Maharashtra Educational Society's

H. K. COLLEGE OF PHARMACY

Pratiksha Nagar, Oshiwara,
Jogeshwari(W), Mumbai - 400 102.

-FOREWORD-

BE SAFE
BE SMART
BE KIND

It is our endeavour at H K C P Bulletin to spill information that is useful for readers.This issue of bulletin talks of many advances that have been made by Pharma Industries.

In first section of bulletin we started with coprocessed excipients which impacts the particle morphology making it more suitable for processing as well as more successfull on commercial aspect.

Second Article gave information for Gas Chromatography linked with Mass spectroscopy which is widely used analytical technique in pharma industry

We also gave information for latest development in the treatment of Asthma.

We sincearly hope that the flip of each page of this issue enlightens your knowledge even more

Happy Reading

Stay Home Stay Safe

Thank You,

Editorial Team

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H K College of Pharmacy

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H. K. COLLEGE OF PHARMACY

Oshiwara, Jogeshwari (W), Mumbai – 400 102.

Vision

To be recognised as the institution providing quality education in pharmacy to serve the healthcare sector.

Mission

- By imparting knowledge in the field of pharmacy through continuous improvement in integrated teaching learning process.
- All-round development of the students by inculcating sense of ethical practices, social empathy and management skills.
- Encourage students towards higher education and research.

Research Capabilities

PHARMACEUTICS DEPARTMENT

- Expertise in the Development of NDDS (SLN & NLC)
- Expertise in Tablet Granulation and Coating
- Lipid drug delivery Technology
- Engineering cellular based carrier
- Expertise in solubilisation techniques
- Design and optimization of orodispersible dosage forms
- Solid dispersion,
- Solid solution,
- Nano-crystals,
- Nano-emulsions
- Drug-polymer conjugates
- Microsphere Drug Delivery
- Advanced characterisation techniques like Raman spectroscopy, Raman imaging, 2D NMR and Atomic force microscopy of solid formulations
- Generic ANDA Development of Dosage forms including Paragraph (IV) projects.
- In Vitro Permeability studies with Porcine and Goat Buccal Mucosa for study of Drug Diffusion.
- Solubility enhancement of poorly soluble drug
- Bioavailability Enhancement of class IV molecules
- Design and development of nano emulsion
- Design and development of lipid based drug delivery systems
- Orodispersible formulations
- Mouth Dissolving Films-Development and evaluation(Provisional Patent Field)
- Orodental and mucoadhesive film-Design Development and evaluation
- Liquid filled hard gelatin capsules
- SMEDDS for colon targeting
- Development of gel and transdermal preparations for allergy burn and wounds
- Evaluation of mouth sprays
- Development of nutraceutical product
- Design and development of generic product for US market with QbD approach.
- In-vitro model for permeability studies
- Continuous HME processing and Process Analytical Tools (PAT).

PHARMACEUTICAL CHEMISTRY AND ANALYSIS DEPARTMENTS

- Molecular modelling
- Target-based designing of novel therapeutic agents
- Ligand – based (pharmacophore, SAR, QSAR) drug designing
- In silico 'mechanism of action' studies
- In silico 'knock-out' / mutation' studies
- In-silico identification of protein target hotspots
- Lead optimisation
- Drug repurposing
- Synthesis of drugs by
- Conventional method
- Solvent-less approach
- Microwave-assisted methods
- Multicomponent / Convergent methods
- Analytical method development and validation of drugs
- Structure elucidation by FTIR, Mass, NMR
- Study of characteristics of drug through FTIR

PHARMACOLOGY DEPARTMENT

- Toxicities Studies (acute, sub-acute & chronic toxicity studies)
- Antimicrobial, Antifungal studies
- Anti-inflammatory research
- Anti-obesity activity for diet-induced model (High fat diet).
- Expertise in development of animal models for
  - Diabetes
  - Burns
- Pharmacokinetic /pharmacodynamics studies.
- Expertise in developing assays using various animal tissues like heart and abdominal muscle preparation.

PHARMACOGNOSY DEPARTMENT

- Design and development of herbal preparations
- Phytochemical evaluation of various natural products
- Standardization of herbal drugs
- Optimization of extraction of herbal drugs and isolation of active constituents
- HPTLC method development and validation for herbal extracts/formulations
- Development and validation of GC method
- Development and standardisation of herbal formulation /nutraceuticals/ cosmeceuticals
- Biological screening of herbal drugs/ formulations
- Optimising solubility of natural products

Research Facilities

INSTRUMENTS & EQUIPMENT IN THE COLLEGE AT A GLANCE

Central Instrument Room	Pilot Plant	Machine Room	Research Lab
UV cabinet	CD 14 Teledyne Hensen Dissolution Apparatus	Single Punch Machine (Table Compressor)	Rotatory Evaporator
Conductivity meter		Liquid Bottle Filling	Micrscopes
Digital Nephelometer		Tray Dryer	Sonicator
Digital Fluorimeter		Hard Gelatin Cap. Filling	Hot plate
Sealer	Rapid mixer granulator-10 ltrs with interchangable bowl 3 ltrs	Bottle Sealing machine	Homoginizer
UV Spectrophotometer	Magnetic stirrer	Ointment Filling	Hot air oven
Digital Potentiometer	Homogenizer with speed regulator	Ball Mill	Electric water Bath
pH meter	Suncoater 300 (12")	Double Cone Blender	Analytical Balance
BrookField Viscometer	PH meter-I & II	Tablet Coating	Microwave oven
Double beam UV spectrophotometer	Electronic weighing Machine		Mechanical stirrer
Water bath Shaker	Rotatory Tablet Press (Mini press)		Vortex mixer
Digital ultrasonic cleaner	Electronic Weighing Balance I & II		Magnetic stirrer(Digital)
Gel electrophoresis	Vibroshifter		Magnetic stirrer
BOD incubator	Multimill		Magnetic stirrer with hot plate
Micro controller Top shaking incubator	Octagonal blender 10 with interchangable bin 3 ltrs		
Cooling Centrifuge			
Ion exchanger			
Flame photometer			
Computer systems			
Magneticc stirrer			
Magnetic stirrer(Digital)			

MISSING ROLE OF INDIAN PHARMACISTS IN PUBLIC HEALTHCARE

Challenges And Opportunities

Dr. M.N.Saraf , H.K.College of Pharmacy, H.K.Campus, Pratiksha Nagar, Jogeshwari (W), Mumbai-102

Covid-19 pandemic has affected vast number of people across the globe. It is realised that changes in incidence and prevalence of Covid-19 infection are strongly associated with immunization rate and coverage. Low immunization rate is a major health concern and there is a need to stimulate national efforts to increase vaccination and complete the mission of vaccination for all. In addition to personal protection, vaccination also benefits whole community when majority of population is immunized, and transmission of disease is interrupted.

Pharmacists play a role in vaccination advocacy and patients' education in at least 34 countries and have an active role as immunisers in 27 countries and territories. In countries such as the USA, the UK, Argentina, Canada, Costa Rica, and Portugal pharmacies are authorised to administer a broad range of vaccines. Government and Policy makers have been realising that increasing vaccination coverage is a public health imperative and that pharmacists should be part of the solution. Although the effectiveness of vaccination is well documented barriers to immunization which include misinformation, vaccination administration, accessibility, distribution, storage, and constraints to vaccination provision by pharmacist have a significant impact on vaccination rates and prevalence of vaccine preventable diseases.[6]

It is estimated that ten million lives per year could be saved by increasing access to medicines and vaccinations. Indian community pharmacists are expected to provide a major contribution to public health due to their accessibility, distribution network and available medicines expertise.

