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PHARMA PRO&PACK

An official Publication of Indian Pharma Machinery Manufacturers' Association (IPMMA)

Focus Country

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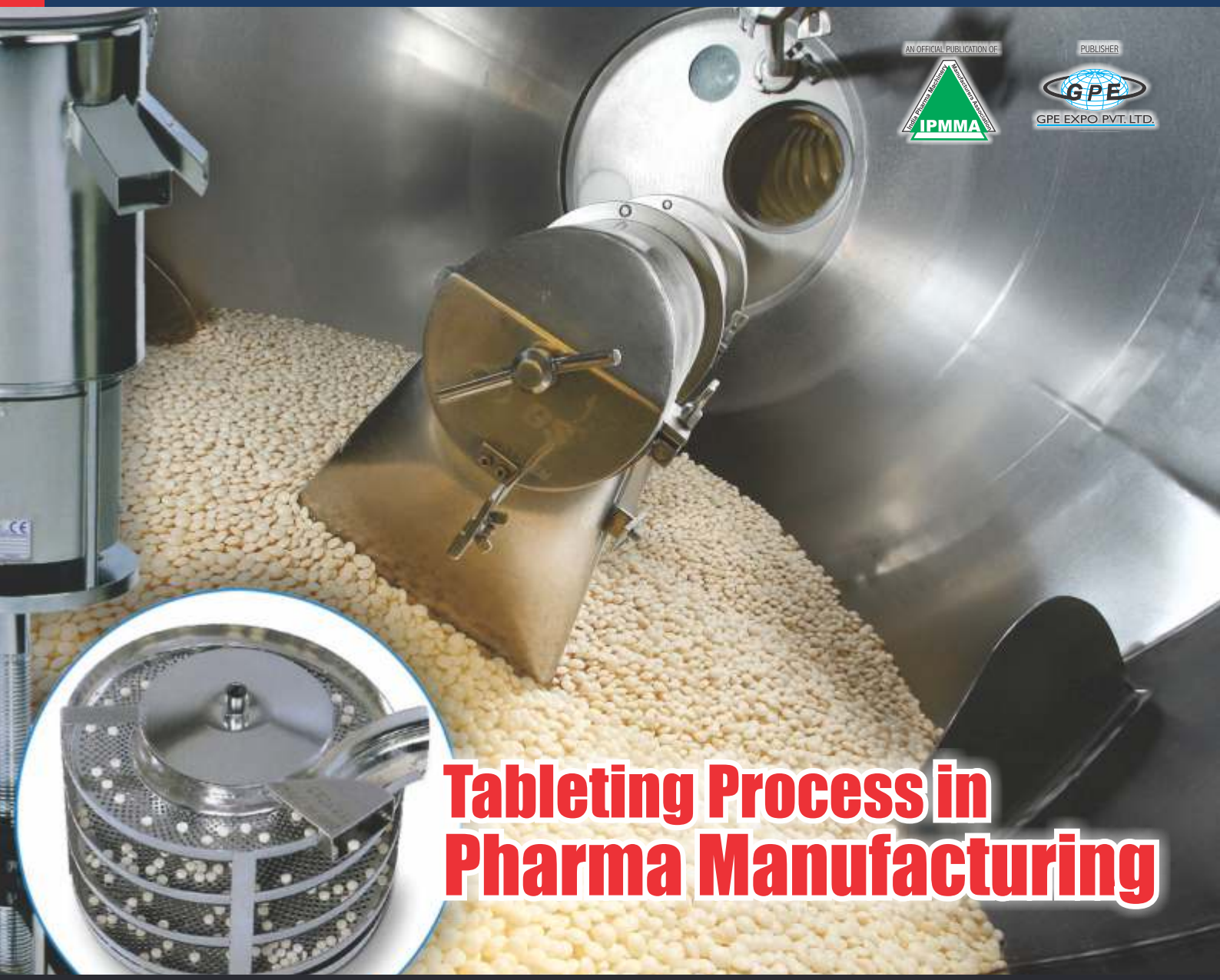

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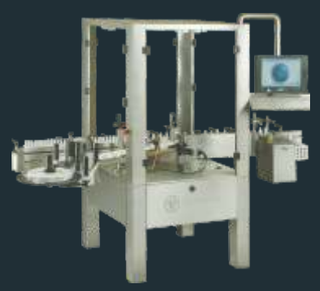

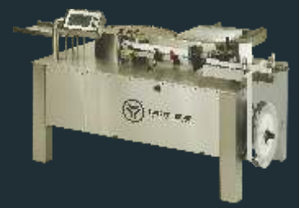

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Editorial

Rajesh Shah
Editor-in-Chief
PHARMA Pro&Pack

In today's fast changing world, the pharma industry is no exception. Pharmaceutical technologies are not only very sophisticated, but they are changing rapidly. Throughout the pharma industry, companies are enhancing older processes and exploring innovative alternatives. Tableting – one of the very important sectors of pharma industry is also on the threshold of change. Several new practices and technologies are shaping today's rapidly changing pharmaceutical tableting and capsule industry.

There have been many advances in tablet ingredient characterization, formulation development, material processing, and also in other topics vital to successful tableting and capsule operations. New concepts, new ideas, new technologies, new processes and procedures are knocking on the doors of the basic principles and current industrial practices of pharmaceutical tablet and capsule production. Pharma utilities are embracing state-of-the-art technologies and cost-effective approaches to manufacturing dosage forms with uniform content and consistent physical properties.

Take the example of the QbD (Quality by Design) concept which is creating a place of its own in tableting. QbD is a systematic approach to development of products and processes that begins with predefined objectives and emphasizes product and process understanding and process control based on sound science, statistical methods and quality risk management. In an attempt to curb rising development costs and regulatory barriers to innovation and creativity, the FDA and ICH have recently started promoting QbD in the pharmaceutical industry. QbD is partially based on the application of multivariate statistical methods and a statistical Design of Experiments strategy to the development of both analytical methods and pharmaceutical formulations. A process is well understood when all critical sources of variability are identified and explained, variability is managed by the process, and product quality attributes can be accurately and reliably predicted over the design space. The elements of Quality by Design (QbD) are examined and a consistent nomenclature for quality by design, critical quality attribute, critical process parameter, critical material attribute, and control strategy is proposed.

By staying up-to-date with current practices and new advances, you can help ensure the continued competitiveness of your organization. Keep Up to Date and & Keep Productive!

I also take this opportunity to remind all of you about the forthcoming PHARMA Pro&Pack Expo 2014 (PPPE 2014), a three day international exhibition on the entire spectrum of pharma machineries and allied industries to be held at the Mumbai Exhibition Centre, Mumbai, India during May 21 to 23, 2014 at Mumbai Exhibition Center, Mumbai, India. After the successful inaugural edition of the Exhibition in 2013, this would be the second such exhibition. Note down the dates in your diaries and pack your bags well in advance.

Also wishing you a very informative reading and looking forward to meeting you at PHARMA Pro&Pack Expo 2014 at Mumbai in May 2014..!

From the Desk of the Publisher

Paresh Jhurmurvala
Publisher

Legendary boxer and sportsperson of the century Mohammed Ali once said; *"It is lack of faith that makes people afraid of meeting challenges, and I believed in myself."* Faith – the all important word. Faith – not only in ourselves but FAITH the pharma industry of India in general and the pharma machinery manufacturers of India placed in us propelled us to launch the PHARMA Pro&Pack magazine. It is indeed with great pride and happiness that I can say this that it was because of your FAITH that PHARMA Pro&Pack has successfully completed three years. With great joy, I place before you the inaugural issue of 2014. As Martin Luther King Junior rightly said; *"Faith is taking the first step even when you don't see the whole staircase."* So may I take this opportunity to extend my sincere and heartfelt gratitude, appreciation and thanks to one and all who have contributed in making a true success of PHARMA Pro&Pack? Also on the horizon I can see much hope, trust and anticipation that this cooperation and collaboration towards Pharma Pro&Pack will continue in the days, month and years to come. Surely PHARMA Pro&Pack will continue to lead the way as the torchbearer of the Indian pharma industry and the Indian pharma machinery sector.

In this 2014 inaugural issue, we have focussed on the tableting sector. We have tried to bring before you a bouquet of different developments and industry trends taking place in this all important sector. I am hopeful you will like it. We also have all the regular features like industry updates, country profiles and reports on forthcoming shows.

As rightly stated by the Editor-in-Chief Mr. Rajesh Shah, one of the most important events coming up is the PHARMA Pro&Pack Expo 2014 (PPPE 2014) during May 21 to 23, 2014 at Mumbai Exhibition Center, Mumbai, India. The Exhibition having a special focus on promoting '***BRAND INDIA***' to both the Indian and world pharma industry is being jointly organised by the Indian Pharma Machinery Manufacturers' Association (IPMMA) and GPE Expo Pvt. Ltd.

So see you all in Mumbai..! Also please do not forget to write to us with your valuable feedback. We will be more than happy to know what you feel about PHARMA Pro & Pack.

Happy & Inspired Reading of this latest issue of PHARMA Pro & Pack to All of You..!

Unprecedented response to PHARMA Pro&Pack Expo Road Shows

PHARMA Pro&Pack Expo reaches out to pharma clusters in India and international markets

An initiative to reach out directly at the doorsteps in various pharma clusters across India and internationally through pharma fraternity gathering has received an unparallel welcome and response from the pharma trade professionals engaged in different positions at the pharma manufacturing facilities.

The fundamental aspects of these gatherings are to create an awareness about the PHARMA Pro&Pack Expo 2014, Mumbai Exhibition among the pharma fraternity pan-India and internationally too, and disseminate the information about the benefit of attending such international exhibition featuring complete spectrum of the TOTAL pharma manufacturing technologies featuring Brand INDIA products & services at one place during three-days.

Very carefully selected more than 12 national and international pharma hubs were the prime locations to have highly impressive attendance from the industry. These clusters were Pune (Central Maharashtra pharma region), Baddi (Baddi, Solan, Nalagarh pharma regions), Panchkula (Chandigarh, Panchkula & Mohali pharma regions), Indore (Indore, Pithampur, Dewas pharma regions), Hyderabad, Bangalore, Dehradun (Dehradun, Selaqui, Rushikesh, Haridwar, Ponta Sahib, Rurkee pharma regions), Goa, Daman (UT) (Vapi, Daman, Selvass pharma regions) in India and Bangladesh, Egypt, Nepal were international locations.

PHARMA Pro&Pack Expo 2014 Exhibition is scheduled during May 21 to 23, 2014 at Mumbai Exhibition Center, Mumbai, India and being jointly organized by the Indian Pharma Machinery Manufacturers' Association (IPMMA) and GPE EXPO PVT. LTD. A special pavilion – PharmaLAB Expo 2014 featuring Analytical Lab Equipments & Services during the Show. More than 14 national and international trade Associations and Export Promotion Councils, Govt. of India are supporting the Exhibition. iPHEX 2014 – an international exhibition on pharmaceuticals & healthcare is the Co-located Exhibition and being organized by PHARMEXCIL (Pharmaceutical Export Promotion Council, Govt. of India). More than 480 exhibiting companies from 18 countries are displaying their latest technologies and product / services and more than 20,000 pharma trade professionals including 1,400 international buyers from 140 nations are expected to attend these Exhibitions.

At Pune, 78 professionals representing Emcure Pharmaceuticals Ltd., SAI Life Sciences Ltd., Hindustan Antibiotics Ltd., Centaur Pharmaceuticals Pvt. Ltd., Parle Global technologies, Nulife Pharmaceuticals, Indus Biotech Pvt. Ltd., Libra Drugs India, Maxim Pharmaceuticals Pvt. Ltd., Brihans Laboratories Pvt. Ltd., Cadmach machinery Co. Pvt. Ltd., SVE Chem, The Varma Pharmacy Pvt. Ltd., Technofour Electronics Pvt. Ltd., Eisen Pharmaceuticals Co. Pvt. Ltd., Intervet India Pvt. Ltd., Venky's (India) Ltd., Agasti Pharmaceuticals, Somsukh Polymers Pvt. Ltd., Kokan Ayur Pharma Pvt. Ltd., Futurol Enterprises, Pharmachine India, Mothers' Recipe, BV Bio-Corp Pvt. Ltd. attended the gathering.

Moreover, PHARMA Pro&Pack Expo 2014 marked an outstanding presence at the Pharmaceutical Expo 2013, the concurrent event of the Indian Pharmaceutical Congress 2013, New Delhi; where senior professionals of pharma industry and pharma fraternity attended the presentation on PHARMA Pro&Pack Expo 2014 including senior dignitaries like; Dr. P.V. Appaji Rao (Director General of PHARMEXCIL), Dr. H. G. Koshia (Commissionaire of FDCA), Dr. Bhagirath Patel (President - West Zone, IPGA), Mr. Oliver van der Spek (FIP), Mr. Shyam Mohan (Affy Pharma Pvt. Ltd.), Mr. Sagar Samant (Johnson & Johanson Ltd.), Dr. S. K. Sharma (M. A. Health Management Policy & Planning (Leeds, U.K.), Mr. Inam–Ur-Rehman (Director, Ravenbhel Healthcare, Jammu), and many more.

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A remarkable presence of 178 senior pharma professionals from Baddi, Nalgarh & Solan pharma region and 134 senior pharma professionals from Panchkula, Chandigarh, Mohali pharma region attended the road shows organized on 3rd & 4th January 2014 at Baddi and Panchkula respectively. The companies attended at Baddi and Panchkula are among Abbott Healthcare, Alkem Laboratories, Amway India, Aristo Pharma, BRD MediLabs, Cachet Pharmaceuticals, Galpha Laboratories, Glenmark Pharmaceuticals, Himachal Drug Manufacturers Association, Him India Envirocare & Services, Vishwakarma Industries, Immacule Lifesciences, IPCA, Kanha Biogenetic Laboratories, Macleods Pharmaceuticals, MDC Pharmaceuticals, Morepen Laboratories, Naxpar Lab, Panacea Biotech, Ranbaxy, Sarvotham Care, SGPTC Pvt. Ltd., Solrex Pharmaceuticals, Unichem Laboratories, Unix Biotech, USV Ltd, Zeiss Pharmaceuticals, and many more.

PHARMA Pro&Pack Expo 2014 Road Shows were organized at Indore to focus Central Indian pharma region – Indore, Pithampur, Dewas, where 94 companies representatives participated at Indore, including Cadmach, Cipla Ltd., Ecobuild Engineers & Contractors, Elite Industries, Erweka India, Fluidpack Machines, Glenmark Generics Ltd., IPCA Laboratories Ltd., Magadh Precision Equipment Ltd., MCW Healthcare Pvt. Ltd., MK. Technology, Pharma Herbs, Pharmaceutical Machinery Mfg. Works, Piramal Healthcare Ltd., Pithampur Audhyogik Sangatha, Parle Elizabeth, Plethico Pharmaceuticals Ltd., Pharmachine India, Promed Laboratories Pvt. Ltd., Parth Engineers & Consultants, Ranbaxy Laboratories Ltd., Schon Pharmaceuticals Ltd., Shail Group of Institutions, Shilpa Chem, Swaarnim RexTranter, Vindas Chemical Ind. Pvt. Ltd., Vishal Pharmaceutical

Laboratories, Zest Pharma.

