chaudeur S., Berthiaux H., Dodds J.A.** The development of a static segregation test to evaluate the robustness of various types of powder mixtures. *Trans IChemE, Part C - Food & Bio-products Processing.* 2003. V. 81. P. 106-118.
5. **Popplewell L.M , Campanella O.H., Sapru V., Peleg M.** Theoretical comparison of two segrega-tion indices for binary powder mixtures. *Powd. Technol*. 1989. V. 58. P. 55-68.
6. **Harris J.F.G., Hildon A.M.** Reducing segregation in binary powder mixtures with particular refe-rence to oxygenated washing powders. *Indust. Eng. Chem. Proc. Design Develop*. 1970. V. 9. P. 363-379.
7. **Schneider B.** Tests for animal nutrition laboratory. BASF Internal report. 2001. May.
8. **Pernenkil L., Cooney C.L.** A review on the continuous blending of powders. *Chem. Eng. Sci.* 2006. V. 61. P. 720-742.
9. **Williams J.** Continuous mixing of solids, a review. *Powd. Technol*. 1976. V. 15. P. 237-243.
10. **Bridgwater J.** Mixing of particles and powders: Where next? *Particuology*. 2010. V. 8. P. 563-567.
11. **Ehrhardt N., Montagne M., Berthiaux H., Gatumel C., Dalloz-Dubrujeaud B.** Assessing the ho-mogeneity of binary and ternary powder mixtures by on-line electrical capacitance. *Chem. Eng. Proc*. 2005. V. 44. P. 397-403.
12. **Muerza S., Berthiaux H., Massol-Chaudeur S., Thomas G.** A dynamic study of static mixing using on-line image analysis. *Powd. Technol.* 2002. V. 128 (2-3). P. 195-204.
13. **Berthiaux H., Mosorov V., Tomczak L., Gatumel C., Demeyre J.F.** Principal Component Analysis for characterising homogeneity in powder mixing using image analysis. *Chem. Eng. Proc.* 2006. V. 45. P. 397-403.
14. **Ammarcha C., Gatumel C., Dirion J.L., Cabassud M., Berthiaux H.** Continuous powder mixing of segregating mixtures under steady and unsteady state regimes: Homogeneity assessment by real-time on-line image analysis. *Powd. Technol*. 2017. V. 315. P. 39-52.