In the Indian context public health workers are primarily considered to include physicians and nurses. However, it has been realised that these healthcare professionals are falling short to effectively manage vast Indian population particularly in the pandemic situations like Covid-19. It is also realised that unexpected outbreaks of preventable communicable disease will happen again and again particularly due to rapid emergence of mutant strains of disease producing microorganisms. Although in India there are large number of qualified pharmacists, their services as healthcare professionals are not utilized for want of proper training and skills as well as apathy of the government & policy makers to improve healthcare resources at par with developed countries.

The role of pharmacists as educators, facilitators and immunizers is particularly important in pandemic situations like Covid-19 that can reduce morbidity and mortality of general population across the globe.

Role as educators: Community Pharmacies are really approachable and can lead on vaccination advocacy and promotion drives, facilitate clarification on possible doubts and apprehensions of taking vaccines by communicating the risks and benefits of vaccination and educating public at large about immunization. Pharmacists can easily identify patients at higher risk and specific target group for vaccination, provide necessary advice and actively participate in reminder / recall systems to ensure vaccination schedule are achieved. Pharmacists can as well play an important role in vaccine storage and distribution3. It is unfortunate that in India services of Pharmacists are not utilised for Immunization and allied healthcare requirements. The primary reason for this is lack of specific training and skills in areas like immunization and lack of government policies in this regard.

Explicit legal requirements, guideline and robust procedures to facilitate utilization of pharmacists as immunizers should be set by the government on top priority.

Targeted Training for pharmacists and access to training are key ingredient in procuring the expansion of vaccination services.

Implementation of robust Pharmacy Training: [5]

There is established evidence of the advantages of Pharmacists extended role in immunization and vaccination including increase accessibility, increased public vaccination rates and coverage of public acceptance, trust and support.

A comprehensive training programme should address the following [5]

1) Epidemiology and patient population at risk for vaccine preventable diseases

2) Public health goals

3) Vaccine safety (risk benefit analysis)

4)Screening for contraindication and precautions in vaccination in each patient

5)Vaccine stability, transport, storage, requirements

6) Immunologic Drug interaction

7) Vaccine dosing

8) Proper dose preparation and injection technique.

9) Signs and Symptoms of adverse drug reactions (ADRs) to vaccine and emergency procedures

10) Documentations

11) Reporting to primary healthcare or health Department

This could be achieved through well designed academic plan focussed on imparting knowledge and practical skill to diploma and degree levels pharmacy students and accreditation of these academic program by the regulatory agencies The ministry of skill development and Entrepreneurship, Government of India and the healthcare sector skill council have a mission of imparting education and hospital training to large number of students to develop skilled work force particularly to cater to management of pandemic situations like Covid-19.

This is an opportune situation for training and skill development of pharmacists in the country. After training and acquiring requisite skills, their professional services can be utilised in primary healthcare centres as well as at other healthcare facilities.

International Pharmaceutical Federation reports that ensuring early access of the pharmacy work force to safe and effective Covid-19 vaccine will contribute to accelerating access to vaccine for all as well as continually of treatments and essential services, medical products and medical devices provided by pharmacists and pharmacy team on the frontline.[4,6]

The national health scheme in England provides online e-learning programs for hands on training for vaccination to community pharmacist. India has large number of community pharmacist network. However, they need to be trained for vaccination and allied healthcare services through an organized service of training and accreditation. The government of India must start a special training drive for the Indian pharmacist to train them as immunizers. Online e-learning platform should be optimally used to impart training along with hands on training for immunization. This will reduce burden of physicians and nurses for preventive care as well as monitoring patients post immunization and can serve as an important co-ordinator of mass immunization process to meet the target of vaccination to all.

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Co-processed excipients: An overview

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Abstract:

As the pharmaceutical sector thrives to meet the time-bound demand of medicine supplies, the excipient industry consistently upgrades their product range to support the formulators. One of these upgradations is improving the functionality of the existing excipients by co-processing them. This processing positively impacts the particle morphology making it more suitable for direct compression approach and thus, avoiding the tedious granulation process. Co-processed excipients not only involve low development cost but also shorter development time. The current discussion highlights the concept of co-processed excipients, benefits over the conventional excipients, regulatory aspect and the commercially successful co-processed excipients.

Key words: Co-processed excipients; particle morphology; direct compression

Introduction:

For development of any tablet dosage form, direct compression process stands to be the most preferred approach owing to its simplicity and cost-effectiveness over the granulation process. Particle morphology greatly influence the binding characteristics, blend flow, content uniformity and compressibility. Solid materials can be classified into the below mentioned types based on their nature of deformation when an external force is applied

- Elastic: Deformation is completely reversible (Starch, sodium starch glycollate)
- Plastic: Deformation is irreversible, but material is intact (Microcrystalline cellulose)
- Brittle: Deformation is irreversible and results in formation of fragments (Lactose monohydrate, Dicalcium phosphate) [1]

Pharmaceutical excipients exhibit all the three characteristics, with one of them being the predominant, thus making it difficult to clearly demarcate the property favorable for compressibility. As there is no single excipient that possess all the desired physico-mechanical properties for this purpose, there was a need of introducing the concept of co-processed excipients.[2, 3]

Co-processed excipients:

Co-processed excipient is a compound or a product of two or more excipients obtained after processing them together by spray-drying, granulation, solvent evaporation methods and others. These processes help in the surface modification of the original particle and do not result in any chemical modification or formation of covalent bonds. In this way, these compounds retain their functional characteristic but with particle improvisation.[4] Elastic material like starch is used as disintegrant while mannitol is brittle in nature and used as diluent. Pearlitol Flash is a co-processed excipient that combines these two properties to offer a single excipient for formulation of ODTs, fast-melt tablets. In the similar manner, Avicel DG is combination of MCC (plastic) and dicalcium phosphate anhydrous (brittle) which give superior compactability desired for dry granulation process.

Apart from particle morphology, co-processed excipients are also prepared to combine functional characteristics of two or more excipients. In Avicel RC/CL grades, the original crystalline areas of MCC fibers are combined with sodium carboxymethylcellulose (NaCMC) to produce the colloidal product. NaCMC, hereby serves as a protective colloid and also aids in dispersion of the product. These are used for liquid oral or powder for reconstitution formulations.