Other subsequent road shows organized in Indore and Hyderabad, where 94 and 144 pharma professionals marked their presence respectively.
Program for Hyderabad and Bangalore pharma clusters were organized on February 10 & 14, 204 respectively, and remarkable attendance from the industry was noticed. At Hyderabad, 144 and at Bangalore 120 company representatives joined the PHARMA Pro&Pack Expo 2014 Road Shows. At Hyderabad,

Aurobindo Pharma Ltd., Hetero Labs Ltd., Qualtek Engineers, Sarvotham Care Ltd., Dr. Reddy's Laboratories Ltd., Mylan Laboratories Ltd., Optival Health Solutions Pvt. Ltd., Costarica Pharmaceuticals, Technofour Electronics Pvt. Ltd., Osworld Scientific Eqpts Pvt. Ltd, Maharshi, Everest Engineering & Allied Products Pvt. Ltd., Disto Pharmaceuticals Pvt. Ltd., Hysecbfl, Channel Bio-Sciences, Indian Pharmaceutical Association (IPA), Vivimed Labs Ltd., Hetero Labs Ltd., Natco Pharma Ltd., Sarvotham Care Ltd., Parle Global Technologies Pvt. Ltd., Concept Engg. Co., Appidi Technologies Pvt. Ltd., Erweka India, SpaceAge, Aastha Cleanroom Systems are few to name. While at Bangalore companies including Agila Specialties Pvt. Ltd., Apotex, Adept Engineers, Bal Pharma Ltd., Bioplus, Concept Engg. Co., Dr. Reddy's Laboratories Ltd., EIPL, Erweka India, Fluidpack , Group Pharmaceutical Ltd., GVK Biosciences Pvt. Ltd., Harikrushna Machinetech Pvt. Ltd., Jagdale Scientific Research Foundation, Karnataka Antibiotics & Pharmaceuticals Ltd., Karnataka Drugs & Pharmaceuticals Manufacturer's Association, Kemwell Biopharma Pvt. Ltd., Kluber Lubrication India Pvt. Ltd., Isher Labs, Maharshi, Mahendra Labs Pvt. Ltd., Medismith Pharma Lab, Mediplus Pharma Lab, Micro Labs Ltd., Ontop Pharmaceuticals Pvt. Ltd., Parle Global Technologies, Remidex Pharma Pvt. Ltd., Sandilyam Automation Systems Pvt. Ltd., Semler Research Centre Pvt. Ltd., SLS, Spaceage Aquatechs, SPL

Pharma, SSPM Systems & Engineers, Strides Arcolab Ltd., Strides arcolab Unit Ltd., Sureseal Pvt. Ltd., Technofour Electronics Pvt. Ltd., Bluefish Pharma, SpaceAge, Aastha Cleanroom Systems, Stridesarco, Sterlinglab.
The Road Show for the Selaqui, Daheradun, Poanta Sahib, Rurkee, Haridwar and Rushikesh pharma clusters was organized at Dehradun and such activity to prioritize the pharma professionals inviting at PHARMA Pro&Pack Expo 2014, Mumbai Exhibition was highly regarded by the attendees. The pharma professionals participated at Dehradun are from IPCA Laboratories Ltd., Sarvear Pharmaceuticals U.A., Valcab Technical Solutons, Cooper Pharma Ltd., Ayushman Engineering, Rhydburg Pharmaceuticals Ltd., Intas Pharmaceuticals, Coral Laboratories Ltd., Sidmak Laboratories India Pvt. Ltd., Concept Pharmaceuticals Ltd., Parle Global Technologies Pvt. Ltd., The Shahnaz Husain Group of Companies, Harikrushna Machinetech Pvt. Ltd., Mepromax Life Sciences, Super Max, Rusan Ltd., Tirupati, Ruby Biotec, Sharon Bio-Medicine Ltd., Akron India Pvt. Ltd., Alkem Laboratories Ltd., Tirupati Medicare Ltd., Tirupati Lifesciences, Mankind Pharma Ltd., Ranbaxy Laboratories Ltd., Sukra Enterprises, Suncare Formulation Pvt. Ltd., Synergy Thrislington, Endolabs Healthcare Pvt. Ltd., Syncom Healthcare Ltd., Indian Drugs & Pharmaceuticals Ltd., Elder Pharmaceuticals Ltd., Vishwakarma Industries, Oasis Laboratories, Uni Medico Labs, Cu-V-Kar Genetic Medicines Pvt. Ltd., Aastha Cleanroom Systems, Ishida India Pvt. Ltd., Mancare Laboratories Pvt. Ltd., Verve Human Care Laboratories , Falcon Machineries, Biological E. Ltd. are few to name
The Road Show at Goa was highly recognized by 105 pharma professionals and appreciated such novel approach to reach out to create the awareness about such international exhibition – PHARMA Pro&Pack Expo 2014, Mumbai Exhibition among the pan-India pharma fraternity. Such programs are also highly informative as the industry stalwarts share their thoughts and views on various aspects of technology trends, pharma manufacturing practices, about Indian pharma machineries, etc. The company representatives attended at Goa are including Sanofi, Centaur Pharmaceuticals Pvt. Ltd., Centaur Pharmaceuticals Pvt. Ltd, Blue cross laboratories Ltd, Cipla, Micro Labs Ltd., Marksans Pharma Ltd., Abbott, Parle Elizabeth, Petals Innovative Machines Pvt. Ltd., DCI Pharmaceutical Pvt. Ltd, Lupin Ltd., The Bombay Engineering Works, Erweka India, Pharma Chem Machineries, Kaizen International, Citizen Scale, Mabpharm, Judou, Zydus Cadila Healthacre Ltd., Ambica Pharma Machines Pvt. Ltd., Mar VI Trac System, Indoco Remedies Ltd., Glenmark Generics Ltd., Unichem, Propack Technologies Pvt. Ltd, Encube, Ranbaxy Laboratires Ltd.

The Road Show focusing the Daman, Vapi and Silvassa pharma manufacturing hubs was organized at Daman (Union Territory), where more 146 pharma professionals representing --- appreciated such efforts to disseminate the information about the PHARMA Pro&Pack Expo 2014, Mumbai Exhibition and bringing together pharma professionals of the same region to share the professional experience and evolve new concepts.

The global presence and promotions of PHARMA Pro&Pack Expo 2014 Exhibition in the first quarter of 2014 AD held at different locations, including at Dhaka (Bangladesh), Kathmandu (Nepal) and Cairo (Egypt). These three back-to-back programs had generated the momentum not only among the professionals of these 3 nations, but extended to all the participants including from the neighboring countries, too.

In a special time slot allotment during the Annual General Meeting (AGM) of the Bangladesh Association of Pharmaceutical Industries, the presentation on PHARMA Pro&Pack Expo 2014 Exhibition was made and confirmative response in terms of their support and presence at the Exhibition received from the industry. In a special gathering of the Association of Pharmaceutical Producers of Nepal (APPON) alongside the 5th Nepal Pharma Expo 2014 at Kathmandu, Nepal; entire Nepal pharmaceutical manufacturing industry appreciated the efforts of organizing PHARMA Pro&Pack Expo 2014 on such large scale and confirmed their visit at the exhibition.

The debut presentation on PHARMA Pro&Pack Expo 2014 presentation done during the Pharmaconex 2014, Egypt. An excellent response from the pharma fraternity from Egypt as well North Africa received and on wide scale the information about the PHARMA Pro&Pack Expo 2014 shared among the pharma professionals.

All these Road Shows were proven a panacea for business networking and development. Attendees were provided in depth information about how they can get benefited by attending PHARMA Pro&Pack Expo 2014. The overall profile of the attendees include; Director, Director – R&D Formulations, CEO, President, Vice President, Sr. Research Fellow – Formulations R&D Center, Principal Scientist R&D Scientist, Head – Plant / Manufacturing, Works Manager, GM – Management & Technical Services, Dy. GM – Tech Transfer / Production / R&D, Sr. Manager – Engineering / Production / Packaging / QA / QC, Project Manager, GMP Consultant, Trade Associations, Regulatory Organizations, etc.

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PHARMA PRO&PACK EXPO 2014
Mumbai Exhibition Center, Mumbai INDIA
May 21-22-23, 2014

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Tablet Technologies in the 21st century

Patient compliance, high-precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice. Excipient and equipment choices will be significantly affected should solid dosage form technologies change in response to the unprecedented shifts in drug discovery such as genomics. Should next generation drugs be predominantly protein or peptide based, tablets may no longer be the dominant format given the difficulty of dosing such moieties orally.

Injections generally are not favored for use by patients unless facilitated by sophisticated auto-injectors such as the one used with GlaxoSmithKline's sumatriptan migraine treatment. Inhalation is one alternative, but chitosan-enhanced protein/peptide delivery has led to a rise in nasal delivery products such as the ChySys system (West Pharmaceutical Services, Lionville , PA). However, the increased research into biopharmaceuticals so far has generated predominantly chemical entities with low molecular weights, and at the same time, the development of enhanced oral protein delivery technologies continues to advance.

Modern rotary tablet machines look more sophisticated and have more instrumentation today, but the basic technology has not significantly changed in several decades. Tablet development still requires a degree of skill and art, primarily because of the uncertainty of the physics within the material under compaction that thwarts the simple correlation of raw-material properties with finished tablet properties, even for the simplest direct compression processes. Wet and dry granulation methods add further complexity to the manufacturing process. Compaction simulators, process analytical technologies (PAT), and advanced computational techniques increasingly are used to minimize this tableting black box, but fundamental predictability remains elusive.

Compaction simulators

Compaction simulators are generally single-punch compaction machines under computer-controlled hydraulic actuation to simulate other tablet machine geometries and speeds. A novel alternative is the "Prester" model (Metropolitan Computing Corporation, East Hanover, NJ), in which a tooling assembly is fired on a rail through a single set of compaction rollers (a linear analogue of the rotary turntable). Compaction simulators are becoming more common, not just within the major pharmaceutical companies but also among tablleting excipient suppliers, to maintain consistency, assist tablet development, and troubleshoot problems. Equality of compaction profile does not rule out other excipient differences that may be significant in terms of tablet production.

Modern rotary machines are capable of production rates in excess of a million tablets per hour, which can be boosted, using multiple tools per die, to the tens of million tablets per hour. However, such outputs are the exception rather than the rule because of the small volume batch-centered approach of the pharmaceutical industry, both for preliminary blending or granulation and subsequent film coating. It is not feasible to optimize every new tablet formulation for high-speed production, because most formulations do not make it through to market. Second-generation production-optimized formulations and processes can be developed later but are subject to regulatory and validation constraints that tend to discourage such improvements.

Enhancements to tablleting technology include ultrasound during tablleting to improve compactability and a novel centrifugally fed tablet machine (IMA, Bologna, Italy). Contrary to expectation, the latter did not improve powder flow to the dies, which may explain the limited adoption of the most radical tablet machine redesign in recent years.

Improving tableting with PAT

The use of PAT is another approach to improving manufacturing processes such as tableting. PAT is a general term covering the application to drug manufacturing of process analytical chemistry tools, feedback process controls, information management, and product/process optimization. The implementation of these technologies involves the online measurement of quality and performance together with multivariate statistical and pattern recognition methods. PAT has been strongly advocated by FDA to encourage innovation and improvement in an industry in which manufacturing processes have long been recognized as relatively inefficient. The conventional approach of testing quality after each stage of

manufacturing, to allow progression to the next stage, means that tablets typically spend more time awaiting release than it takes to manufacture them. PAT attempts to drive intrinsic quality using nonparametric release, which is a challenge for tableting given the dependence on destructive test methods (disintegration, dissolution, and hardness) that do not lend themselves to on-line testing. A good example of a PAT method is nondestructive tablet hardness testing using near infrared (NIR) spectroscopy. PAT may pose challenges to some tableting processes, however, if the insight gained is not matched by commensurate process control. Closer scrutiny could reveal variations in existing products missed by current sampling and testing. Although a grace period for reducing or eliminating such variations may be allowed, regulatory authorities will expect the industry to improve manufacturing processes.

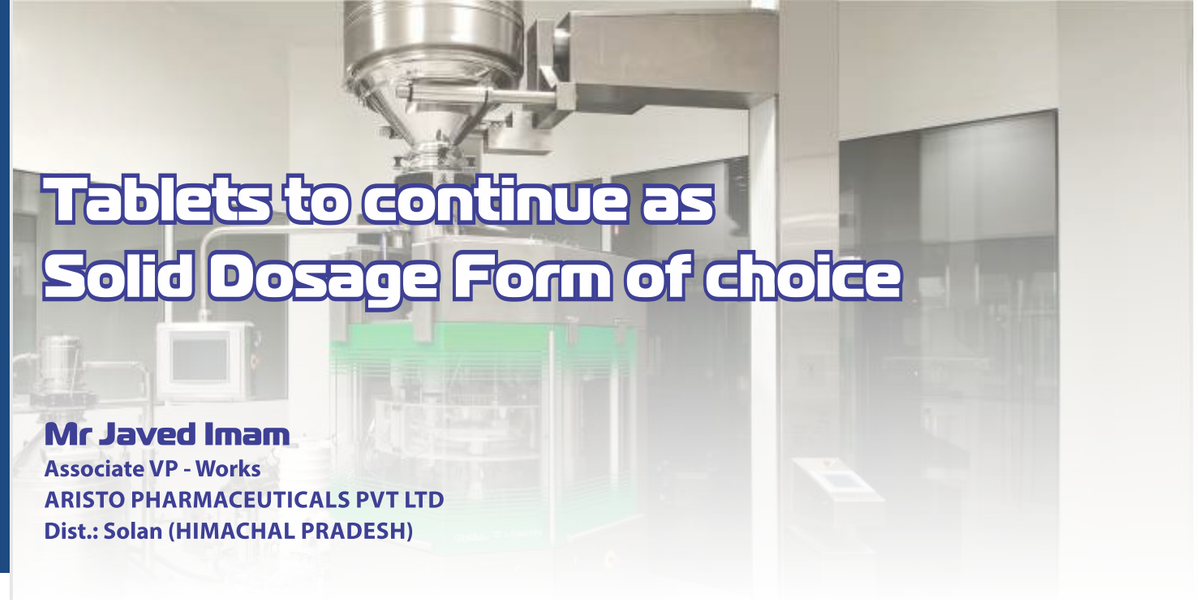
New technologies

New technologies exist that do not yet match current tableting production output rates, but these alternatives could be more attractive in the future if the art of tablet development becomes rate limiting or if drugs in general become sufficiently potent to challenge the content uniformity limits of existing tableting technologies. These newer technologies afford greater scope for validation and control and are relatively free from scale-up problems--the few units produced for early clinical trials will be identical to production units, with scale-up in output only a matter of equipment multiplication.

One example of a new technology is the "Delsys AccuDep System" (Sarnoff Corporation, Princeton, NJ), which uses electrostatic deposition of pure drug substance onto a film substrate. Dosing is controlled by applying an electrostatic charge to spots on the film so that a cloud of oppositely charged drug particles deposits the target dose at point-of-charge neutralization. The drug-loaded film is laminated to seal the deposited doses, which can then be punched out and encapsulated or embedded in a tablet. The deposition process itself is excipient-free, but edible films are required as a substrate, and conventional excipients would be used for subsequent encapsulation or embedding in a tablet. The low levels of drug loading that are possible with this method make it best-suited for potent compounds. The "LeQtradose" (Phoqus, Kent, UK) process uses electrostatic dry powder coating of conventional tablets to provide visually distinct coated tablets, but the coating could also be used to precision-load placebo tablets with low drug doses, provided the drug is not affected by the hot annealing process used to seal and bond the deposited powder coatings onto the tablet. The film formers must be electrostatically chargeable and thermally annealable. "Three Dimensional Printing" (Aprecia Pharmaceuticals, Langhorne, PA, under license from the Massachusetts Institute of Technology) uses the precision of ink-jet printing with multiple print layers to build three-dimensional constructs in which the loading and spatial distribution of a drug is precisely controlled, together with a similar control of barrier materials to modify release in a programmable manner. Diffusion path lengths, the diffusivity of the polymers used, the thickness of the diffusion barriers, and the number of barriers can be varied. This system offers wide latitude in drug loading and excipient choice.