15. **Hailey P.A., Doherty P., Tapsell P., Oliver T., Aldridge P.K.** Automated system for the on-line monitoring of powder blending processes using near-infra-red spectroscopy – 1. system development and control. *J. Pharmaceut. Biomed. Anal.* 2000. V. 14. N 5. P. 551-559.
16. **Koller, D.M., Posch A., Hörl G., Voura C., Radl S., Urbanetz N.** Continuous quantitative moni-toring of powder mixing dynamics by near-infrared spectroscopy. *Powd. Technol*. 2011. V. 205. P. 87-96.
17. **Martinez L., Peinado A., Liesum L., Betz G.** Use of near-infrared spectroscopy to quantify drug content on a continuous blending process: influence of mass flow and rotation speed variations. *Eur. J. Pharmaceut. Biopharmaceut*. 2013. V. 84. N 3. P. 606-615.
18. **Vanarase A.U., Järvinen M., Paaso J., Muzzio F.J.** Development of a methodology to estimate error in the on-line measurements of blend uniformity in a continuous powder mixing process. *Powd. Technol*. 2013. V. 241. P. 241-263.
19. **Vergote G.J., DeBeer T.R.M., Vervaet C., Remon J.P.** In-line monitoring of a pharma-ceutical blending process using FT-Raman spectroscopy. *Eur. J. Pharmaceut. Sci.* 2004. V. 21. N 4. P. 479-485.
20. **De Beer T.R.M., Bodson C., Dejaegher B., Waleczak B., Vercruysse P., Burggraeve A.** Raman Spectroscopy as a Process Analytical Technology (PAT) tool for the in-line monitoring and unders-tanding of a powder blending process. *J. Pharmaceut. Biochem. Anal*. 2008. V. 48. P. 83-90.
21. **Lai C.K., Holt D., Leung J.C., Cooney C.L., Raju,G.K., Hansen P.** Real-time and non-invasive monitoring of dry powder blend homogeneity. *AIChE J.* 2001. V. 47. N 11. P. 2618-2622.
22. **Ierapetritou M., Muzzio F., Reklaitis G.** Perspectives on the continuous manufacturing of powder-based pharmaceutical processes. *AIChE J.* 2016. V. 62. N 6. P. 1846-1862.
23. **Marikh K., Berthiaux H., Gatumel C., Mizonov V., Barantseva E.** Influence of stirrer type in continuous powder mixing : a model case and a pharmaceutical case. *Chem. Eng. Res. Design*. 2008. V. 86. P. 1027-1037.
24. **Marikh K.** Mélange des poudres en continu: dynamique et modélisation. PhD thesis. INPL. 2003.
25. **Mizonov V., Berthiaux H., Gatumal C., Barantseva E., Khokhlova Y.** Influence of crosswise non-homogeneity of particulate flow on residence time distribution in a continuous mixer. *Powd. Technol*. 2009. V. 190. P. 6-9.
26. **André C., Demeyre J.F., Gatumel C., Berthiaux H., Delaplace C.** Dimensional analysis for planetary mixer homogenizing granular materials: mixing time and Froude numbers. *Chem. Eng. J.* 2012. V. 198-199. P. 771-778.
27. **Legoix L., Gatumel C., Milhé M., Berthiaux H.** Characterizing powders in order to determine their flow behavior in a mixer: from small scale observations to macroscopic in-mixer rheology for powders of various flowabilities. *Powd. Technol*. 2017. V. 322. P. 314-331.
28. **Legoix L., Gatumel C., Milhé M., Berthiaux H.** Analysis of powder flow and in-system rheo-logy in a horizontal convective mixer with reclining blades. *Particul. Sci. Technol: An Internat. J.* 2018. V. 36. P. 955-966.
29. **Roche F., Page T., Seville J.** Non-stop pharma: centuries in the making. *Chem. Eng.* 2013. February. P. 28-31.
30. **Christofides P.D., El Farra N., Li M., Mhaskar P.** Model-based control of particulate processes. *Chem. Eng. Sci*. 2008. V. 63. P. 1156-1172.
31. **Ramachandran R., Arjunan J., Chaudhury A., Ierapetritou M.G.** Model-based control-loop performance of a continuous direct compaction process. *J. Pharmaceut. Innovat*. 2011. V. 6. P. 249-263.
32. **Zhao X.** Contribution to the implementation of a process control system for continuous powder mixing. PhD thesis. Toulouse University. 2013.
33. **Danckwerts P.V.** Theory of mixtures and mixing. Research (London). 1953. V. 6. P. 355-361.
34. **Gyenis J.** Assesment of mixing mechanisms on the basis of concentration patterns. *Chem. Eng. Proc.* 2000. V. 38. P. 665-674.
35. **Ennis B.J.** Unto dust shalt thou return. Powders & Grains 97. Behringer & Jenkins ed. P. 13-23.
36. **Bell T.A.** Challenges in the scale-up of particulate processes – an industrial perspective. *Powd. Technol*. 2005. V. 150. P. 60-71.
37. **Jacob K.** An industrial perspective on the future needs in solids processing research and educa-tion. Plenary lecture at 8th World Congress on Particle Technology. Orlando. April 2018.
38. **Choplin L.** Mixing in cosmetics and personal care industries. The 5th International Syposium on Mixing in Industrial Processes (ISMIP 5). Sevilla. June 2004.
39. **Berthiaux H., Mizonov V.** Applications of Markov chains in particulate process engineering – A review. *Canad. J. Chem. Eng*. 2004. V. 82. P. 1114-1168.

Поступила в редакцию 02.08.2018
Принята к опубликованию 30.10.2018

Received 02.08.2018
Accepted 30.10.2018