Steps for co-processing:

The preparation of co-processed excipient involves incorporation of one excipient onto the particle structure of another, using one of the appropriate methods described below. Figure 1 provides a brief overview of the co-processing methodology.[5, 6]

Methods to prepare multi-functional co-processed excipient:

There are several methods for developing co-processed excipients depending on the characteristics and intended functionality of individual components as listed with elaborations on few [7,8]:

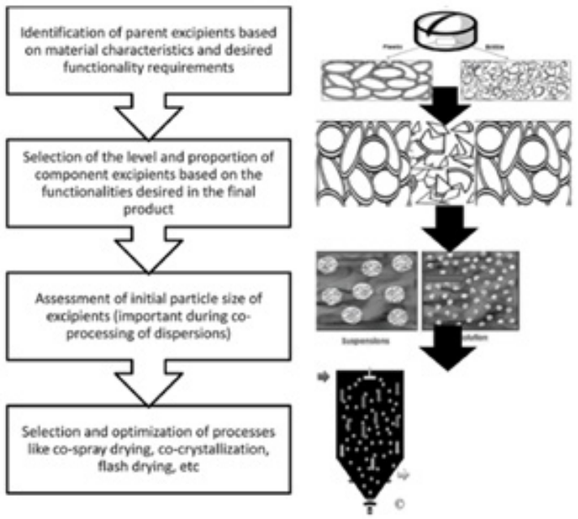

Figure 1: Co-processing methodology[5]

1. **Spray drying**

It is a continuous particle processing-drying operation in which two or more excipients, in its fluid state (solution, suspension, dispersion or emulsion), are converted into particulate form by spraying this fluid in a hot drying medium.

Examples: Cellactose 80, MicroceLac 100, Pearlitol Flash, SmartEx

2. **Fluid Bed Granulation / Agglomeration**

This involves top-spray granulation process. In this process, one of the excipient can be dissolved in the granulating fluid and then granulated with the second excipient; or, both the excipients can be blended together and granulated by a granulating agent.

Examples: RetaLac

3. **Solvent evaporation technique**

In this process, the coating excipient is dissolved in a volatile solvent, which is immiscible with the liquid manufacturing vehicle phase. The core excipient being microencapsulated is then dispersed in the coating polymer solution followed by dispersion of core-coating solution mixture in the liquid manufacturing vehicle phase to obtain appropriate size microcapsule with continuous agitation. The mixture is then heated (if necessary) to evaporate the organic solvent.

Examples: Aquacoat ECD 30, Aquacoat CPD

Apart from the above-mentioned methods, other methods like dry granulation by roller compaction, hot melt extrusion, freeze-thawing, co-crystallization can also be implemented.

Table 1 - Commercially available co-processed excipients:

Type	Brand name (Excipient combination)	Key application	Manufacturer
Microcrystalline cellulose (MCC) based	Avicel DG (MCC-Anhydrous DCP)	Specialty binder for dry granulation process	DuPont
	Avicel RC-591 (MCC- Carmellose sodium)	Ready-to-use suspension Nasal formulation	
	Avicel CL-611 (MCC- Carmellose sodium)	Dry suspension Nasal formulation	
	Avicel HFE 102 (MCC-Mannitol)	Chewable tablet, fast dissolving tablets	
	Avicel CE-15 (MCC-Guar gum)	Diluent for Chewable tablets with superior sensory characteristics	
	Avicel SMCC (Silicifed microcrystalline cellulose)	Diluent for direct compression process MUPS based tablet	
Lactose based	Cellactose 80 (Lactose monohydrate-Powdered cellulose)	Diluent for direct compression and dry granulation process Low dose formulation	Meggle
	MicroceLac 100 (Lactose monohydrate-MCC)		
	CombiLac (Lactose monohydrate-MCC-Maize starch)		
	StarLac (Lactose monohydrate-Maize starch)	ODTs, Fast-melt tablets Low dose formulation	
	RetaLac (Lactose monohydrate-Hypromellose)	Sustained release formulation by direct compression MUPS and mini tablets	
Mannitol based	Pearlitol Flash (Mannitol-Starch)	ODTs, Fast-melt tablets	Roquette Freres
	RetaM (Mannitol – Hypromellose)	Lactose-free diluent for sustained release formulation	Meggle
	SmartEx (Mannitol-Low substituted hydroxy-propyl cellulose – polyvinyl acetate)	ODTs with superior sensory characteristics	Shin-Etsu
Sucrose based	Compressuc MS (Sucrose-Maltodextrin)	Diluent for direct compression	Tereos
	Pharm-a-spheres (Sucrose-Maize starch)	Neutral cores for pellet-based formulation	Hanns G. Werner
Calcium carbonate based	Scoralite DC 90ST (Calcium carbonate-Starch)	Diluent for direct compression Antacid preparations	ICL
	Scoralite DC 90MD (Calcium carbonate-Maltodextrin)		
Xylitol based	Xylisorb XTAB 240 (Xylitol- Dextrin)	Diluent for direct compression process Chewable tablets, sachet	Roquette Freres
	Xylitab XTAB 400 (Xylitol- Carmellose sodium)		
Calcium phosphate based	A-Tab MD (Dicalcium phosphate anhydrous – Maltodextrin)	Diluent for direct compression process Nutraceutical formulation Source of calcium and phosphate	Innophos
	NutraTab (Tricalcium phosphate – Guar gum)		
	Tri-Tab – PVP (Tricalcium phosphate – Polyvinylpyr-rolidone)		

Conclusion:

Co-processed excipients not only improve the functionality of the blend but also reduce the number of ingredients involved in a formulation. This is an added advantage for the manufacturing plant when maintaining the plant inventory. Moreover, co-processed excipients help the formulators in by-passing intellectual property associated with competitor and accelerating the launch of their product.

Although there are several benefits, co-processed excipients have the below limitations

- *Ratio of the excipients in a mixture is fixed hence, optimization is not possible*
- *Not all co-processed excipients have pharmacopoeial acceptance and a DMF status is required*
- *The cost is comparatively higher than the individual excipients*

There are certain obstacles in using co-processed excipient due to lack of its pharmacopoeial compliance, however, IPEC has made a way by permitting the evaluation of toxicological data of individual excipients and characterizing the analytical parameters of the co-processed excipients

Signet Excipients Pvt. Ltd., India's largest distributor of specialty and diverse excipients for the pharmaceutical, biopharmaceutical and nutraceutical industry, offers a wide range of option for troubleshooting their formulation development with co-processed excipients. India's largest distributor of specialty and diverse excipients for the pharmaceutical, biopharmaceutical and nutraceutical industry.

You can also send us your enquiries on sales@signetexcipients.com or visit our website www.signetexcipients.com

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GCMS as an Analytical technique in Pharmaceutical Industry

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Gas chromatography is an analytical technique for the separation of compounds in complex mixtures based on the polarity and boiling points of compounds. This separation technique can be used only for compounds that are volatile and thermally stable. Non-volatile compounds can be made volatile by chemical derivatization using suitable derivatizing agents. GC is one of the widely accepted tools for the separation of compounds because of its simplicity, sensitivity and effectiveness. The principle of separation of compounds depends on the partitioning behaviour difference between mobile and stationary phases. The sample to be separated is carried by a moving gas stream through a tube packed with a finely divided solid or may be coated with a film of a liquid. Different types of columns having various composition of stationary phase are available for the separation of different classes of compounds. The sample to be separated is introduced through the injector maintained at higher temperature which is capable of volatilizing the compound into the column.

Sample components get separated inside the column on the basis of either adsorption or partition depending on the type of column used. Depending on the type of stationary phase used, GC can be classified as Gas Solid Chromatography (GSC) or Gas Liquid Chromatography (GLC). In GSC, a solid adsorbent is used as stationary phase and the separation takes place on the basis of adsorption. In GLC, a liquid is used as the stationary phase and the separation takes place on the basis of partition. The carrier gas (mobile phase) is an inert gas like Hydrogen, Helium or Nitrogen of high purity. The compounds having greater interaction with the stationary phase are retained for longer time in the column whereas compounds having weak interactions with the stationary phase are retained for lesser amount of time. Hence depending upon the difference in the degree of interaction with the stationary phase, different compounds move through the column at different speeds and elute out of the column at different times. When a compound elutes out of the column, it enters the detector and the detector produces a signal proportional to the concentration of the compound. Hence different compounds will have different retention times (RT) based on their polarity or boiling points.