Conclusion

Existing tableting technologies are well suited for high production rates and continuous production applications. However, if increased tablet formulation throughput (and the associated skills) prove rate limiting, the new technologies may potentially be attractive, because they are more amenable to scale-up, validation and the PAT-driven shift to nonparametric release. PPP



Tablets to continue as Solid Dosage Form of choice

Mr Javed Imam
Associate VP - Works
ARISTO PHARMACEUTICALS PVT LTD
Dist.: Solan (HIMACHAL PRADESH)

Mr Javed Imam is a well known name in the Indian and global pharmaceutical industry. Mr Imam has over 25 years of experience in the field of pharmaceutical operations, facility designing and has a thorough understanding of national and international regulatory norms.

Mr. Imam is a regular at national and international seminars and workshops. He is a pharmacist by education and training and he has also completed his management studies from Bhopal University. He has rendered his services to various reputed companies in India and abroad. At present he is associated with Aristo Pharma as Associate Vice President (Works). Aristo Pharma is over four decades old company with over 20 different products.

As a team leader, Mr. Imam leads his team to success with his unmatched strategic planning and execution and motivational skills. Setting up the goals and converting those goals into success has become his habit. Mr. Imam is also a well known orator and has conducted training programs on wide range of subjects.

Mr. Imam is a life member of the IPA and is associated with various social and professional organisations including the Rotary Club.

How has the market developed for this sector in India? And what does the future hold?
The pharmaceutical industry of India is the third largest in terms of volume in the world, with a total turnover of US $21.04 billion. According to the Brand India Equity Foundation, it is likely to grow at the rate of 14% to 17% from 2012 to 2016. The 74 US-FDA approved manufacturing units in India (more than any other country except USA) is a sign of India becoming a global player and further consolidating its position in the years to come.

Tablet market size in India is estimated at Rs.12,235crore accounting for about 55% of the total domestic pharmaceutical industry. Tablets are consumed in about 15 major therapeutic segments in India. Top nine therapeutic segments account for about 71% of the total domestic tablet sales. Within the tablet market, Antibiotic, Antibacterial, Anti-inflammatory and Anti-rheumatic categories are most important and together account for about 35% of the All India tablet market.

The tablet market is estimated to grow at about 8% to 9% over next 10 years. I see a bright future full of growth for the Indian pharmaceutical industry and the tablet dosage form.

How equipment choices would be affected should solid dosage form technologies change in response to the unprecedented shifts in drug discovery such as genomics?
Single pot processors that are capable of mixing granulation, drying and even palletisation coating are now available and having advantages in commercial terms and the overall quality of product.

Patient compliance, high-precision dosing, and manufacturing efficiency make tablets the solid dosage form of choice today. Yes next generation drugs will be predominantly protein or peptide based, tablets may no longer be the dominant format given the difficulty of dosing such moieties orally and hence technology will need a change.

What is role of granulation in pharma industry to obtain the optimum results in Tabletting Process?
Granulation has an important role in getting optimum results in tabletting process. Granulation helps in getting optimum & uniform mass of powder to get good flow properties for compression.

Granulation is done to prevent segregation of constituents due to difference in size and density. It also serves the purpose of improvement of the flow property of cohesive & low density materials which otherwise fails to flow freely. Role of granulation is size enlargement process which converts fine or coarse particles into physically stronger and larger agglomerates having good flow property, better compression characteristics and uniformity.

In the pharmaceutical industry, granulation refers to the act or process in which primary powder particles are made to adhere to form larger, multi-particle entities called granules. It is the

process of collecting particles together by creating bonds between them. Bonds are formed by compression or by using a binding agent. Granulation is extensively used in the manufacturing of tablets and pellets (or spheroids).
The granulation process combines one or more powder particles and forms a granule that will allow tableting or spheronization process to be within required limits. This way predictable and repeatable process is possible and quality tablets or pellets can be produced using tabletting or spheronization equipment.

Which are the different techniques of Granulation technology on large scale in pharma industry?
(1) Dry granulation
(2) Wet granulation
(2A) Aqueous granulation (P. water + Binder)
(2B) Non Aqueous Granulation

Dry granulation involves granule formation without using liquid solution as the product may be sensitive to moisture and heat. In this process dry powder particles may be brought together mechanically by compression into slugs or by roller compression to obtained flakes.

Wet granulation is the most widely used process of granulation in the pharmaceutical industry. It involves addition of a liquid solution (with or without binder) to powders, to form a wet mass or it forms granules by adding the powder together with an adhesive, instead of by compaction.

Following are the 4 major techniques which are used for wet granulation process.
a) High shear mixture granulation b) Fluid bed granulation
c) Extrusion-Spheronization
d) Spray drying

What are granulation properties that need to be verified before compression?
(1) Moisture content
(2) Bulk density of powder
(3) Angle of repose
(4) Carr Index.

Following properties should be verified before compression:

1. Particle size & shape: Particle size of granulation affect the average tablet weight, weight variation, disintegration time, friability, granule flow ability. The methods for determine particle size and size distribution are sieving, microscopy and sedimentation.

2. Surface area: Dissolution of a drug depends on surface area of powder
materials or granules. The most common method for determination of surface area is gas adsorption and air permeability.

3. Density: Granule density may influence compressibility, tablet porosity, dissolution and other properties. Generally three types of density arises for

4. Strength & Friability: After formation of granules these are used for tableting. Granules are aggregation of component particles that is held together by bonds of infinite strength. Measurement of granule strength is estimation of attractive forces seeking to hold the granules together. Friability is the ability to formation of fines or fragments. Strength can be measure by placing the granules between two anvils (flat face) and force required to break the granules is measured.

5. Flow properties: For the movement of granules from hopper to die cavity sufficient flow properties are essential. Improper flow causes weight variation of content uniformity. Factors affecting flow properties are:
(a) Frictional forces
(b) Surface tension forces
(c) Mechanical forces caused by interlocking of particles of irregular shape
(d) Electrostatic forces
(e) Cohesive or Van der Waals forces.

Flow properties of granules can be measure by two methods:
(a) Angle of Repose
(b) Hopper Flow Rate

6. Compaction: This measure the force applied during compression. Tablet presses are instrumented by affixing transducers to measure the forces. The signals produced by transducers are converted to digital output by computer.

Studies say should next generation drugs be predominantly protein or peptide based, tablets may no longer be the dominant format given the difficulty of dosing such moieties orally. What is your take on this?
Agreed, implant technology, micro spheres and liosome, formulations are on the increas for poorly soluble drugs. The increased research into biopharmaceuticals so far has generated predominantly chemical entities with low molecular weights. The developments of enhanced oral protein delivery technology by immediate release tablets which may release the drugs at an enhanced rate are very promising for the delivery of poorly soluble drugs high molecular weight protein and peptide. The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and ease of administration lead to high levels of patient compliance.

Modern rotary tablet machines look more sophisticated and have more instrumentation today, but why the basic technology has not significantly changed in several decades?
Introduction of specially headed tools (that increase the dwell time) and exchangeable turrets are the signs of further improvement in the technology of tabletting machines. All these machines work on basic principle of compaction.

a) There are different types of tooling with the same principle of compaction.
b) Modern rotary tablet machines look more sophisticated and have more instrumentation today. But the basic technology has not significantly changed in several decades. Tablet development still requires a degree of skill and art, primarily because of the uncertainty of the physics within the material under compaction that thwarts the simple correlation of raw-material properties with finished tablet properties, even for the simplest direct compression processes. Wet and Dry granulation methods add further complexity to the manufacturing process. Compaction simulators, process analytical technologies (PAT), and

advanced computational techniques increasingly are used to minimize this tabletting black box, but fundamental predictability remains elusive.

How do you deal with drugs that resist compression into dense compacts, owing to amorphous nature and low density character?

By slugging followed by the conversion of fine and amorphous order to crystalline high dense material to increase flow property and compressibility and by compaction -- with the help of a compactor -- We can deal with this type of drugs by adopting compaction process and increasing no of compaction cycles or by wet granulation process using binder/adhesive to get desire buck density.

How do you view the use of PAT (Process Analytical Technologies) hailed as another approach to improving manufacturing processes such as tableting?

1. Real time quality assurance.
2. Reduce cycle time (lead time of testing)
3. Enhance root cause Analyses tool (first time right)

a) Yield equipment opportunity with PAT.

b) PAT is a general term covering the application to drug manufacturing of process analytical chemistry tools, feedback process controls, information management, and product / process optimization. The implementation of these technologies involves the online measurement of quality and performance together with multivariate statistical and pattern recognition methods. PAT has been strongly advocated by FDA to encourage innovation and improvement in an industry in which manufacturing processes have long been recognized as relatively inefficient.

Which are different types of Coatings applied for Tablets?

1. Sugar Coated Tablets (SCT)
2. Film Coated Tablet (FCT)
3. Enteric Coated Tablet (ECT)
4. Compression Coating
5. Gelatin coated Tablet

What are the crucial parameters and role of Coating the Table in pharma industry?

To ensure the consistent product quality, certain elements of process need to be controlled regardless of coating pan system. The crucial parameters to be controlled in pan-spray film coating process are:

Pan Variables: Pan design / baffling, Speed, Pan Load.

Process Air: Air quality, Temperature, Air flow rate / volume.

Spray Variables: Spray rate, Degree of automisation, Spray pattern, Nozzle to bed distance.

What are the solutions on offer for drugs with poor wetting and slow dissolution properties?

Various techniques are used for the enhancement of the solubility of poorly soluble drugs which include physical and chemical modifications of drug and other methods like particle size reduction, crystal engineering, salt formation, solid dispersion, use of surfactant, complexation, and so forth. Selection of solubility improving method depends on drug property, site of absorption, and required dosage form characteristics.

What are the stages involved in Dissolution Testing and Interpretation?

1. Preparation of suitable need ie
2. Equilibration of media
3. Liberation of solute or drug from formulation matrix (Disintegration)
4. Solubilisation of drug particle in liquid medium and dissolution under level S1, S2 S3.

(a) Stages are S1, S2 & S3

Stages	No. tested	Acceptance criteria
S1	06	each tablet is not less than Q+5%
S2	06	avg. of 12 tabs (S1+S2) is =>Q and no tab is less than Q-15%
S3	12	avg. of 24 tabs (S1+S2+S3) is =>Q and more than 2 tabs are less than Q-15% and no tab is less than Q-25%

Please give us details of various types of the Dissolution Testers and Physical Testers manufactured / available in market

a. 1) Basket method (USP apparatus -1)
2) Paddle method (USP apparatus)
3) Reciprocating cylinder (USP method-3)
4) Flow through cell (USP Method-4)

b. 1) Lab India
2) Electro Lab
3) Simadzu

Why does the industry have a small volume batch-centred approach both for preliminary blending or granulation and subsequent film coating?

a. Industry encourages small batch size to avoid risk involved in bigger batch size and to prove the repeated CQA (quality attributes) and CPP (critical process parameters) in lab scale batches before going to scale up batches.

b. Workings in small batches ensure that start up can minimise the expenditure of the time, money and effort that ultimately turns out to have been wasted. Risk with product can be minimized with a smaller batch.

Do you agree that tablet development still requires a degree of skill and art, primarily because of the uncertainty of the physics within the material under compaction that thwarts the simple correlation of raw-material properties with finished tablet properties, even for the simplest direct compression processes? Also wet and dry granulation methods add further complexity to the manufacturing process.

Agreed! Various classifications of powder properties require different methods of manufacturing. Yes, I believe that there is always a scope for further advancement in the technology that can reduce the complexity of the manufacturing process. Modern rotary tablet machines look more sophisticated and have more instrumentation today, but the basic technology has not significantly changed in several decades. Tablet development still requires a degree of skill and art, primarily because of the uncertainty of the physics within the material under compaction that thwarts the simple correlation of raw-material properties with finished tablet properties, even for the simplest direct compression processes. Wet and dry granulation methods add further complexity to the manufacturing process. Compaction simulators, process analytical technologies (PAT), and advanced computational techniques increasingly are used to minimize this tableting black box, but fundamental predictability remains elusive.

Are tablets still the solid dosage form of choice because of patient compliance, high-precision dosing, and manufacturing efficiency?

Yes. Tablets are still the first and primary choice. Tablets have the minimal risk and cost than any other dosage form. Among all dosage forms tablet is the most popular dosage form existing today because of its convenience of self administration, compactness and easy manufacturing. Immediate drug release dosage forms disintegrate rapidly after administration with enhanced rate of dissolution. The oral route remains the perfect route for the administration of therapeutic agents because the low cost of therapy, manufacturing and ease of administration lead to high levels of patient compliance.

What are the disadvantages of tablet dosage form?

A. 1) Can not be given to an unconscious patient
2) Low bioavailability than solution and parentals

B.

1) It involves several steps that causes loss of ingredients including API.
2) A good and compatible formulation requires a number of hit and trials.
3) Difficulty in swallowing (in some patients).
4) Absorption of the active drug depends upon the formulation.

C. Difficult to swallow in case of children and unconscious patients.

Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.

Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.

Irritant effects on the GI mucosa by some solids (e.g., aspirin).

Possibility of bioavailability problems resulting from slow disintegration and dissolution.

What is role of particle detection in table ting process?

A. For online detection unwanted metal particles in tablets.

B. Unwanted / contaminated particles can be detected and simultaneously rejected online with the help of particle detection devices.

C. Each year metal contamination leads to prompts warning letters and recalls of pharmaceutical products. This problem can be minimized through the use of metal detectors at critical points in the pharmaceutical and packaging process.

Today's highly sensitive units not only can detect minute particles of ferrous and nonferrous metals as well as nonmagnetic stainless steel, but also can locate contaminants in products packaged in foil or metalized film.

Can you please elaborate different types of Metal Detectors / Particle Detection Machines?

A. 1) Ferrous, non Ferrous and heavy metal detectors
2) Electromagnetic and eddy current based detectors.

B. 1) Electromagnetic induction measurement type.
2) Multi frequency transmission type
3) Radio frequency transmission type.

C. Type of Metal Detectors:

1) E-Z Tec Pharmaceutical Metal Detector- from Eriez.
2) Goring Kerr DSP IP metal detector- from Thermo Goring Kerr.
3) Lock MET 30+ metal detector - from Lock Inspection Systems, Inc

What are phases and applications of the Inspection Machines in tableting process in pharma industry?

a) Inspection of tablets during compression to know the physical defects of tablets.

b) Inspection of coated tablet to know the good quality of tablets.

c) The tablet inspection machine is widely used in the pharmaceutical industry for carrying out the inspection process on various tablets/capsules.

There are two stages of the inspection process:-

Tablets can be inspected on the upper side and first operator can easily eject the unqualified tablets.

A special conveyor system will automatically flip the tablets to have them inspected and ejected at the bottom sides by the second operator. During both inspection stages the product lies flat on the belt. PPP

A Novel Fast Dissolving / Fast Disintegrating Tablet (FDDT) Technology

Oral delivery is currently the gold standard in the pharmaceutical industry where it is regarded as the safest, most convenient and most economical method of drug delivery having the highest patient compliance.

The tablet is the most widely utilised oral dose format. A novel tablet concept which offers ease of oral administration and benefits of increased patient compliance is the fast dissolving/disintegrating tablet (FDDT). This tablet format is designed to allow administration of an oral solid dose form in the absence of water or fluid intake. Such tablets readily dissolve or disintegrate in the saliva generally within <60 seconds. A number of FDDTs are commercially available for human use using technologies developed by pharmaceutical companies such as Cardinal Healthcare, Jannsen Pharmaceutical, Bioavail, Eurand Yamanouchi.

However, these technologies use either expensive processing technology producing fragile tablets that require costly specialised packaging or use conventional tabletting procedures which give longer than desired disintegration & still require specialised packaging.

Dr Zeibun Ramtoola and her team at the Royal College of Surgeons in Ireland have addressed the above shortcomings by developing a novel, cost effective one step FDDT manufacturing process using conventional tabletting technology for the production of robust tablets suitable for conventional packaging. This proprietary technology is applicable to a wide range of therapeutic agents including generics, thereby adding value, i.e. 'supergenerics' for veterinary or human application.

The oral drug delivery market was estimated to be worth $35bn in 2006 & forecast to reach $52bn by 2010 with a CAGR of 10%. Of this, the FDDT, taste masked & micro emulsion formulation segments constitute a 22% share with an expected CAGR of 17% to 2010. There is a clear opportunity for new enhanced oral products arising within this market segment.

Approximately one-third of the population, primarily the geriatric and pediatric populations, has swallowing difficulties, resulting in poor compliance with oral tablet drug therapy which leads to reduced overall therapy effectiveness. A new tablet dosage format, the fast dissolving tablet has been developed which offers the combined advantages of ease of dosing and convenience of dosing in the absence of water or fluid. These tablets are designed to dissolve or disintegrate rapidly in the saliva generally within <60 seconds (range of 5-50seconds). Due to the constraints of the current FDDT technologies as highlighted above, there is an unmet need for improved manufacturing processes for fast dissolving tablets that are mechanically strong, allowing ease of handling and packaging and with production costs similar to that of conventional tablets.

Formulation advances using a conventional tabletting process have led to the development of mechanically robust tablets which readily dissolve/disintegrate within <50 seconds and can be formulated in a range of sizes from 10 -15mm. The tablets produced are stable, and can withstand shipment in conventional tablet containers without loss of integrity.

Pre-clinical canine studies with a range of formulations have demonstrated palatability and ease of administration. A number of FDDT products for human and veterinary administration are currently under development by the RCSI team for the delivery of water soluble as well as lipophilic drug compounds.

The good news is that there is competitive advantage. It has lower production, packaging and distribution costs compared to current commercially available products. Also the technology is versatile and suitable for the development of enhanced products for veterinary medicines, OTC, Rx medicines & line extensions.

The new proprietary method allows the incorporation of microencapsulated drugs for enhanced bioavailability, flexibility of dosing & immediate and/or controlled release for superior therapeutic benefit. Also patent applications have been filed in 2007 at the EPO & the USPTO to protect this technology and concurrent products. PPP

Solid Oral Drug Testing Equipment market growing at a healthy pace in India

Mr. Sandeep Shah
Managing Director
Erweka India

The market in India for this sector is developing at a healthy pace. Indian market in general is good so far. In the near future it will definitely grow well, as most of the companies are launching their products in solid dosage form. Most of the companies are upgrading the overall Quality Standards and looking for quality instruments, which not only give consistent performance, but also compliance to all regulatory bodies like USFDA and MHRA amongst others.

At Erweka we manufacture and supply a full range of Dissolution Testers and Physical Testers. We are having full range of Dissolution Testers starting from USP-1 to USP-7 (basket, paddle, paddle over disk, rotating cylinder, bio-dis, flow through cell,) in standalone mode as well as in offline mode with Auto Sampler and Online with UV and with HPLC also. For Oncology and Hormones product we are having ROBODIS-II. It is a fully automatic machine compliant with USP / EP and also extremely useful for huge volume products, where continuous Dissolution Testing is to be done. For media preparation we are having Mediprep 820.

For Physical Parameter Testing we have Disintegration Testers – Manual as well as with Automatic Detection used in combination with CFR 21 / part 11 Compliance Software. In Tablet Hardness Testing we have the widest possible range – right from manual testing–model iHT 100 to fully automatic Multicheck 5.1 to test up to approximately 1200 in single loading. And of course specialized software is also available in the form of MC.Net again with CFR 21 / Part-11 Compliant.

Other routine equipments like Friability Tester, Leak Detection Tester, Tap Density Tester and Powder Flow-ability Tester for measurement of Angle of Repose is also available from many years. And last but not the least, Erweka's flagship product– the all purpose equipment with various attachments, which was the first product from ERWEKA way back in 1951. This product is very popular in R&D as well as academic institutions like universities.

Let me now talk about the trends being witnessed in this sector. Equipment choices would be affected should solid dosage form technologies change in response to the unprecedented shifts in drug discovery such as genomics. There will be huge change in selection of equipments not only to manufacture but also to test, if change happens from Solid Dosage to Genomics. It will be very big impact and lot will be required to be done.

Also studies being conducted give an indication to another interesting trend - should next generation drugs be predominantly protein or peptide based, tablets may no longer be the dominant format given the difficulty of dosing such moieties orally. Nowadays so many companies are investing a lot of money for novel drug delivery systems like drugs which can be directly injected in veins, or chewable or even to use on medical devices like Sten. Definitely it has various advantages than solid dosage. But tablets are still the most used form of drug delivery and it will take very long time to see major impact. And I am sure many scientists are working to find more suitable options for drug delivery.

Let us also take a look at the modern rotary tablet machine. The modern rotary tablet machines look more sophisticated and have more instrumentation today, but basic technology has not significantly changed in several decades. As rotary tableting machine is a production equipment so the industry also always looks for technology, which can give higher & higher productivity. Unless and until new formulation is developed in innovative way, the basic technology will remain the same. To manufacture the tablet, one needs to mix powder–blend–sieve and compress in tableting machine. Unless, new way is found to compress the granules there cannot be any change in basic technology. But of course, improvements happen in increased precision and consistency supported by documentary evidence.

Of late there has also been a lot of discussion on the pros and cons of tablet dosage. But I believe like any other thing, tablet dosage form also has its own benefits and disadvantages. Carrying the required quantity of tablets as well as swallowing the same is major disadvantages of tablet dosage form. Also few molecules are difficult to compress and few other have taste issues. Apart from these manufacturing issues–the process time, involvement of various equipments, etc are some other disadvantages.

One should also remember designing formulation process is also important as dealing with drugs that resist compression into

dense compacts, owing to amorphous nature and low density character is a challenge. In formulation there are two methods of formulation one is Wet Formulation and second is Dry Formulation. Today, most of the drugs are developed by Wet Formulation. Some drugs that resist compression into dense compacts are required to add some binders and / or lubricants. Usually for low density drug more suitable is Dry Granulation method. So depending on behavioral pattern of molecule, the process is designed.

But for drugs with poor wetting and slow dissolution properties, it might be required to verify the effects by changing the Excipients and / or Binders etc. Also we need to verify what is the location intended for drug release like whether it is the stomach or the upper or lower intestine. The intended location can decide whether the drug is Immediate Release or Sustained / Modified Release. One of the physical parameter-Hardness also plays a role. If the Hardness is higher, Dissolution is slow. So we need to reconfirm the desired Hardness.

Before undertaking compression one has to verify granulation properties like percentage of active ingredient, non-active ingredient, excipient, lubricant, binders, process temperature, process RPM, mixing time and granules size. These are the properties that need to be verified before compression. As any one of these or in combination of, has great impact on tablet

Many in the industry are also talking about the use of PAT (Process Analytical Technologies) hailed as another approach to improving manufacturing processes such as tableting. But Dissolution Tester by itself does not Analyze and need UV and / or HPLC. Hence as far as the Dissolution Tester is concerned the role of PAT is very limited. However, in Hardness Tester, when it is connected to Tablet Press online, it measures the Hardness–compares with predefined requirement and gives the feedback to Tablet Press–again depending on understanding of Protocol and level of Automation incorporated in Tablet Press, such feedback of Hardness Tester is analyzed and corrective action is taken by Tablet Press. So in such case, PAT is very useful tool.

We should take into account that the industry at large has a small volume batch-centered approach both for preliminary blending or granulation and subsequent film coating because a small volume batch is very cost effective approach and especially useful for the companies who are into manufacturing of wide product range. It is not only easy for material saving – providing better yield, but also space and set up cost for equipments is less.

Tablet development still requires a degree of skill and art, primarily because of the uncertainty of the physics within the material under compaction that thwarts the simple correlation of raw-material properties with finished tablet properties, even for

compression. I would also like to list out the following stages which are involved in Dissolution Testing and Interpretation. The typical stages are as below:

PREPARATION OF INSTRUMENT–In this instrument calibration is done mechanically, followed by RS (Reference Standard) tablets. Detailed information is provided in respective Pharmacopeia on how to perform such procedures. After the proper qualification, instrument is cleared to carry out the test.

PREPARATION OF MEDIA–Media is required to prepare as per the product monograph and also need to follow the procedures like Media Degassing – very detailed information is available in Pharmacopeia on this.

SAMPLE WITHDRAWAL–A sample or series of samples are required to be withdrawn depending on Product monograph at precise time at the "midway zone" in required volume and if necessary Media replacement to be done.

ANALYSIS–Once the sample are withdrawn, the analysis is done either on UV-Spectrophotometer or HPLC - with or without dilution to check the absorption.

the simplest direct compression processes. Yes I believe that to develop a tablet, it requires high degree of skill because at each and every stage close monitoring is required. Of course, now with PAT and in-process tests have come into play to assist. Even if detailed SOP is prepared and is being followed very strictly, visual inspection is of great help. And things also boil down to the skill of the machine operator, which he / she has gained over a period of time. Apart from all this, compliance for various Pharmacopeia and methods of manufacturing Wet or Dry makes things more & more complicated. Hence, it is not only just science, but skill that also that plays a major role. So I can say that it is combination of both!

In the end I will only say that tablets are still preferred choice in solid dosage (solid dosage itself is preferred way of drug delivery) because of patient compliance, high-precision dosing, and manufacturing efficiency. Also we need to understand that it is easy to handle, easy to pack, high precision dosage. Most of the drug release is developed on Solid Dosage so far and more than 70% of drugs today are in the form of Solid Dosage. Other drug delivery / novel drug delivery concept is not so old compared to Solid Dosage. PPP

MDTs (Mouth Dissolving Tablets) – Trends in Formulation Technology

Path breaking research in formulation is breaking barriers of conventional methods. Mouth Dissolving Tablets (MDTs) have taken over an important, vital and niche position in the pharma industry by overcoming administration problems and contributing to extension of a patient's life, having difficulty in swallowing tablets and capsules.

Upon introduction into the mouth, these tablets dissolve/disintegrate in the mouth without additional water for easy administration of pharmaceutical ingredients. These dosage forms are also used to attain instant a higher concentration of drug in body for immediate actions. These are novel dosage forms which dissolve in mouth cavity within a few seconds. This article attempts at discussing the ideal properties, advantages, limitation, choice of drug candidates, need of formulation, approaches for preparation of MDTs, Patented technologies on MDTs and Evaluation tests of MDTs.

Mouth dissolving tablet offer's numerous advantages over conventional dosage forms because of improved efficacy, better patient compliance, and acceptance. Mouth dissolving tablet have characteristic advantages such as administration without water, anywhere, anytime lead to their increased patient compliance in today's scenario of hectic life. Considering the many benefits of Mouth dissolving tablets, a number of formulations are prepared in MDT forms by most of the pharmaceutical companies. By Using the Mouth dissolving tablet the bioavailability of drug and rapid onset can be achieved.

INTRODUCTION

The concept of Mouth dissolving dosage forms has emerged from the desire to provide patients with more conventional means of taking their medication. Interestingly, the demand for MDT's has enormously increased during the last decade, particularly for geriatric and paediatric patients who experience difficulty in swallowing conventional tablets and capsules.

Since the development cost of a new drug molecule is very high, efforts are now being made by pharmaceutical companies to focus on the development of new drug dosage forms for existing drugs with improved safety and efficacy together with reduced dosing frequency, and the production of more cost effective dosage forms. Among the dosage forms developed for facilitating ease of medication, the mouth disintegrating systems have been the favourite of product development scientists.

For most therapeutic agents used to produce systemic effects, the oral route still represents the preferred way of administration, owing to its several advantages and high patient compliance compared to many other routes.

However, many patient groups such as the elderly, children and patients who are mentally retarded, uncooperative, nauseated or on reduced liquid-intake/diets have difficulties swallowing these dosage forms.

Mouth Dissolving tablets are oral solid dosage forms that disintegrate in the oral cavity in easy swallow residue. Mouth dissolving tablets are also known as 'Orodispersible tablets', 'Orally disintegrating tablets', 'Melt-in-mouth', 'Fast dissolving drug delivery', 'Rapimelts tablets', 'Porous tablets', 'Quick dissolving tablets' etc.

Recently ODT terminology has been approved by United States Pharmacopoeia, British Pharmacopoeia, and Centre for Drug Evaluation and Research (CDER).

Mouth dissolving tablet (MDT)

It is a tablet that disintegrates and dissolves rapidly in the saliva, within a few seconds without the need of drinking water or chewing. A mouth dissolving tablet usually dissolves in the oral cavity within 15 s to 3 min. Most of the MDTs include certain super disintegrates and taste masking agents.

Ideal properties of Mouth Dissolving Tablets

The MDTs performance is depends on the manufacturing technology and the most necessary property of such a dosage form is the ability of rapidly disintegrating and dispersing or dissolving in the saliva, Therefore there is no need to take water along with MDTs. Important desirable characteristics of these dosage forms includes;

- Should dissolve or disintegrate in the mouth within a few

seconds.
- High drug loading should be allowed.
- They should be compatible with taste masking and other excipients.
- The mouth feel should be pleasant.
- After oral administration they should leave minimal or no residue in mouth.
- To withstand the rigors of the manufacturing process and post manufacturing handling, they must have sufficient strength.
- They should be less sensitive to environmental conditions such as humidity and temperature.
- The cost of manufacturing of tablets should be low.

The Need for Development of MDTS

The need for Mouth Dissolving drug delivery systems persists due to patient's poor acceptance and or compliance. Mouth dissolving dosage forms are particularly suitable for patients, who have inconvenience to swallow traditional tablets and capsules.

These include the following:
- Paediatric and geriatric patients who have difficulty in swallowing or chewing solid dosage forms
- An eight-year old with allergies who desires a more convenient dosage form than antihistamine syrup.
- A middle-aged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her H2-blocker.
- Patients who are unwilling to take solid preparation due to fear of choking.
- Very elderly patients who may not be able to swallow a daily dose of antidepressant.
- A schizophrenic patient in an institutional setting who may try to hide a conventional tablet under his or her tongue to avoid their daily dose of an atypical antipsychotic.
- A patient with persistent nausea, who may be journey, or has little or no access to water.

Advantages of Mouth Dissolving Tablets
- Patient's compliance for disabled bedridden patients and for travelling and busy people who do not have ready access to water.
- Ease of administration to patients who cannot swallow, such as the elderly, stroke victims and bedridden patients; patients who should not swallow, such as renal failure patients; and who refuse to swallow, such as paediatrics, geriatric and psychiatric patients.
- Pre-gastric absorption can result in improved bioavailability, reduced dose and improved clinical performance by reducing side effects.
- Good mouth feel property of Mouth Dissolving Drug Delivery System helps to change the basic view of medication drugs.
- Convenience of administration and accurate dosing as compared to liquid formulations.
- Benefit of liquid medication in the form of solid preparation.
- More rapid drug absorption from the pre-gastric area i.e. mouth, pharynx and esophagus which may produce rapid onset of action.
- New business opportunities: product differentiation, line extension and lifecycle management, exclusivity of product promotion and patent-life extension.