There are different types of detectors available for GC. Some of the commonly used detectors are Flame Ionization Detector (FID), Thermal Conductivity Detector (TCD), Electron Capture Detector (ECD), Nitrogen

Phosphorous Detector (NPD), Flame Photometric Detector (FPD) & Mass Spectroscopic Detector (MSD, single and triple quadruple modes).

In combination with different detectors, gas chromatography finds application in the qualitative and quantitative analysis in various fields like environment, pharmaceuticals, petroleum industries, perfumery, food testing etc. Various applications of GC in pharmaceutical fields include:

1) Residual solvent analysis in Active Pharmaceutical Ingredients (API)

2) Percentage purity of pharmaceutical compounds

3) Analysis of drugs of abuse

4) Identification of natural products

5) Residual solvents in packaging materials.

While GC is an excellent separation technique, it has a limitation when it comes to qualitative identification of the separated compounds. For separated compounds to be identified, reference standards are required. Identity of the compound is established by comparing the retention times of the compound and the reference standard after both are analyzed under identical conditions. This can be a very cumbersome process. Also availability of reference standards can be another major problem. It is in this context that a GCMS scores over a conventional GC.

Gas Chromatography- Mass Spectrometry:

GCMS is a hyphenated system, where a Mass Spectrometer is connected to a Gas Chromatograph. Here, MS is a detector for the GC and it has got a distinct advantage over all the conventional detectors in GC

While all conventional detectors provide good sensitivity, they fail to identify the separated sample components on their own. Identification will remain the responsibility of the user with the help of authentic standards. An MS detector on the other hand can carry out a sensitive analysis like any other conventional detector along with a positive qualitative identification without the need for an authentic standard. Compounds will be identified on the basis of their mass spectra.

In GCMS, one end of the column is connected to the heated injection port while the other end goes to the mass spectrometer through a heated interface. While the GC is at atmospheric pressure, MS is maintained under vacuum. The three important parts of an MS are the Ion Source, Mass Analyzer and the Detector. All the three parts are connected to a powerful vacuum pump. The compound eluting out of the column will enter the ion source and will get fragmented (ionized).

Depending on the type of compound, many fragments are produced with each fragment having a certain m/z ratio. All these fragments are separated by the mass analyzer on the basis of their mass number and they are all directed to the detector. The detector gives an output which is a mass spectrum. The mass spectrum is a finger print of the compound and forms the basis for it's identification.

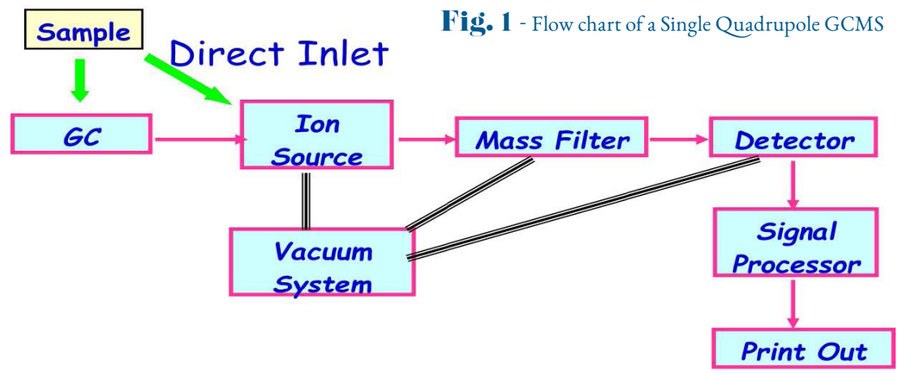


Fig. 1 - Flow chart of a Single Quadrupole GCMS

"The basis of MS (mass spectrometry) is the production of ions that are subsequently separated or filtered according to their mass-to-charge (m/z) ratio and detected. The resulting mass spectrum is a plot of the abundance of the produced ions (relative intensity) as a function of the m/z ratio."

The ionization techniques in GCMS include Electron Impact Ionization (EI), Positive Chemical Ionization (PCI) and Negative Chemical Ionization (NCI). For qualitative identification, the sample is to be analyzed under EI mode. PCI mode is used for the determination of molecular weight of a compound, while NCI mode is used for the trace analysis of electrophylic compounds.

Different types of mass analyzers are available for GCMS. One of the most popular one is a Quadrupole mass analyzer. With the help of a quadrupole mass analyzer, all the fragments that are produced in the ion source can be separated on the basis of the mass number in a very short period of time and they all can be sent to the detector resulting in the formation of a mass spectrum.

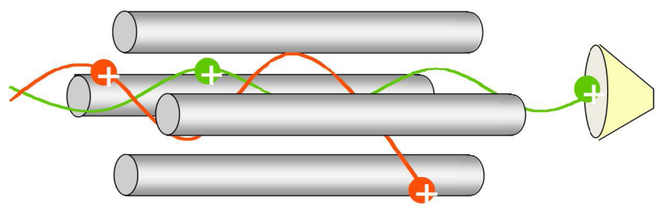
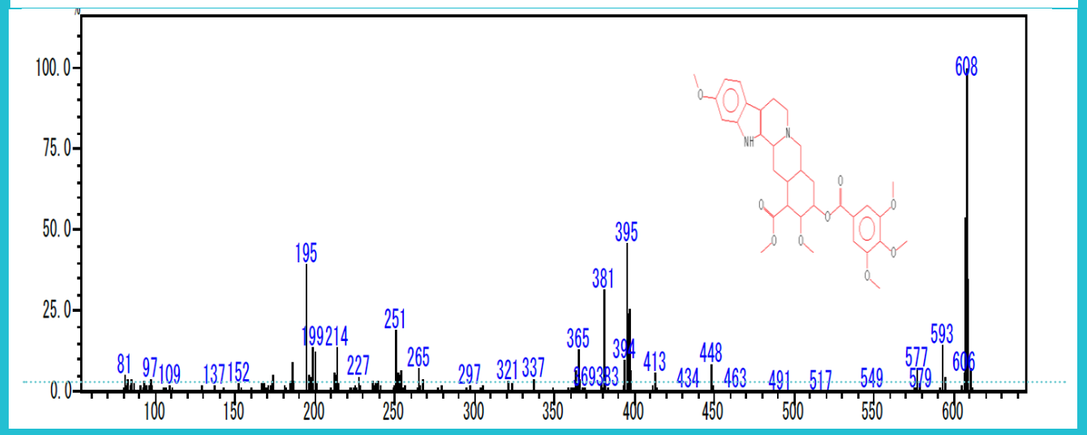


Fig.2. Quadrupole Mass Analyzer

GCMS can be used for both qualitative as well as quantitative analysis. The two main modes of operations in GCMS are Scan mode and SIM mode. While Scan mode is used for qualitative identification, SIM mode (Selected ion Monitoring) mode is used for quantification. If a compound is a pure one, with no impurities to be separated by acolumn, then we can introduce a very small quantity of the compound directly into the MS with the help of a Direct Inlet Probe. The analysis can be completed in a very short period of time. This is a very useful mode especially for the analysis of pure pharmaceutical drugs.