However, mouth dissolving tablets have their own limitations. The tablets usually have insufficient mechanical strength. Hence, careful handling is required. Also the tablets may leave unpleasant taste and/or grittiness in mouth if not formulated properly.

Important is the drug selection criteria in a MDT. So the ideal characteristics of a drug for Mouth Dissolving Tablet include ability to permeate the oral mucosa, should be at least partially non-ionized at the oral cavity pH. The MDT should have the ability to diffuse and partition into the epithelium of the upper GIT and should have small to moderate molecular weight. The MDT should also have low dose drugs preferably less than 50 mg and should have short half life as frequent dosing drugs are unsuitable for MDT. Drugs used in MDT should have good stability in saliva and water. Very bitter or unacceptable taste and odour drugs are unsuitable for MDT.

Also the role of excipients is important in the formulation of Mouth Dissolving tablets.

These inactive food-grade ingredients, when incorporated in the formulation, impart the desired organoleptic properties and product efficacy. Excipients are general and can be used for a broad range of actives, except some actives that require masking agents.

Binders keep the composition of these Mouth Dissolving tablets together during the compression stage. Important ingredients that are used in the formulation of MDTs should allow quick release of the drug, resulting in faster dissolution. This includes both the actives and the excipients. Disintegration and solubilzation of a directly compressed tablet depend on single or combined effects of disintegrants, water-soluble excipients and effervescent agents.

Technologies used in preparation of Mouth Dissolving Tablets

The basic approaches to developing MDTs include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent, and using highly water-soluble excipients in the formulation. Various technologies used in the manufacture of MDTs are as follows:

Conventional Technologies

Lyophilization or Freeze drying method

A process in which water is sublimated from the product after freezing is called as Lyophilization – a pharmaceutical jargon which allows drying of heat sensitive drugs and biological at low temperature under conditions that allow removal of water by sublimation. Lyophilization results in preparations, which are highly porous, with a very high specific surface area, and which dissolve rapidly and show improved absorption and bioavailability.

Lyophilization was also used to create an oral pharmaceutical preparation that not only dissolves rapidly but also improved the bioavailability of several drugs such as spironolactone and trolendomycin.

Over the years, studies were carried out of various formulation and process parameters by using hydrochlorothiazide as a model drug on the basis of which US Patent 6,010,719 was granted. Tablets prepared by lyophilization, are fragile and possess low mechanical strength, which make them difficult to handle and they also exhibit poor stability on storage under stressed conditions.

Sublimation

Sublimation has been used to produce MDTs with high porosity. A porous matrix is formed by compressing the volatile ingredients along with other excipients into tablets, which are finally subjected to a process of sublimation. Inert solid ingredients with high volatility (e.g. ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethylenetetramine, naphthalene, phthalic anhydride, urea and urethane) have been used for this purpose. Solvents such as cyclohexane and benzene were also suggested for generating the porosity in the matrix.

Molding

The major components of molded tablets typically are water-soluble ingredients. The powder mixture is moistened with a solvent (usually ethanol or water), and then the mixture is molded into tablets under pressures lower than those used in conventional tablet compression. (This process is known as compression molding.) Then the solvent can be removed by air drying. Because molded tablets are usually compressed at a lower pressure than are conventional compressed tablets, a higher porous structure is created to enhance the dissolution. To improve the dissolution rate, the powder blend usually has to be passed through a very fine screen. Recently, the molded forms have also been prepared directly from a molten matrix in which the drug is dissolved or dispersed (known as heat molding) or by evaporating the solvent from a drug solution or suspension at ambient pressure (novacuum lyophilization).

Spray Drying

Spray drying is a process by which highly porous, fine powders can be produced. Spray-dryers are invariably used in the pharmaceutical industry to produce highly porous powders. There have been reports of applying this process to the production of fast dissolving tablets. The formulations that were produced contained hydrolyzed and unhydrolyzed gelatine as a support agent for the matrix, mannitol as a bulking agent, and sodium starch glycolate or crosscarmellose as a disintegrant. Disintegration and dissolution was further enhanced by adding an acid (e.g. citric acid) or an alkali (e.g., sodium bicarbonate). The formulation was spray dried to yield a porous powder. Tablets manufactured from this powder disintegrated in less than 20 second in an aqueous medium.

Mass Extrusion

In this technique, a blend of active drug and other ingredients is softened using solvent mixture of water soluble polyethylene glycol, using methanol and then the softened mass is extruded through the extruder or syringe to get a cylinder of product, which is finally cut into even segments with the help of heated blades to get tablets. The dried cylinder can be used to coat the granules of bitter tasting drugs and thereby masking their bitter taste.

Direct Compression

Easiest way to manufacture tablets is direct compression. Low manufacturing cost, conventional equipments and limited number of processing steps led this technique to be a preferable one. However disintegration and dissolution of directly compressed tablets depend on single or combined effect of disintegrant, water soluble excipients and effervescing agents. It is essential to choose a suitable and an optimum concentration of disintegrant to ensure quick disintegration and dissolution.

Super disintegrants are newer substances which are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. Effective super disintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high dose drugs.

The type of disintegrants and its proportion are of prime importance. Also factors to be considered are particle size distribution, contact angle, pore size distribution and water absorption capacity. Studies revealed that the water insoluble super disintegrants like sodium starch glycolate and Croscarmellose sodium show better disintegration property than the slightly water soluble agents like crospovidone, since they do not have a tendency to swell. Superdisintegrants that tend to swell show slight retardation of the disintegration property due to formation of viscous barrier. There is no particular upper limit regarding the amount of superdisintegrant as long as the mechanical properties of the tablet are compatible with its intended use. The superdisintegrant may be used alone or in combination with other superdisintegrants.

Patented Technologies for MDTs

Zydis Technology

Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolved within the matrix of fast dissolving carrier material. When Zydis units are put into the mouth, the freeze-dried structure disintegrates instantaneously and does not require water to aid swallowing. The Zydis matrix is composed of many materials designed to achieve a number of objectives like imparting strength and resilience during handling. Polymers such as gelatin, dextran or alginates are incorporated. These form a glossy amorphous structure, which imparts strength.

Durasolv Technology

Durasolv is the patented technology of CIMA labs. The tablets made by this technology consist of drug, filler and a lubricant. Tablets are prepared by using conventional tabletting equipment and have good rigidity. These can be packaged into conventional packaging system like blisters. Durasolv is an appropriate technology for product requiring low amounts of active ingredients.

OraSolv Technology

CIMA labs have developed OraSolv Technology. In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimize oral dissolution time. Conventional blenders and tablet machine 100 is used to produce the tablets. The tablets produced are soft and friable.

Flash Dose Technology

Flash dose technology has been patented by Fuisz Technologies. Nurofen meltlets, a new form of ibuprofen as melt in mouth tablets prepared using flash dose technology is the first commercial product launched by Biovail Corporation. Flash

dose tablets consist of self-binding shear form matrix termed as "floss". Shear form matrices are prepared by flash heat processing.

Wow Tab Technology
Wow tab technology is patented by Yamanouchi Pharmaceutical Co. WOW means 'Without Water'. In this process, combination of low mouldability saccharides and high mouldability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide (e.g. lactose, glucose, and mannitol), granulated with a high mouldability saccharide (e.g. Maltose, oligosaccharides) and then compressed into tablet.

Flash Tab Technology
Prographarm Laboratories have patented the Flash Tab Technology. Tablet prepared by this system consists of an active ingredient in the form of micro crystals. Drug micro granules may be prepared by using the conventional techniques like coacervation, micro encapsulation and extrusion spheronisation. All the processing utilized conventional tabletting technology.

EVALUATION OF MOUTH DISSOLVING TABLETS

Tablet Thickness
Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Thickness was recorded using micrometer.

Weight Variation
Standard procedures are followed as described in the official books.

Friability
Friability Attempts for decreasing the disintegration time increase the friability of MDTs than the conventional tablets. Dosage forms like Zydis are very fragile. Friability is a measure of mechanical strength of the tablet. If a tablet has more friability it may not remain intact during packaging, transport or handling. Roche friabilator is used to determine the friability by following procedure. Pre weighed tablets are placed in the friabilator. Friabilator consist of a plastic chamber that revolves at 25 rpm, dropping those tablets at a distance of 6 inches with each revolution. The tablets are rotated in the friabilator for at least 4 minutes. At the end of test tablets are dusted and reweighed; the loss in the weight of tablet is the measure of friability and is expressed in percentage as: % Friability = 1- (loss in weight / Initial weight) X 100.

Hardness (Crushing Strength) Tablet hardness is measured with hardness testers like Monsanto. A tablet is placed in the hardness tester and load required to crush the tablet is measured. The hardness of MDTs is generally kept lower than conventional tablets as increased hardness delays the disintegration of the tablet. A good compromise between mechanical strength and disintegration time is achieved for a satisfactory mouth dissolving formulation.

Wetting Time & Water Absorption Ratio
Wetting time of dosage form is related to with the contact angle. Wetting time of the MDT is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablet. Lower wetting time implies a quicker disintegration of the tablet. Five circular tissue papers of 10cm diameter are placed in a Petri dish. Ten millilitres of water soluble dye solution is added to Petri dish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as the wetting time. For measuring water absorption ration the weight of the tablet before keeping in the Petri dish is noted (Wb). The wetted tablet from the Petri dish is taken and reweighed (Wa). The water absorption ratio, R can be the determined according to the following equation. R = 100 (Wa-Wb)/Wb.

Disintegration Time
According to the European pharmacopoeia the fast disintegrating or Orodispersible tablets should disintegrate within 3 minutes without leaving any residue on the screen.

However it is difficult to assess the disintegration rate even in small amounts of water. Further the conventional test employs a volume of 900 ml of distilled water compared to the volume of saliva in humans, which is limited to a few ml. Thus the disintegration rate obtained from conventional test does not appear to reflect the actual disintegration rate in human mouth. To overcome these problems, several new methods have been proposed. One of these methods uses a Charge Couple Device (CCD) camera or texture analyzer to evaluate the disintegration time of tablets. In another method, a modified DT apparatus is used. Here a wire basket of 3cm height and 2 cm diameter and mesh size of #10 is placed above a beaker containing 900 ml of simulated saliva. The basket is so positioned in the liquid that it contains only 6 ml of the liquid. The assembly is supported with a heater to maintain temperature at 37°C and a magnetic stirrer. DT is noted at 25 rpm. One of the simplest methods is to take 6ml of simulated saliva in a measuring cylinder and place the tablet in it. The liquid is neither shaken nor stirred and DT is noted.

In Vivo Disintegration Time
In vivo disintegration time is determined using a panel of healthy human volunteers. The DT noted by the volunteers by placing the tablet in mouth.

Dissolution Test
The dissolution method for oral disintegrating tablets is the same as that of conventional tablets. USP 2 paddle apparatus is most suitable and common choice for dissolution test of oral disintegrating tablets, where the paddle speed is 50 rpm is used. The USP 1 (basket) apparatus may have certain application for such tablets but is used less frequently due to specific physical properties of tablets.

Stability Study (Temperature Dependent)
The mouth dissolving tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies. (i) 40 ± 1 °C (ii) 50 ± 1°c (iii) 37 ±1 ° C and RH 75% ± 5%. The tablets were withdrawn after 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability, Disintegrations, and Dissolution etc.) and drug content.

Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25 °

Selection of right equipment and right validation of paramount importance in tabletting process

Mr. V. Balaji
Business Head – Press Division
Parle Elizabeth Tools Pvt. Ltd.

Please give us a bird's eye view of the specialised sector you deal in?
Parle Elizabeth press range is mainly targeted at the electronic and instrumented end of the press to R&D – Pilot Scale – Commercial Scale with our models of EP 200 – EP 200L – EP 400 and EP 700. All the models above are with instrumentation to acquire data through high speed processors and with automatic control of tablet weight by compression force.

How has the market developed for this sector in India? And what does the future hold?
This market is fairly matured with the presence of imported machines from the USA, Europe and other Asian countries. Machines from the USA and Europe are not easily available to Indian companies catering the vast domestic market. Some of the Indian manufacturers have found the export market lucrative with their semi instrumented and not instrumented machines than the domestic market. Parle's focus will be to tap the domestic pharma companies and the market being currently catered by the European machinery manufacturers.

How equipment choices would be affected should solid dosage form technologies change in response to the unprecedented shifts in drug discovery such as genomics?
Gene therapy could be useful in preventing life threatening genetic or hereditary ailments or ailments related to metabolism, but there is a lot of knowledge that needs to be gained before the genetic mapping of Humans(with more than 50,000 genes) to have fail proof therapy. Additionally there is the issue of offspring of genetically modified humans. It is our earnest belief that solid dosage market will not diminish in the near future.

What is role of Granulation in pharma industry to obtain the optimum results in Tableting Process?
The best suited granulation process to obtain optimum results are dependent on product characteristics and machine being employed. There are different challenges in each process. For instance, wet granulation could be a preferred process for tablet compression, but from the point of view of validation of scale up procedure from pilot to commercial, wet granulation process poses many hurdles. Dry granulation is easier to scale up and validate, but cannot be applied for very many products. Hence, product characteristics determine the process and the equipment efficiency will vary based on the measurements and controls that are available. By and large electronic presses are in a better position to handle any type of granulation delivering consistent quality at medium speeds of the presses.

Which are the different techniques of granulation technology on large scale in pharma industry?
By and large wet granulation, but the consistency is determined by the selection of the process equipment with controls

What are granulation properties that need to be verified before compression?
Flow properties of the blend, compressibility index, sieve size uniformity, bulk density are few properties that govern the tablet test results.

Studies say should next generation drugs be predominantly protein or peptide based, tablets may no longer be the dominant format given the difficulty of dosing such moieties orally. What is your take on this?
Even today, more than 80 % of the products are in solid dosage forms owing to the buying capability of the patients. Even many developed countries in order to cap the growing health care costs and insurance costs are opting for cheaper generics alternative. In such a scenario, the solid dosage forms will be the most preferred form of administering medicines + patient compliance as well for these easily administrable and economic option available.

Modern rotary tablet machines look more sophisticated and have more instrumentation today, but why the basic technology has not significantly changed in several decades?
There has been many changes and very significant in the last few years. Most primitive presses such as single stroke presses were used in R&D for a very long time, but today many companies are investing in presses that have capabilities similar to the production presses. Weight control of tablet in the early instrumented presses were limited to single layer tablets, but today, we have presses such as our EP 400 which measure and

control individual layer weights in bi layer tablets.

Sampling of 1st layer tablet individually was not available, now we have the option, right from our R&D presses with option of making a hard 1st layer tablet during sampling. The current electronic and instrumented presses available provide enough information to develop products with designed/desired end test results.

Like any other industry, the process has not changed, but how the process is measured, governed and controlled to get consistent results have improved and developed multiple times. The significant increase in yield, output and consistent quality has reduced the cost of manufacturing.

How do you deal with drugs that resist compression into dense compacts, owing to amorphous nature and low density character?
There is a common misconception that if the press is equipped with 100KN pre compression and 100Kn main compression, then the machine is best suited for compressing any product, which is not true. 95% of the products are compressed at forces less than 35kn and the remaining could be compressing at 39kn-45KN max. What is important is uniform filling of blend, drive which can deliver constant torque, sturdy construction to deliver the necessary inertia. This is not achieved with just metal mass, but designing and executing a balanced press with proper metallurgy and reinforcement construction through the path of force distribution. Precision machine components reduce the noise, vibration significantly and produces tablets are much lesser compression forces. Producing tablets at high compression forces also reduces the bio availability of the product.

How do you view the use of PAT (Process Analytical Technologies) hailed as another approach to improving manufacturing processes such as tableting?
Any measurement and control of process produce consistent results and Electronic presses are in-built with such features which deliver the benefits of PAT even without practising them consciously.

Which are different types of Coatings applied for Tablets?
Be it film or sugar, the industry is moving towards functional coating methods for achieving the necessary product results in medication.

What are the crucial parameters and role of Coating the Table in pharma industry?
Coating is 3Ds – Dosing, Distributing and Drying. Measure and control theses parameters scientifically, rest all takes care by itself.

What are the solutions on offer for drugs with poor wetting and slow dissolution properties?
Fibrous product absorbs moisture slowly and releases slowly. Compression coating could be a solution i.e. core tablet coating. This process gives greater control over the coating process.

Why does the industry have a small volume batch-centered approach both for preliminary blending or granulation and subsequent film coating?
The reason could be to reduce the process time and queue time. There is no balanced plant; it is about balancing the flow of material. The process time should be such that, there is no huge WIP waiting to be processed in front of a bottle neck process or machine. Longer process means, higher WIP as longer the process, longer is the time material spends inside the plant from being raw material to finished component.

Do you agree that tablet development still requires a degree of skill and art, primarily because of the uncertainty of the physics within the material under compaction that thwarts the simple correlation of raw-material properties with finished tablet properties, even for the simplest direct compression processes?
Process stability decides the necessity of being skillful or whether a scientific approach is needed towards achieving consistency and repeatability. Of course, variation in raw material increases the variables, but today every process provides information and data to analyse, to correct and refine the process and the end product result, it is not an art and skill, but selection of right equipment and validation of the process.

What are the disadvantages of tablet dosage form?
Yes, tablets are the most preferred form owing to its stability, economics and the ease of manufacturing. If we have claim in disadvantage in tablet formulation, it could be the necessity of excipients addition to make the product with LOW API content.

What is role of particle detection in tabletting process?
Metal particles find itself in the tablets because of USER'S ignorance of the process and the failure of components in contact with the product. The role of the metal detector is not to allow tablets with metal particles of more than 0.3 to 0.5mm pass through successfully to good tablet bin.

Can you please elaborate different types of Metal Detectors/Particle Detection Machines?
There are broadly digital and analog type metal detectors with self correction. Vision inspection system for cosmetic application is manual type and automatic type.

What are phases and applications of the Inspection Machines in tableting process in pharma industry?
100% finished product inspection is not mandatory, but is practiced till the manufacturing process is stabilized and for batches wherever there is a doubt over any surface defects. Many companies does 100% inspection for regulated market like JAPAN, USA & UK and for high value products.

QbD in Tabletting Process:
Can you please give an overview on optimizing Tabletting Processes with Quality by Design?
Adopting QbD helps in providing necessary data for analysis to determine the best suited manufacturing practice for the product to get the desired tablet compressibility, tablet parameters to achieve the designed results analytically and clinically.

Success in tabletting does indeed depend on many factors. It is important, for example, to control the flowabilty and compressibility of the tabletting blend, as well as any tendency towards segregation, to ensure the production of uniform tablets at the required rate. Particle size and particle size distribution are recognised as critical material attributes because they are known to directly impact these properties, as well as others such as solubility and bioavailability, which may

define clinical efficacy as highlighted in ICH Q6A.

This guideline is intended to assist to the extent possible, in the establishment of a single set of global specifications for new drug substances and new drug products. It provides guidance on the setting and justification of acceptance criteria and the selection of test procedures for new drug substances of synthetic chemical origin, and new drug products produced from them, which have not been registered previously in the United States, the European Union, or Japan.

Can you please highlight the QbD approaches to tabletting and granulation processes?
The pharmaceutical industry is undergoing change. Under fire by political pressures to drive down the cost per tablet, compounded by new drug discovery becoming more

challenging escalating research costs, therefore, the industry is looking to unleash its efficiency shackles of the past. With both the regulators, such as the FDA, recognizing change is needed and an increase in demand for low cost essential drugs from new growth markets and developing nations provides an opportunity to capitalize on efficiency gains with the right technologies. The industry is steeped in a history of batch based manufacturing unlike other sectors such as food and bulk chemicals. This is to give the accountability and traceability required to ensure drug safety to the public. After several years of focus on establishing new ways of analyzing drug variability and quality in the various manufacturing process stages, under the Process Analytical Technology (PAT) initiative, the industry is now able to move to advanced techniques to analyze consistency on a time based approach (RTRT) rather than conventional batch sampling and analysis. The challenge is now for the industry to take this QbD concept and look at its manufacturing processes in 'lean' terms to start to adapt for a more efficient future.

What is the significance of QbD places emphasis on controlling process output, rather than the fixed definition of operating conditions?
In tabletting, a QbD approach would focus on the defining characteristics of the finished product, such as content uniformity and dissolution or disintegration properties.

Which are the key challenges in understanding particle attributes in a tabletting and granulation process
1. Particle size & shape
2. Surface area
3. Density
4. Strength & Friability
5. Flow properties

Factors affecting flow properties are:
(a) Frictional forces
(b) Surface tension forces
(c) Mechanical forces caused by interlocking of particles of irregular shape
(d) Electrostatic forces
(e) Cohesive forces

Flow properties of granules can be measure by two methods:
(a) Angle of repose
(b) Hopper Flow rate PPP

Convert your Double Sided Tablet Press into Bi-Layer Production Machine

Mr. Manoj Singhania
Partner & Technical Director
Adept Engineers

Mr. Manoj Singhania is a graduate of Mechanical Engineering and he is one of the key members of ADEPT Engineers (Singhania Group of companies). He has been associated with the two group companies ADEPT Engineers and Concept Engineering since 1992. ADEPT and Concept are one of the leading manufacturers of Tablet Presses & Tablet Compression Tools in India. Concept has been manufacturing Punches and Dies for over 40 years. Today it's the most reputed manufacturer of Tablet Tooling in India, a result of its unflinching commitment to quality since inception. Founded in 1989 ADEPT has been instrumental in contributing towards the Tablet Making Process; Tablet Press. ADEPT was the first company to introduce the "A" Tooling in the year 1996. These are smaller toolings that can give a much higher output. Also R&D Turrets with different Tooling in the same Turret was introduced by ADEPT. One of the most recent development introduced by ADEPT is the 'Food Grade Multi-Chamber Feed Frame' made of polymer to eliminate the black particles and tablet contamination due to metal feeders. Need to know more on Tablet Presses & Tablet Compression Tools simply connect with Adept Engineers at manoj@adeptexport.com.

Bi-Layer tablets are suitable for sequential release of two incompatible drugs in combination. It is mainly for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. The production of two layer tablets has been an increasingly popular method for increasing sales appeal. This is a good method to make a product instantly identifiable in the consumers mind. The popularity of these kinds of tablets has been on the rise.

It is possible to produce Bi-Layer tablets on any double sided press with two separate compression stations and two separate feeders for each station. The change over process from single layer to bi layer process is fairly simple procedure with minor modifications. The main challenge lies in keeping the two colours totally separate during production and maintaining the correct weight of the two layers. The requirement of a two layer tablet needs two different colour materials that should be free of mixing and have a clearly defined demarcation line showing separate layers.

In a single layer tablet being produced on a double side tablet press, the two feeders complement each other. Excess granules or overflow from one feeder normally flows into the feeder on the other side as mixing of the granules is not a problem.

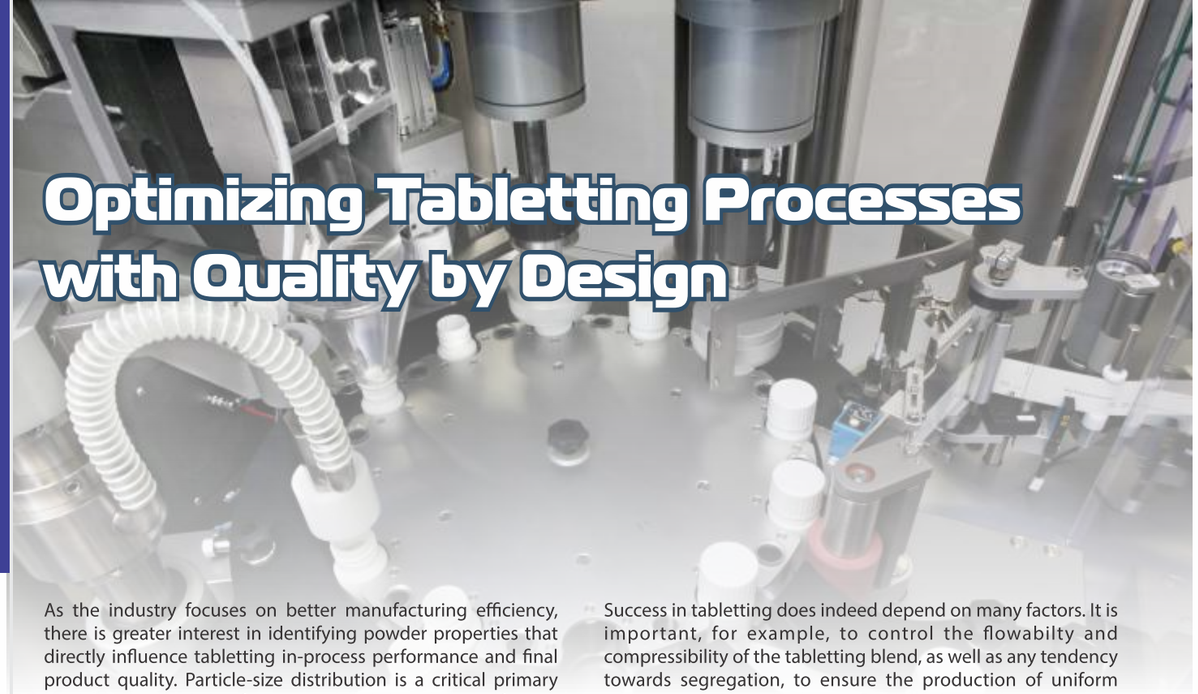
In a Bi-Layer tablet, since the 2 powders are of different material and colours, mixing cannot be allowed. The two layers have to be completely separate. This effects the look of the final tablet as it requires a definite separation line showing two different colours.

Below is a sketch showing the sequence of Bi-Layer Tablets production.

Procedure: In the sketch below the first layer has blue granules and the second layer has red granules.

1. Two special feeders are required that prevent mixing of the two colours. The granules from the first layer are allowed to go around the turret and renter in to the same feeder. The excess granules from the second layer are not allowed to move on to the turret and are collected through a separate outlet.
2. To avoid the ejection of the first layer, the ejection can take place after the first layer feeder has to be removed. This is to enable the second colour to fill on top of the first colour.
3. Press must have a dust extraction system. The feeders have a dust suction facility that can be connected to the dust extraction system. This is extremely useful in preventing the two colours from mixing.
4. It is advisable to put the layer with the higher weight as the first layer and the layer with the lesser weight as the second layer. As the filling in the second layer is limited and it depends on the upper punch entry into the die. The maximum amount of fill of the second layer can be controlled by adjusting the upper penetration system.
5. It is always advisable to put in only the first layer and set its weight. Once the weight of the first layer is set then the second powder is to be introduced and we can set the weight of the final tablet.

If during production the weights of the separate layers need to be checked, then the pressure at the first layer needs to be slightly increased so that the first layer does not bond with the second layer and the two layers come out separate during final ejection. PPP



Optimizing Tabletting Processes with Quality by Design

As the industry focuses on better manufacturing efficiency, there is greater interest in identifying powder properties that directly influence tabletting in-process performance and final product quality. Particle-size distribution is a critical primary particle characteristic of powders, but it is only one of many variables that impact bulk powder properties, which in turn dictate in-process behaviour and product quality. Bulk property measurements can be an efficient way of accelerating and supporting process optimization studies because they quantify the net effect of all primary particle properties (e.g., size, shape, texture, surface energy and porosity), whether these can be measured directly or not. Furthermore, even if all primary particle properties that influence in-process behaviour could be measured, the mathematical relationship between bulk powder behaviour and particle characteristics remains elusive and highly complex. Hence, the most effective way forward is to measure process relevant characteristics of the bulk powder.

Tablet production can be divided into at least four discrete processes:

- Discharge from the hopper
- Flow into and through the feed frame
- Die filling
- Compression
- Each of these processes subjects the powder to a specific set of environmental conditions (e.g., flow rates, stresses, and equipment surface properties), making different bulk properties more relevant at different stages.
- The following are as especially valuable:
- Dynamic flow properties (including Basic Flowability Energy, Specific Energy, Aerated Energy, and Flow Rate Index): To optimise the flow regime in the feed frame and the efficiency of die filling, to investigate the effect of paddle geometry, to assess the likelihood of attrition, segregation and agglomeration.
- Shear properties: For optimising flow from the feed hopper, where shear properties of powder–powder and powder–wall are important.
- Permeability and compressibility: For assessing how easily the powder can transmit air and the impact of compression on the powder. Both characteristics are important during the filling and compression steps.

Success in tabletting does indeed depend on many factors. It is important, for example, to control the flowabilty and compressibility of the tabletting blend, as well as any tendency towards segregation, to ensure the production of uniform tablets at the required rate. Particle size and particle size distribution are recognised as critical material attributes because they are known to directly impact these properties, as well as others such as solubility and bioavailability, which may define clinical efficacy.

As analytical techniques evolve, however, it is becoming easier to identify other parameters that also impact behaviour in the tablet press. Highlighting particle shape, a parameter like particle size, is known to affect powder flowability and segregation. In the past, shape information was gathered by microscopy, but the advent of automated imaging has made it much faster and easier to access statistically relevant data. Such information forms a foundation for scientific investigation of the impact of shape and supports the development of more successful tabletting blends.

QbD approaches to tabletting and granulation processes

QbD calls for product quality to be 'designed in' rather than tested for in postproduction. It requires a detailed understanding of all the factors that can impact product quality and clinical efficacy, including those related to the materials employed and the process itself. Traditionally, it has been assumed that raw materials and intermediates can be suitably qualified and the process can be fixed, resulting in a consistent high-quality product. However, this is only achieved by knowing what material properties need to be qualified. While particle size distribution is important, there are many other particle properties that rarely feature in the specification, but that can be as influential as particle size, such as particle shape and particle surface roughness. Excluding these properties from the quality specification allows variation in raw materials to go undetected, resulting in variable in-process performance and product quality. Adopting a QbD approach requires an acceptance that raw materials are likely to vary batch to batch, while simultaneously demonstrating a good grasp of how to configure the process settings within the 'control space' to accommodate the unavoidable variation in material properties,

and ultimately achieve consistent product with the desired attributes.

Considering a granulation process as an example, this might conventionally be defined in the following terms: Process for A minutes at an impeller speed of B rpm, whilst adding C% of water at a consistent addition rate. Processing conditions are essentially fixed and applied to each new batch of feed. This means that there is little flexibility to respond to variability arising from any source, such as a new batch of excipient or inadequate control of an upstream operation, for example. Furthermore, problems are usually detected only when granulation is complete.

QbD places emphasis on controlling process output, rather than the fixed definition of operating conditions. For granulation, the process definition might change to: manipulate impeller speed, amount of water, and/or processing time, to produce granules with these specific properties. Adopting this approach, however, relies on being able to identify those specific properties—the criteria for success—and also learning how to control them.