Fig.3. Mass Spectrum of Reserpine by DI-MS



GCMS has applications in different fields like Pharmaceuticals, Foods, Perfumery, Flavour, Cosmetics, Polymers, Petroleum etc.

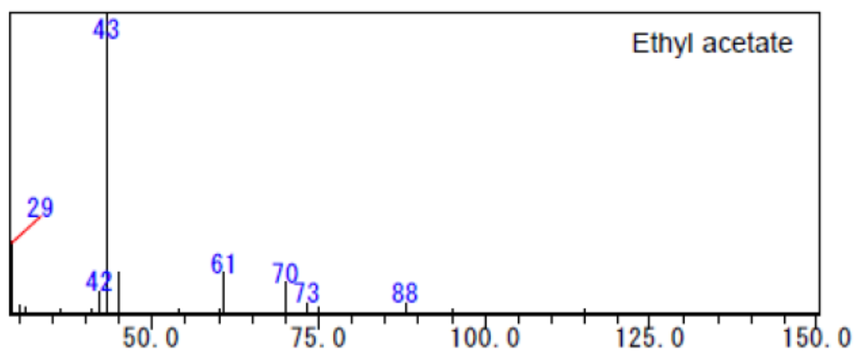
Pharmaceutical applications:

GCMS has got many applications in Pharmaceutical science. Some of the major applications include:

1. Residual solvents in API: Residual solvents in API can be classified into 3 groups: Class 1, Class 2 and Class 3. Class 1 and 2 solvents can be identified and quantified by GCMS in combination with a Head Space Analyzer as per USP Method 467. Head Space is an injection technique for the determination of volatile compounds in a non-volatile sample.

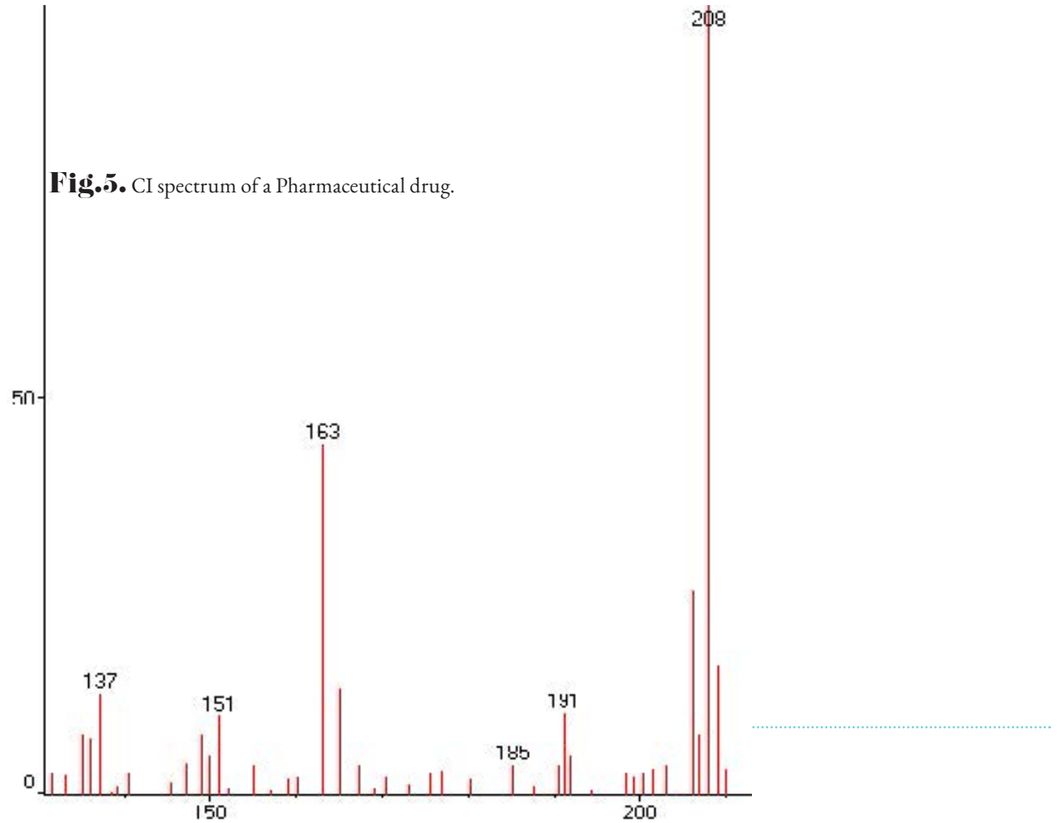
2. Residual solvents in packaging materials is another important analysis in pharmaceutical as well as food industry. These can be identified and quantified with GCMS along with a head space analyzer.

Fig.4. Mass spectrum of EtAc (residual solvent) in a drug



3. Determination of molecular weight: Molecular weights of drugs can be found out by GCMS analysis using CI mode of ionization. The method is very simple and quick. The CI spectrum of a drug sample is shown below.

Fig.5. CI spectrum of a Pharmaceutical drug.



4. Genotoxic impurities: Methane sulfonic acid (mesylate), benzene sulfonic acid (besilate), and p-toluene sulfonic acid (tosylate), chemicals used in the process of synthesizing active pharmaceutical ingredients, are likely to generate sulfonic acid esters as reaction by products. These compounds are known as potential genotoxic impurities (PGI) and are a significant cause for concern among pharmaceutical manufacturers. These sulphonic acid esters can be determined by GCMS.

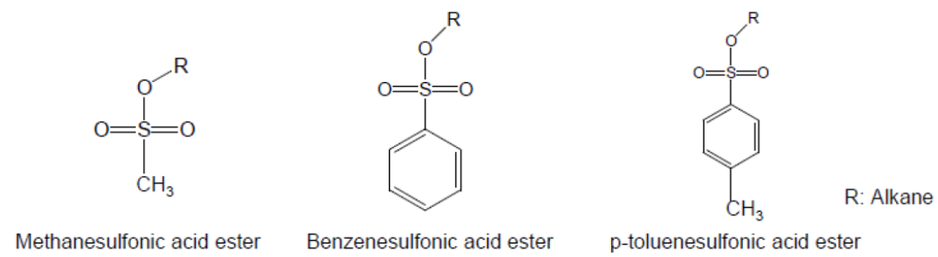


Fig.6. Structural formula of different sulfonic acid esters

5. Analysis of Nirosamine impurities in Sartan type drug substances:

Nitrosamines are highly carcinogenic compounds and their presence in drug substances is a major matter of concern. GCMS can be used to quantify nitrosamines like N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA).

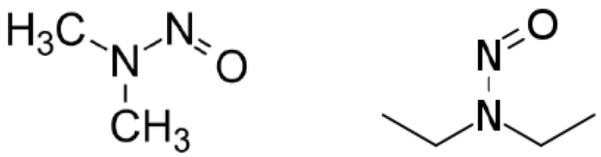


Fig.7. Structure of NDMA and NDEA

QP2020NX is a Single Quadrupole GCMS from Shimadzu, which offers Smart Performance, Smart Productivity and Smart Operation. It has got a very wide mass range with various advanced features. All the three ionization modes, EI, PCI & NCI can be used in this model. A Direct Inlet Probe (DIP) is also available for that can be used for pure samples for DI-MS analysis. Various accessories are available that can be attached to this for different types of applications. The software has also many advanced features.