In the same way, in tabletting, a QbD approach would focus on the defining characteristics of the finished product, such as content uniformity and dissolution or disintegration properties. Process development then works back from that point, identifying all the factors that influence these properties.

Successful implementation of QbD relies on understanding both the process and product in detail. The focus is on fully evaluating the impact of all variables that influence product quality, and learning how to control them effectively, rather than just identifying a manufacturing route that works. QbD extends through to control of the commercial process so it serves to highlight areas where real-time monitoring can be beneficially applied to meet processing targets.

One important feature of particle size analysis is that, unlike many analytical techniques, it is already a proven technology for real-time plant monitoring. In granulation processes, for example, both in-line probes based on spatial particle velocimetry and on-line laser diffraction particle size analysers are regularly used for real-time measurement. Both enable the continuous tracking of particle size growth during the granulation process towards an established endpoint.

Endpoint detection is a notoriously difficult aspect of granulation so this ability to continuously monitor particle size is extremely useful when manufacturing to meet a defined output, as advocated by QbD. In addition, however, real-time measurement is extremely valuable during design space scoping studies because it enables rapid and reliable assessment of the impact of a change in operating conditions. Continuous particle-size measurement can therefore accelerate and improve the process development studies associated with QbD.

Key challenges in understanding particle attributes in a tabletting and granulation process

The bulk properties that define process ability depend on a wide array of particle attributes, such as particle size and shape, roughness, surface charge, density and porosity. Learning how to control tabletting and granulation processes relies, in part, on understanding the relationships between particle attributes and bulk powder properties. This is an area of specific interest and involved in a number of experimental studies, with industrial partners, to investigate. E.g. what is the influence of particle size and shape and/of surface charge, on powder flowability, shear properties and bulk parameters, such as compressibility and permeability. Because QbD places emphasis on thoroughly understanding the impact of all processing variables, it may call for information that is not easily accessed using conventional testing methods. As a result, the implementation of QbD is encouraging the pharmaceutical industry to adopt new analytical technologies as they become available. One such technology is morphologically directed imaging, which can combine imaging technology with spectroscopy, such as Raman, to provide chemical identification alongside size and shape measurement. It allows different particles in a dispersed sample, often initially screened on the basis of size or shape, to be reliably identified as specific chemical entities.

A conventional way to assay a tablet is to dissolve it and carry out high-performance liquid chromatography analysis. This gives an averaged measure of the concentration of the active that can be used to assess dose consistency, but it provides no information about the size of discrete active particles that are delivered to the body as the tablet disintegrates.

In contrast, applying morphologically directed imaging to a disintegrated tablet sample allows differently sized elements of the resulting powder to be precisely identified as active or excipient. This not only generates useful information for engineering sophisticated drug delivery profiles, but also provides evidence to support claims of bioequivalence for a generic product.

Challenges in bulk powder attributes

The ability of the pharmaceutical industry to understand how bulk powder properties impact process behaviour is constrained because of lack of reliable bulk powder property data. The reproducible measurement of defining powder characteristics, such as flowabilty, has long been a goal, but the results have been mixed. Traditional techniques, such as flow through an orifice and tapped density methods, are not ideal for the extended, detailed experimental work required to support QbD. Shear-cell measurements are ideal for understanding flow in hoppers, but are less useful for understanding lower stress processes, such as mixing, filling and aerosolization. Here, different measurement techniques are required.

Powder testing has developed considerably in the past decade, including the introduction of dynamic testing. Dynamic characterization reproducibly and directly measures powder flowabilty, for conditioned powders and for those that are consolidated or aerated, thereby generating reliable and valuable information for process development. Used in combination with bulk and shear property measurement, dynamic testing enables the kind of multifaceted powder characterization required to fully rationalise in-process behaviour.

With these techniques in place, it is now possible to develop a detailed understanding of the way bulk properties influence tabletting, granulation and many other frequently employed unit operations. This type of knowledge development remains a work in progress, but the goalposts shift too. Faster tabletting speeds are one example, but the long-term objectives of continuous production in integrated manufacturing suites adds another layer of complexity, requiring testing strategies that provide the deepest and most comprehensive information.

Best practices in application of QbD to tableting and granulation

QbD relies heavily on engineering an optimized, well-understood process. It is therefore important, from the outset, to work out how to gather analytical data that will accurately reflect process performance. Effective powder handling is central to the success of tableting, granulation and a wide range of other pharmaceutical unit operations. Appropriate powder characterization techniques are, therefore, an essential prerequisite.

The number of powder testing techniques available reflects both the importance of such testing and its difficulties. When choosing which techniques to apply for QbD studies, I would suggest assessing against a number of criteria including:

- Reproducibility and sensitivity
- Process relevance
- Ease of use

One of the biggest challenges for those applying QbD is how to access and gather the necessary information. The full implementation of QbD demands a comprehensive understanding of process and product, and the identification of an effective control strategy for the manufacturing process15. Choice of analytical instrumentation is therefore crucial.

With well-established techniques such as laser diffraction particle-size measurement, customers can rightly expect the highest levels of automation and analytical productivity. Some systems can extend the efficiencies of dry measurement to more samples and combine rapid measurement times with assured data quality, to push analytical productivity to high levels for all users.

Of equal importance, however, are continuous laser diffraction particle size analyzers that offer real-time measurement for pilot-scale studies and commercial plant monitoring and control. These systems can significantly accelerate QbD studies. Running a pilot plant with real-time monitoring in place enables consistent control at the experimental conditions of interest and makes the impact of changes in operating variables instantly obvious.

For some types of analysis, the technology is newer, but it is vital to recognize what can now be achieved.

Returning to the example of morphologically directed imaging, these systems involve considerable investment but can deliver significant value over the long term. Being able to measure not just size and shape but also the distribution of different chemical species within a dispersed sample, such as a disintegrated tablet, can be invaluable when trying to really understand how the process works and how to optimize it.

Conclusion

A combination of analytical and statistical methods could be used to improve a tablet tabletting process guided by quality by design (QbD) principles. A solid dosage form product was found to intermittently exhibit bad taste. A suspected cause was the variability in tabletting thickness which could lead to the subject tasting the active ingredient in some tablets. PPP

IRAQ
The Next Big Pharma Market

Iraq is set to become an exceedingly attractive pharmaceutical and healthcare investment destination in the long term as the government continues to increase funding for healthcare infrastructure development and medical training and services on the back of growing oil revenue. This is expected to spur huge demand for medical equipment and services and attract foreign interest in the country's healthcare market estimated to be worth some US$10-12 billion by 2014. However, numerous challenges remain, not least of which is the sectarian violence which continues to flare up sporadically. The Iraq Government has expressed its commitment to improving the pharmaceutical and healthcare sector through increased investment in funding, training and infrastructure development. This in turn is expected to spur huge demand for medical equipment and services. The country is not short of money. The healthcare budget was increased to US$6 billion in 2012 from $4.5bn in 2011 and $3.8bn in 2010. These increases come on the back of strong GDP growth – forecast at 14.7% for 2013.

With a population of 32 million people, growing at a rate of 9.5%, with a GDP of more than $ 143 billion, with 128 billion barrels of proven oil reserves and with a growing demand for both preventive and curative healthcare systems, Iraq is the key emerging pharmaceutical and healthcare destination in the MENA region.Iraqi Government is allocating $ 12 billion in 2014 to ensure improvement of its healthcare sector that will be available to all its citizens. With multiple hospital projects underway and no local manufacturing facility to meet the demand, the demand is expected to increase exponentially.

Firms looking to develop partnerships with the Ministry of Health (MoH) and take advantage of business opportunities in Iraq will need to develop thoughtful strategies in order to penetrate this uniquely challenging but rewarding market. Local partnerships are particularly important when pursuing business opportunities with the MoH. In addition to standard business registration practices, medical and health-related goods also require registration in Iraq.

Iraq has a special pharma and healthcare sector private investment policy. Iraq's pharma and health sector investment strategy is based on the following principles like promotion of private sector involvement though opportunities to invest in healthcare facilities, and pharmaceutical and medical device manufacturing, privatise state-owned healthcare facilities, privatize state-owned pharmaceutical and medical device companies, attract modern healthcare consulting service providers to promote system and practice modernization, establishment of greenfield healthcare facilities including integrated medical cities & complexes, hospitals, medical laboratories, and primary healthcare clinics. Also management and operation of privatized state-owned hospitals, management of specialized health centers through direct contract, providing general healthcare consulting services including advising on healthcare systems modernization, establishment of greenfield pharmaceutical and medical device manufacturing facilities, privatization of existing pharmaceutical and medical device manufacturing and distribution companies, providing consulting services for updating the public company for marketing drugs and medical appliances management's (KIMADIA) enterprise systems (includes systems for testing, registration, warehousing, distribution, and marketing).

KIMADIA is Iraq's pharmaceutical and medical device supply and resupply system to MoH and other GoI facilities. Several suggestions for privatization or selling KIMADIA have arisen over the past two years but have met resistance. Pharmaceutical accountability and control lags behind modern standards. A nationwide logistical system for pharmaceuticals and medical equipment/supplies is urgently needed.MoH KIMADIA retains a domestic market share of 40% of Iraq's medical supplies and seeks an investor to manage and operate their plant. The goal is to rehabilitate and upgrade KIMADIA's plant with modern technology in return for a share in production.Emergency response and ambulance support is ill-defined and uncoordinated throughout Iraq. National standards of response are not always applied, and training, qualifications testing, and a certification process is necessary.

Under the health care investment opportunities there are 208 state-owned, government-run hospitals, with 40 situated in Baghdad. There are also approximately 2,000 Private Heath Clinics (PHCs) scattered throughout Iraq. Generally, all primary

care and preventive medicine is provided for free. PHCs provide a limited range of service. Power outages are frequent and can last for many hours. Diagnostic equipment is not generally available. The MoH is seeking investments including pharmaceutical and medical device industry opportunities. Several opportunities exist for investors interested in Iraq's pharmaceutical and medical device industry. The MoH has outlined the following three areas of opportunity for investors:

The Republic of Iraq has a land area of 437,072 sq km. Iraq is distinguished by the variety of its geographic landforms, including level sedimentary plains and mountains. The country is divided into a mountainous northern area, a desert area in the west, and a large fertile plain in the middle and south of the country that is watered by the two rivers, the Tigris and the Euphrates. Iraq has a population of 34M, most of whom live in towns and cities. Iraq is bordered by Turkey to the North; Saudi Arabia, Kuwait, and the Arab Gulf to the South; Iran to the East; and Syria and Jordan to the West.

Iraq is divided into 18 provinces. The capital city is Baghdad; in addition to Baghdad, major cities include Mosul, Basrah, and Erbil. Iraq's major resources consist of oil, natural gas, sulphur, phosphate, iron, kaoline, bauxite, limestone, gravel, and sand.Iraq has about 34M citizens, with a yearly population growth rate of 2.6%. The population is young, with more than half less than 20 years old. Over two-thirds of the population lives in urban areas.
Iraq has the capacity to be a thriving, middle class country. With a long trading history, deep commercial traditions, and vast natural resources - including the world's second largest proven oil reserves; Iraq, at the crossroad of culture and commerce, has enormous potential.

Today Iraq is on the rebound. As security improves, and as oil exports and internal commerce recover, GDP has risen. GDP has grown from $180B USD in 2011 to $210B USD in 2012. GDP per capita has surpassed $3,000 USD and is forecast to exceed $5000 USD by 2014.Moreover, as Iraq reintegrates into the world community, a growing number of agreements will help restart the Iraqi economy. Among key successes: The Paris Club announced in November 2004, a deal to write off 80% of Iraq's debt. When fully implemented, the agreement will yield $100 B USD of debt relief to Iraq, a major boost to long-term economic growth. Also Iraq has completed over three years of standby arrangements with the International Monetary Fund (IMF). The final arrangement expired in March 2009, triggering the final stage of Iraq's Paris Club debt reduction agreement.The World Trade Organization (WTO) agreed in December 2004 to open membership talks with Iraq. Iraq has been a WTO observer since February 2004. A working party to examine the application of Iraq was established. The Working Party met for a second time in April 2008 to continue the examination of Iraq's foreign trade regime. Iraq hopes to gain membership in 2013.

Democracy is now a fact of life in Iraq. The late-January provincial elections confirmed the general upturn in the political environment, showing that a new politics is emerging within the country. Iraq's constitution has established a parliamentary democracy. The next general election for the Council of Representatives of Iraq (CRI) will take place in 2014. The CRI is the main legislative body. It sits for a four year term and elects a speaker, the President, the Prime Minister and the cabinet. The country is divided into 18 provinces or governorates, whose assemblies are elected for four year terms. The most recent elections in 12 of the provinces took place in April 2013. They were peaceful and well-ordered. PPP

The APPON Honour Recognition of pioneership in establishing pharma industry in Nepal

The Executive Committee of the Association of Pharmaceutical Producers of Nepal (APPON) – the apex trade association representing the Nepal pharmaceutical manufacturers and the Organising Committee of Nepal Pharma Expo 2014, Kathmandu Exhibition have conferred the APPON Honour on Mr. Paresh Jhurmarvala, Publisher of the PHARMA Pro&Pack, the official journal of the Indian Pharmaceutical Machinery Manufacturers Association (IPMMA). Mr. Jhurmarvala is also the CEO–GPE EXPO Pvt Ltd. The award was given to Shri Jhurmarvala as a mark of recognition towards his pioneering and expert role in establishing pharma industries in Nepal. The honour was conferred by the Chief Guest Honorable Mr. Khag Raj Adhikari Nepal's Health and Population Minister during the inauguration of Nepal Pharma Expo 2014 on February 28 at Bhrikuti Mandap, Kathmandu - the venue of the Nepal Pharma Expo 2014.

Amongst the guests who remained present during the inauguration program were Mr. Umesh Lal Shrestha (President–APPON), Advisors-Mr. Mahesh Gorkhali, Mr. Shanker Ghimire, Mr. Sanjay Agrawal, Coordinators Mr. Deepak Prasad Daha and Mr. Deepak Pradhan. The 5th Nepal Pharma Expo 2014 Exhibition was organized by APPON in association with the Government of Nepal-Department of Drug Administration (DDA), Federation of Nepalese Chambers of Commerce & Industry (FNCCI) and Nepal Pharmaceutical Association (NPA).

PPP

The Pharmtech Exhibition: Helping the Russian pharmaceutical industry to move to a development model based on innovation

The 15th Anniversary International Pharmtech - Technologies for the Pharmaceutical Industry took place from the 25th to 28th November 2013 in Moscow in Pavilion 75 of the All-Russian Exhibition Centre alongside the 1st International Exhibition of Raw Materials and Ingredients for pharmaceutical production Pharmingredients+. The organiser of these events was ITE Group, who are the leaders of the Russian exhibition services market and occupy sixths place in the world league table of exhibition organisers.

Technologies for the pharmaceutical industry

Raw materials & ingredients for pharmaceutical production

DATE: 25 - 28 Nov 2014

VENUE:
Russia, Moscow
All-Russian Exhibition Centre

www.pharmtech-expo.ru
www.pharmingredients.ru

The opening ceremony for the two exhibitions featured appearances by Deputy of the State Duma of the Russian Federation, member of the State Duma Committee for Industry Vasily Zhurko, Acting Director of the Department for the Development of Pharmaceutical and Medical Manufacturing of the Ministry of Industry and Trade of the Russian Federation Olga Kolotilova, First Vice President of the Russian Union of Manufacturers and Entrepreneurs Victor Cherepov, Deputy of the Moscow City Duma, Deputy Chairman of the Commission for Economic Policy, Science and Entrepreneurship Ivan Novitskiy, Chairman of Committee on the Development of the Consumer Market of the Chamber of Trade and Industry of the Russian Federation Aleksandr Borisov, Representative of the Association of Russian Pharmaceutical Producers Lilia Titova, Representative of the General Partner of the Pharmtech exhibition, Director of the "Development and registration of medical drugs" magazine Olga Zaleskikh and other prominent guests.

In his opening speech, V. Zhurko congratulated everyone with the opening of the exhibitions on behalf of the Expert Council of the State Duma on Pharmaceutical and Biological Activities and wished everyone to find out something new for themselves at the exhibition. He also noted that 'As a representative of the State Duma, I am ready to work on legislation that will benefit all aspects of pharmaceutical production'.

O. Kolotiva noted in her opening ceremony address that 'the state and the pharmaceutical industry face a task the result of which should be a rise in the production of drugs from the list of vitally important medical substances to 90%. This year we have reached an indicator of 65%'. 'Another issue that should be mentioned is the switch of production to GMP standards in 2014. This task was placed before the pharmaceutical industry in 1991 for the first time. Many things were done over the years. Now, 80% of production in monetary terms and 67% in real terms is produced according to GMP standards.' - she added.

In the opinion of O. Kolotilova, 'all of this shows the relevance of this event, where equipment and ingredients for pharmaceutical production are presented.' She said that she hoped that the exhibitions will make a signigicant input into the development of the national pharmaceutical industry and wished everyone success in their activities, interesting meetings and the fulfilment of their aims.

324 companies from 27 countries exhibited at the Anniversary Pharmtech exhibition. As always, national and foreign producers and suppliers of pharmaceutical equipment, pharmaceutical companies and companies that plan turnkey pharmaceutical production presented their products and services. The exhibitors included leading companies in the industry: SCHOTT, PALL, IMA, Bosch, Groninger, Diosna, Pester Pac Automation, Rolstek, Bausch+Stroebel, SARTORIUS and many others.

The Ministry of Industry and Trade of the Russian Federation presented their own stand at the exhibition for the first time, where they demonstrated an interactive programme with which national developments could be reviewed online. 285 scientific research works carried out on government contract from 2011 until today were presented at the display.

German and Chinese exhibitors demonstrated their products as part of national pavilions. The Danish Export Association presented their display at the Pharmtech exhibition for the first time this year with the aim of helping national producers and service providers to interact with foreign partners. The Association is the largest in its field, with a membership of more than 500 companies.

The 2013 Pharmtech exhibition was held in the same hall as the new Pharmingredients+ exhibition project, which is aimed at specialists in pharmaceutical production as an answer to the current trends in the development of the pharmaceutical market. The purpose of the Pharmingredients+ exhibition is to reflect the rising role of high qualtiy active pharmaceutical ingredients and functional ingredients in the production of modern medical substances. 39 Russian and international companies exhibited at the first exhibition that specialise in the production and delivery of pharmaceutical substances, raw materials, ingredients and additives as well as offering services connected to their development, analysis and registration. Exhibitors included prominent leaders of the industry: BASF, IMCD,Sanofi, Pharmvilar, BION, Chimmed and other well known companies.

The total area of the Pharmtech and Pharmingredients+ exhibitions was over 7 200 $m^{2.}$ The number of visitors at the two events reached 5 236 industry specialists from 38 countries and 53 regions of Russia, 56% of which were Chief Executives, Senior Managers and Heads of Department at production and trading companies.

Business Programme
A rich business programme aimed at the assisting in the development of the industry and discussing the most current and important issues was presented as part of the Pharmtech and Pharmingredients+ exhibitions.

One of the main events was the 'Effectiveness of clusters as an organisational and economic system' organised by the Association of Russian Pharmaceutical Producers and the Pharmtech organising committee.

Representatives of Russian pharmaceutical clusters, representatives of industry related ministries and state bodies, medical drug manufacturers, scientific and educational establishments and the representative office of the Association of Russian Pharmaceutical Producers in China took part in the session. The round table participants examined the results of the work of pharmaceutical clusters until today and discussed the prospects for their development.

One of the key events of the business programme was the annual Pharmtechprom forum, which has established itself as a platform for the exchange of professional opinions and experience between foreign producers of equipment and tehcnologies and producers of medical and cosmetic substances from Russia and the CIS.

The Pharmtech exhibition is making an input into the development of a system for preparing industry specialists through developing the Pharmtech Tutor project. This year, the number of companies participating in the project has doubled and the project has risen to the level of the countries of the CIS. More than 35 companies welcomed 47 students of specialised higher education institutions in Russia and Ukraine at their stands and offered them work experience at the exhibition.

In honour of the 15 year Anniversary of the Pharmtech exhibition the Association of Russian Pharmaceutical Producers and the exhibition organising committee introduced a yearly award 'For a multilateral contribution to the development of national pharmaceutical production". The winner of the award was SCHOTT, with FAVEA and Glatt also included in the nomination. According to Director of the Association of Russian Pharmaceutical Producers Victor Drmitirev SCHOTT did not only make a significant input into the development of the the industry but also actively participated in social and educational projects aimed at finding young talent and preparing staff for pharmaceutical production.
This year, the peer reviewed "Development and registration of medical drugs" magazine acted as the general partner of the exhibition. The magazine is the first free practical publication for specialists involved in medical drug distribution.

Official partner of the exhibition: Luxun, one of the leading engineering companies specialised in the creation and renovation of pharmaceutical production facilities. General partner of the Pharmtechprom forum: FAVEA, the leading European engineer company involved in the design, construction and renovation of pharmaceutical production facilities.

The 16th International Pharmtech - Technologies for the Pharmaceutical Industry exhibition and the 2nd Pharmingredients+ International exhibition of raw materials and ingredients for pharmaceutical production will take place from the 25 - 28 of November 2014 in Pavilion 75 of the All-Russian Exhibition Centre. PPP

Nepal Pharma Expo 2014

Catalysing growing pharma economy in Nepal

The three-day Nepal Pharma Expo 2014 – the 5th edition of exhibition featuring and showcasing the pharmaceutical industry of Nepal was organised from February 28 to March 2, 2014 at Kathmandu, Nepal. The central theme of the expo was 'Sustenance through Quality'. The expo was organized by APPON (Association of Pharmaceutical Producers of Nepal) in association with the Government of Nepal-Department of Drug Administration (DDA), Federation of Nepalese Chambers of Commerce & Industry (FNCCI) and Nepal Pharmaceutical Association (NPA).

Nearly 100 exhibiting companies – a mix of Nepalese pharma manufacturers along with exhibitors from India and Singapore participated at Nepal Pharma Expo 2014. The participation at the expo by the exhibiting companies and the ever increasing trade visitors underlined the ongoing growth amongst the local pharma industry of Nepal.

Nepal Pharma Expo is being held every two years since 2005, with an objective to disseminate information about recent advances and innovations in pharmaceutical sciences and technologies. The expo helps in up-gradation of technological capabilities and skills among the Nepalese experts. Indeed the expo provided a good business platform to the Nepalese pharmaceutical industry and market. PPP

Commerce Ministry reviews move

No immediate implementation of bar-coding on primary level packaging

India's Commerce Ministry may consider putting off implementation of bar-coding on primary level packaging further, after reviewing the compliance report of barcode implementation of the secondary and tertiary level packaging post its implementation. The ministry has already set up an expert committee to review the matter, so that detailed report can be submitted on the feasibility to the government at the earliest.

It is understood that the decision to postpone the implementation will be taken, only after examining the report which will be submitted after a nationwide extensive survey with the drug regulatory officials, custom officers, industry etc on its possible impact. Pharmaceuticals Export Promotion Council of India (Pharmexcil) who have been advocating for the industry stressed said that they are working with the government to hasten the process so that the exporters do not suffer due to this.

After a delay of over a year, the government had decided to implement bar-coding on primary level packaging on export consignment of pharmaceuticals and drugs for tracing and tracking purpose, from July 1, 2014. If extended, this will come as a huge relief for the Indian exporters who have been expressing strong objection over bar-coding due to compliance issues and feasibility. The industry has been stressing that barcode is neither practical nor an ideal solution for tracking spurious or fake drugs.

Dr P V Appaji, director general, Pharmexcil, informed that, the council will request the government give more time to the industry by further extending the implementation date by at least 2 years. The trace and track technology which was adopted by the government to address the issues and apprehensions about the export of spurious drugs from India, was made compulsory for tertiary level packaging from October 1, 2012 secondary level from January 1 last year.

India is the Partner Country at the ITM Poland 2014

The India Show is an initiative of Ministry of Commerce, Government of India to promote Brand India across the globe and provide a platform to Indian exporters to showcase their strengths and capabilities in emerging markets and developing countries.

EEPC India takes 'The India Show' to the economic capital of Poland, Poznan. The India Show, a part of the Innovations Technologies Machines (ITM) is being organised at Poznan International Fair – Miedzynarodowe Targi Poznanskie from 3rd to 6th June 2014. The large number of Indian companies showcasing their products and services at ITM will help them tap newer business opportunities. India is not just participating, but would be a partner at the ITM Poland 2014.

There are several benefits for exhibitors. The first and foremost is the Partner Country status to India which results in additional publicity and VIP presence. Also the exhibitors would get cost efficient advertisement through regional media sources and non-government organizations, meeting with decision makers. Roughly 60% of the total expected visitors can be described as decision makers. The show will prove to be an ideal platform for display of Indian companies potential and products. Also it would be a good opportunity to build networks with different representatives from various sectors.

More than 1000 companies are expected to take part in the Poland show and 1,200 machines and devices will be on display. About 22,000 professionals and trade visitors are expected to turn up for the event.

Gujarat based small drug firms' clock 20% growth in exports

Big players in the Indian pharmaceutical industry may face hurdles on the export front because of issues with the US drug regulator. But small and medium enterprises (SMEs) have seen good growth in formulations exports in the current fiscal clocking a handsome 15 to 20% growth in exports to semi-regulated areas of the world. Gujarat has evolved into pharma hub housing small and medium pharma units of which more than 200 are WHO-Good Manufacturing Practice (GMP) certified manufacturing facilities.

Pharmexcil sources have indicated that while the target growth in exports in the current fiscal was around 15% growth over the 2012-13 exports of Rs 79,500 crore, current conditions indicate that pharma exports will increase by only 10-12 per cent over last fiscal's achievement. Gujarat's share in India's pharma exports was nearly 22 per cent in 2012-13. IDMA sources have also conceded that while the earlier expectation of export growth from Gujarat was around 16%, the current expectation is about 11%. However, SMEs have outperformed big pharma companies in terms of growth rate. Exports to regulated markets like the US and the European Union have been hit. But, as SMEs export to semi-regulated markets, their growth has not been impacted. The share of small and medium enterprises in overall exports from Gujarat is 70-80 per cent.

Most of the small and medium enterprises from Gujarat are exporting to countries such as the Philippines, Sri Lanka and Thailand in the South and South East Asian regions, apart from countries like Nigeria, Kenya and Ghana in the African continent. In contrast, big pharma companies are increasingly coming under scrutiny by the US Food and Drug Administration (USFDA).

Further, in the backdrop of the recently implemented Drug Price Control Order 2013, SME pharma companies are also enhancing their focus on exports, as the domestic market is becoming more competitive. With expected margin erosion in the range of 6%, and reduced cash flows, small and medium enterprises are will find it difficult to pay for the investments needed to diversify into non-Drug Price Control Order products. PPP

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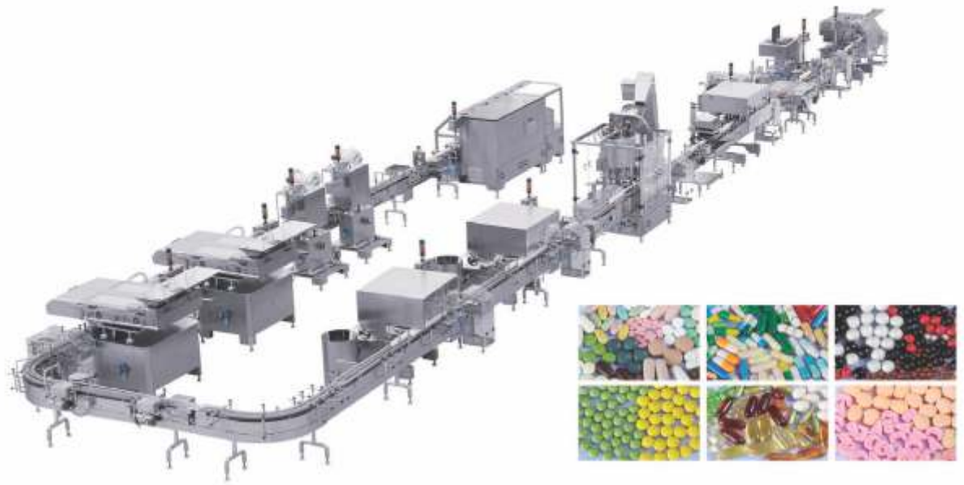

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Pouch Desiccant Inserter

Advantages

- Servo driven
- Synchronous pulley teeth and servo controller ensures accuracy transitting
- Cylinder driven positioning and cutting
- Controllable feeding gate and transparent window ensures broken pouch detecting
- Compact design, huge space saving

Continuous Motion Horizontal Cartoner

Advantages

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- Balcony design
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- Digital display adjusting system
- Overload protection
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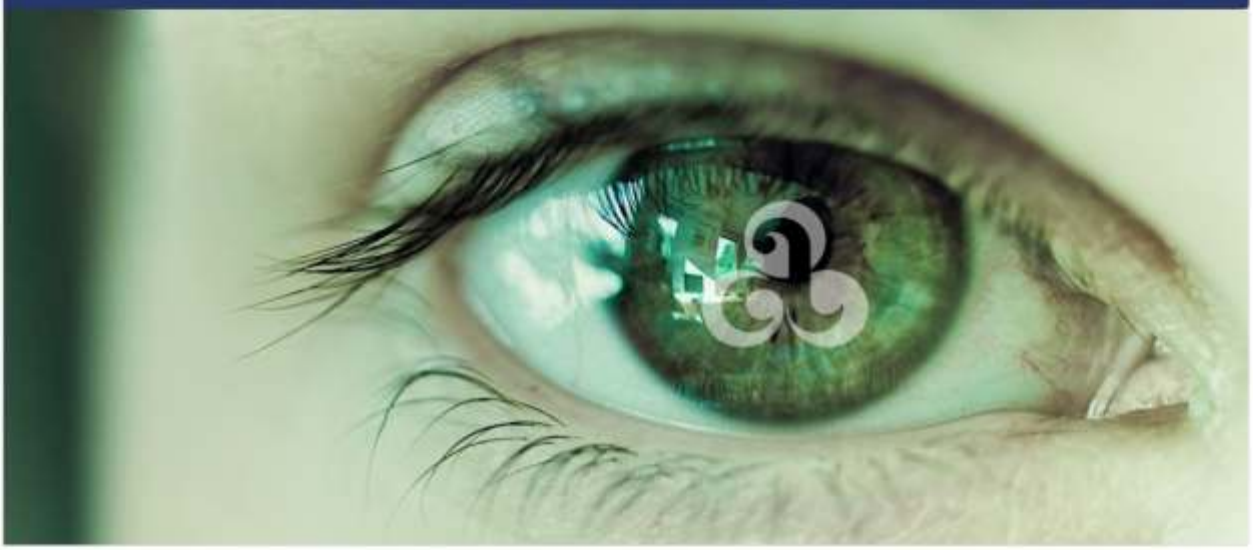

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