Fig.8. Single Quadrupole GCMS QP2020NX

CONCLUSION:

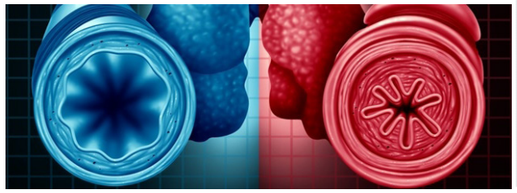
GCMS is an important and very valuable analytical technique in Pharmaceutical industry. Many different applications are possible on a GCMS system. Different accessories are available for GCMS for different types of analysis. One important accessory that is widely used along with a GC or GCMS is a Head Space Sampler. The software is very powerful and user friendly with many important features.

Upcoming Developments in the Treatment of Asthma

Will it be better than existing treatment?

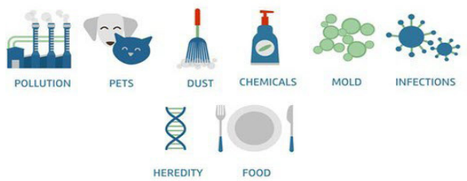
Adnan Siddique, Student: M Pharm (Pharmaceutics)Semester II

1.What is Asthma?



Asthma is an allergy borne condition in which there is constriction of airways and swelling which may produce extra mucus. This can make breathing difficult and trigger coughing, wheezing when you breathe out and shortness of breath. Asthma is a minor problem. But if neglected can become a major problem since the recurrent asthma attacks can interferes with daily activities and may lead to a life-threatening asthma attack. Asthma can't be cured, but its symptoms can be controlled. Patients are usually advised to frequently track their signs and symptoms since the severity of asthma attacks can gradually worsen over a period of time, for this patient should frequently consult their physician.

2.What Causes Asthma?



As such there is no single causative factor that has been identified for asthma. Research shows that the breathing condition is caused by a various factors such as.

- *Genetics:- If a parent or sibling has asthma, you're more likely to develop it.*
- *History of viral infections:- People with a history of severe viral infections during childhood (e.g. RSV) may be more likely to develop the condition.*
- *Allergens:-Airborne allergens, such as pollen, dust mites, mold spores, pet dander or particles of cockroach wasteand other allergic conditions. Air pollutants and irritants, such as smoke*

3.Recent advancement in diagnosis of asthma

Spirometry, methacholine Challenge test and Lung tests in children. These tests were widely used for diagnosis of asthma but recent development of diagnostics method of asthma lead to advancement of methods in terms of their accuracy and sensitivity. Such methods are Fractional Excretion of Nitric Oxides and Mannitol Bronchial Challenge Test

3.1 Fractional Excretion of Nitric Oxide[1]

Measurement of fractional excretion of nitric oxide (FeNO) is a new and efficient method in diagnosis of asthma. Nitric oxide is a gas that is released into the airway It is an indirect marker of eosinophilic airway inflammation. Patients with asthma or active inflammation have higher levels of FeNO as compared to patients without asthma. The normal range of FeNO is 0 to 20 ppb. Levels of FeNO higher than 35 ppb would be consistent with active eosinophilic inflammation This will indicate patient is suffering from asthma.

3.2 Mannitol Bronchial Challenge Test [2,3]

It is a recently developed alternative to the methacholine challenge test, It is better than methacoline test in detection of asthma. It have been approved by the US FDA. Aridol (mannitol inhalation powder; Pharmaxis Ltd, Frenchs Forest, Australia) is available as an bronchial challenge test kit for the assessment of bronchial hyper responsiveness. The advantage of this test is ease of administration, ease of use, and cheaper than methacholine challenge. Aridol can conveniently determine patients who are most likely to respond to anti-inflammatory treatment, it can also elicit patient's specific asthma phenotype.

4. Treatment

4.1 Existing Treatment for asthma

Asthma treatment involves a three-part strategy:

- *provide long-term control medications to prevent symptoms before they start*
- *quick-relief medications to stop asthma attacks*
- *Biologics- Biologic drugs work with your immune system to treat asthma. They block the activity of immune system chemicals that make your airways swell up and* avoiding triggers to reduce the number of attacks

Table no 1:- *Currently available medication for asthma.*

Treatment	Class of drug	Example
Long term control medication	Inhaled corticosteroids Inhaled long-acting beta- agonists leukotriene modifiers Cromolyn sodium (Intal) Theophylline (Theochron)	
Quick relief medication	inhaled short-acting beta-agonists inhaled short-acting anticholinergics combination of an inhaled short-acting anticholinergic and inhaled short-acting beta-agonist	
Biologics	Monoclonal antibodies Leukotriene modifiers	reslizumab(Cinqair), mepolizumab(Nucala), omalizumab (Xolair), benralizumab (Fasenra). montelukast(Singulair), zafirlukast(Accolate), zileuton (Zyflo).

4.2 Future treatment of severe asthma.

Despite widely available and effective treatments, achieving asthma control is still an unmet need for many patients. One of the explanations resides perhaps in the heterogeneity of the disease. Asthma is in fact, as we understand it today, a complex syndrome made up of numerous disease variants or asthma phenotypes; when the different underlying mechanisms are identified, the more ambitious term "endotype" is used, with consequent therapeutic implications. Remarkable efforts have been made to identify the features of difficult-to-control (usually severe) asthma, which are different from those described for mild-to-moderate asthma, setting the stage for the development of new and even individualized therapies. As different drugs target different pathways, it is necessary to determine the individual profile of pathophysiological abnormalities for each patient. The most fascinating options of the new asthma treatments are the monoclonal antibodies targeted against key inflammatory cytokines, and the most proximately available treatments within the next years are discussed here. Also, current evidence and understanding of somehow older therapeutic options, such as anticholinergics, thermoplasty, or omalizumab, are reviewed from a phenotypical approach.

5. Improving what already exists

5.1. New Inhaled corticosteroids (ICS)

For 40 years ICS have been used in asthma; today, their dominance is hard to contest and their achievement difficult to challenge from a scientific point of view. Reduced risk of asthma death is not their only achievement[4] since the global pattern of asthma has changed worldwide, hospital admissions for asthma are becoming rare events[5]. However, ICS' side-effects cannot be ignored since they are now well documented: adrenal insufficiency, diabetes, skin bruising, oral mycosis, reduced bone density and reduced growth in children. Although rare, these events are nonetheless significant, but their incidence rates are insufficient to reverse the very positive benefit/risk balance associated with regular use of ICS in asthma Notably, patients are more interested in these pitfalls than the benefits of ICS, and poor levels of adherence are potentially related to patients, and sometimes doctors, sharing a mistrust of ICS. Developing new ICS with a better pharmacological profile may potentially address most of these issues. Keeping the good effects and removing the bad requires a perfect understanding of mechanisms of action of ICS. In particular, nongenomic activities and/or selectivity for transactivating genomic properties are often seen as culprits, and some interesting attempts to counter these were proposed recently with modified analogues like Improving drug half life of ICS which will increase patient adherence and compliance[5]

5.2. New long-acting β-agonists and long-acting muscarinic agonists

New long-acting β-agonists (LABA) have been developed for chronic obstructive pulmonary disease (COPD) and, a priori, these might also reasonably be expected to be effective against asthma. The recently developed once-daily, very long-acting LABA (indacaterol, vilanterol, olodaterol[6-10] and others potentially offer better bronchodilation patterns relevant to treating severe asthma with persistent airflow obstruction. Long-acting muscarinic antagonists initially developed for COPD are now widely used in asthma and tiotropium was recently approved for this indication[11]

5.3. New combinations: ICS/LABA, LABA/LAMA, and triple therapy LABA/LAMA/ICS [12]

Because combination therapy with ICS and LABA is the usual therapeutic option for the treatment of asthma, there is great interest in developing combinations of administration once a day, in an attempt to simplify treatment and improve treatment compliance, a currently achievable challenge with the new ICSs (such as ciclesonide, mometasone, and fluticasone furoate) and the emergence of new ultra-LABAs (such as indacaterol, vilanterol, and olodaterol), which can be administered in a single-daily dose. Currently, new combination therapies of ultra-LABA/ICS have been developed, are in clinical trial phases II–III, or have even recently marketed (vilanterol/fluticasone furoate), like several other LAMA–LABA combinations for the treatment of COPD: tiotropium / olodaterol, aclidinium/ formoterol, umeclidinium/ indacaterol, vilanterol /umeclidinium, and so on . However, the use of some of these drugs in asthma is still being investigated.

Long-acting muscarinic antagonists (LAMA):

•*Aclidinium bromide (approved for treatment of COPD)*

Ultra-long-acting muscarinic antagonists (ultra-LAMA):

•*Tiotropium bromide (approved for treatment of asthma and COPD)*

•*Glycopyrronium bromide (approved for treatment of COPD)*

Ultra–long-acting beta-2-agonists (ultra-LABA):

•*Indacaterol maleate (approved for treatment of COPD)*

•*Carmoterol hydrochloride, milveterol hydrochloride, olodaterol hydrochloride*

New combinations of ultra–long-acting beta-2-agonists (ultra-LABA) and inhaled corticosteroids (ICS)

•*Vilanterol trifenatate / fluticasone furoate (approved for treatment of asthma and COPD)*

•*Indacaterol maleate / mometasone (MGC-149)*

•*Indacaterol maleate / QAE 397*

New combinations of LAMA or ultra-LAMA and LABA or ultra-LABA:

•*Tiotropium bromide / olodaterol hydrochloride*

• *Indacaterol maleate / glycopyrronium bromide (QVA149)*

•*Umeclidinium bromide / vilanterol trifenatate (approved for COPD)*

•*Formoterol/ aclidinium (approved for COPD)*

Triple therapy of ultra-long-acting beta-2-agonists (ultra-LABA), inhaled corticosteroids (ICS), and ultra–longacting muscarinic antagonists (ultra-LAMA):

•*Vilanterol trifenatate/fluticasone furoate/ umeclidinium bromide*

When talking about the triple combination, it refers to ICSs, such as beta-2-agonist and inhaled anticholinergics, but mainly to long-acting drugs (LAMA–LABA–ICS). The possibility of associating these three drugs can contribute to better compliance, better control of the symptoms, and improved quality of life, as well as to a decrease in exacerbations. There are several clinical studies in development: fluticasone/salmeterol/tiotropium and budesonide/formoterol/tiotropium . The first triple combination formoterol/tiotropium/ciclesonide (Triohale®, Cipla) is now available in India, and its probable effectiveness in asthma is yet to be proven in future clinical trials.

6. Endotype based strategies

6.1 Th2-orientated therapies. Or : Eosinophilic and Th2 high asthma [13]

Th2 cells have more or less all been targeted (interleukin (IL)-4, IL-5, IL-9, IL-13, IL-23, IL-25, IL-33, IgE and thymic stromal lymphopoietin (TSLP)), and probably, others will be targeted in the future. Targeting of the Th2 subset through Th1 promotion or through specific inhibition (GATA3-specific DNAzyme)have been proposed, while the discovery of innate lymphoid cell (ILC)2 allowed their targeting with CRTH2 antagonists, which were rapidly transferred from bench to bedside The ability of each molecule to inhibit the late asthmatic response is now considered an essential avenue of research, even though direct comparisons are difficult.

6.1.1. Anti IL-5 monoclonal antibodies.[14]

Interleukin-5 (IL-5) is a hematopoietic cytokine produced by various cells such as Th2 lymphocytes, eosinophils, basophils, mast cells, and natural killer T-cells, and it is the main eosinophil modulator cytokine because it enhances eosinophil chemotaxis, activation, and degranulation, while reducing apoptosis and prolonging eosinophils' survival. The IL-5 receptor (IL-5R), expressed on both basophils and eosinophils, is made up of two subunits: an α-subunit (IL-5Rα) that is IL-5-specific and a βc-subunit (IL-5Rβc) that is responsible for signal transduction and is shared with the specific α-receptor subunits of IL-3 receptors and granulocyte–macrophage colony–stimulating factor (GM-CSF)

Table no. 1 *Anti-interleukin-5 treatment for patients with severe asthma*

Drug	Dose	Route of administration	Patient type
Reslizumab	3 mg·kg−1	Intravenously once every 4 weeks over 52 weeks	Hypereosinophilic (induced sputum eosinophils >3%), high-dose ICS
Mepolizumab	250 or 750 mg	Intravenously once every 4 weeks over 12 weeks	ACQ >1.5, no OCS useICS <1000mcg per day BDP equivalent
Benralizumab	2, 20 or 100 mg	Subcutaneously once every 4 weeks then every 8 weeks over 52 weeks	Medium/high-dose ICS use, 2–6 exacerbations per year, stratification by eosinophilic status

Mepolizumab [15,16]

Mepolizumab in a fully humanized anti-IL-5 IgG1 mAb that binds to the free IL-5 with high affinity and specificity, thus preventing its binding to the α chain of the IL-5R on the eosinophil cell surface. It was the first IL-5 antagonist used in randomized, controlled trials in patients with mild asthma and with moderate uncontrolled persistent asthma

Reslizumab [17]

Reslizumab, a humanized IgG2, is another IL-5 inhibitor that is administered intravenously, although it has not been studied at such extent as mepolizumab. The only published clinical trial in patients with poorly controlled eosinophilic asthma proved that patients treated with reslizumab showed a significant improvement in FEV1 and, interestingly, patients with concomitant polyposis showed better asthma control compared to the placebo group.

Benralizumab [18]

Benralizumab is a humanized IgG1 mAb targeting IL-5Rα, which reduces eosinophilia by antibody-dependent cell-mediated cytotoxicity. Intravenous benralizumab has shown acceptable safety and

tolerability in a phase I, dose-escalating study, with a marked reduction in circulating eosinophils.
In a phase I, multicenter, double-blind, placebo-controlled study, 13 patients were randomized to receive a single intravenous dose of placebo or 1 mg/kg benralizumab, and other 14 patients were randomized to receive a monthly subcutaneous dose of placebo, or either 100 or 200 mg benralizumab, for 3 months. The study concluded that both the single intravenous dose and the multiple subcutaneous doses of benralizumab reduced the percentage of eosinophils in the bronchial biopsies and in induced sputum and suppressed eosinophil counts in the bone marrow and peripheral blood [60]. Additional studies are further required.

6.2 Interleukin-13 or Anti IL-13 monoclonal antibodies [19]

IL-4 and IL-13 are key therapeutic targets in Th2 high asthma, due to their significant role in Th2 lymphocyte responses and in B lymphocyte isotype switching for IgE synthesis and also for their intervention in mast cell selection. The strong evidence existing upon the involvement of this pathogenic pathway in asthma, initially ranging from genetic studies up to convincing data from animal studies, leads to the development of a wide range of biological agents aimed at these targets, including anti-IL-13, anti-IL-4Rα and anti-IL-13Rα1 mAbs, IL-4Rα/IL-13Rα1 fusion protein, IL-4/IL-13 vaccines, anti-IL-4Rα antisense oligonucleotides, and double mutein IL-4]. However, although many of these drugs are under

Table no. 2 *Anti-interleukin-13 treatment for patients with severe asthma*

Drug	Dose	Route of administration	Patient type
Lebrikizumab	250 mg	Subcutaneously, once-monthly over 6 months	Severe asthma, ICS dose between 200 and 1000 µg fluticasone propionate equivalent
Tralokinumab	150, 300 or 600 mg	Subcutaneously, once every 2 weeks over 13 weeks	Moderate to severe asthma
GSK67958	10 mg·kg–1	Intravenously once-monthly over 12 weeks	Severe asthma, high-dose ICS

development, to date only a few have been evaluated in patients with asthma.

Lebrikizumab [20]

Corren et al. first studied the effects of lebrikizumab in 219 adults with moderate-to-severe persistent uncontrolled asthma. Lebrikizumab was administered subcutaneously every month for 6 months. A significant improvement in prebronchodilator FEV1 was recorded at 12 weeks in patients treated with lebrikizumab when compared to the placebo group. The study drug was significantly more effective in patients with pretreatment circulating periostin levels above the median and also in those with Th2-high phenotype (total IgE > 100 IU/ml and eosinophilia > 140/mm3), when compared to those with Th2-low phenotype. Exacerbations were not significantly reduced in the active group compared to placebo, but when sub analyzed in the Th2-high subgroup, the rate of exacerbations was 60% lower in patients receiving lebrikizumab compared to placebo. These data suggest that therapy with anti-IL-13 antibodies may be more effective when directed to a selected subgroup of patients (i.e. Th2-high –phenotype).

Dupilumab [21]

Dupilumab (Sanofi) is a humanized mAb that targets the α-subunit of the IL-4–IL-13 shared receptor. The efficacy and safety of dupilumab in the treatment of patients with persistent eosinophilic asthma were evaluated in a phase IIa, randomized, double-blind, placebocontrolled study. One hundred and five patients with moderate-to-severe persistent asthma and eosinophilia ≥300/mm3 in blood or ≥3% in sputum were included. All patients were on moderate-to-high doses of ICS and LABA. They were randomized to receive either dupilumab 300 mg (n = 52) or placebo (n = 52), subcutaneously, once a week for 12 weeks, or until the development of a moderate or severe exacerbation (primary endpoint)

7. New anti-IgE agents[24]

ligelizumab and quilizumab The inverse correlation between free IgE levels and asthma control, found in several studies, suggests that a more profound suppression of free IgE could lead to an even more marked clinical improvement, so new, more potent anti-IgE mAbs are currently being assessed in clinical trials.

Ligelizumab.[25]

QGE031B (ligelizumab) is a new anti-IgE mAb (Novartis). It is a humanized IgG1 that binds with higher affinity to the Ce3 region of IgE. QGE031 is designed for greater suppression of IgE, with a dissociation constant (Kd) of 139 pM, representing an increase in almost 50 times of the affinity for IgE when compared with omalizumab (Kd = 6–8 nM). This is hypothesized to overcome some of the limitations associated with the dosage of omalizumab and lead to better clinical outcomes in asthma Ligelizumab was superior to omalizumab in the suppression of free IgE and FceRI expression on surface of basophils. These effects resulted in the almost complete suppression of skin response to allergens, which was higher in extent and duration when compared with omalizumab

Quilizumab [26]

Quilizumab (MEMP1972A, Genentech/Roche), another mAb anti-IgE, is being studied now in a phase IIb, randomized, double-blind, placebo-controlled clinical trial aimed to evaluate the efficacy and safety of three different doses (150, 300, and 450 mg, subcutaneously) in adults with allergic asthma not controlled with ICS and a second controller (NCT01582503). Quilizumab already has been proven effective in decreasing total and specific IgE in patients with allergic rhinitis (NCT01160861) and mild allergic asthma (NCT01196039), with a good safety profile.

8. Non-eosinophilic asthma: Neutrophilic, Th2-low asthma [22,23]

Anti-tumor necrosis factor-α monoclonal antibodies Unfortunately, for patients belonging to severe asthma phenotypes other than eosinophilic asthma, current therapeutic options are scarce, and many of these patients are steroiddependent and even steroid-resistant. Clinical trials with anti-tumour necrosis factor (TNF)- α mAbs (such as infliximab, adalimumab, and golimumab) have been performed with discouraging results. A study including 309 patients with severe persistent asthma, randomized to receive placebo or three different doses of golimumab (50, 100, and 200 mg), showed no significant improvement in any of the efficacy variables . More importantly, the trial had to be prematurely discontinued due to serious adverse events (SAEs), namely infections and malignancies, in the golimumab group. A post-hoc analysis suggested that patients with a prestudy history of sinusitis and FEV1 reversibility (≥12%) who received golimumab (100 and 200 mg) had fewer severe asthma exacerbations, apparently associated with a dose– response effect. Perhaps, if biomarkers were developed for predicting response to anti-TNFα agents, then they could be used for selected subgroups of patients with severe asthma, but the contradictory efficacy results and especially the potential safety concerns have prevented the performance of any additional clinical trials so far.

9. Bronchial thermoplasty [27]

Thermoplasty is a bronchoscopic procedure that reduces the bronchial smooth muscle layer by applying heat by radiofrequency. The results of the studies showed, in patients with moderate and severe asthma, a significant improvement in their quality of life, increased disease control, and a reduction of exacerbations. These results persist for years after the procedure, without medium- to long-term secondary effects . While new evidence is needed to identify the ideal candidate, it is currently considered to be preferably indicated in patients with severe uncontrolled asthma, with chronic airflow limitation (FEV1 > 50% and < 80%) , and without bronchial hypersecretion. Likewise, its application is recommended to be performed in centers with experienced and sufficiently trained endoscopists.

10. Differences in Newer and Older Asthma Treatments

Long-term control treatments help you to avoid an asthma flare up. They should be taken even when you don't have asthma symptoms.

Quick-relief medications are only for when you need them. They are called rescue methods because of their ability to ease or stop symptoms of an asthma attack. You should not take them every day, and you should tell your doctor if you feel the need to take rescue asthma drugs more than the suggested amount. You should only use newer, injectable biologics if other asthma treatments aren't enough for you. If you begin taking biologics, it's important that you still take all of your other long-term or quick-relief asthma medications unless your doctor tells you to stop. Keep up with your asthma checkups, and ask your doctor if you should still take certain medications once you start biologic

Conclusion:

We are observing fast growth in development of newer molecules and also new combinations in terms of efficacy, safety, and dosage for the treatment of asthma, except for treatment of patients suffering from severe non-eosinophilic asthma, in which therapeutic options still remain limited. Given the disease's heterogeneity, it is critical to create the phenotype or endotype as a first step toward "personalized" medicine in asthma.

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