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Prevalence, Pattern and Impact of Self Medication of Anti-Infective Agents during COVID-19 Outbreak in Dhaka City

By Nasir M, Mannan M, Chowdhury ASM, Zahan T & Perveen RA

Abstract- Background: The outbreak of coronavirus disease-2019 is putting a massive strain on the vulnerable healthcare systems in low and middle-income countries like Bangladesh. Inequitable access to healthcare is further widened by the socio-economic gap and sense of insecurity during this pandemic. Self-medication is a common practice in Bangladesh as it provides a low-cost alternative for people, which involves inappropriate and injudicious use of medicines to treat self-recognized symptoms by the people. During the outbreak of COVID-19 in Dhaka city, the tendency of taking medicines by own decision was increased alarmingly due to unusual distress, caused by high self-awareness of their health and buying capacity of medication.

Objectives: To observe the prevalence, pattern, sources, and impact of self-medication practice among the respondents with high socio-economic standings and education.

Setting: Citizens living in Dhaka city, Bangladesh, during the COVID-19 outbreak from April 2020 to May 2020. **Method:** Cross-sectional online survey conducted on 626 citizens without having a background of medical knowledge or related to any healthcare services (doctors, nurses, pharmacists, medical students) by structured questionnaires during the COVID-19 outbreak.

Outcome measures: Frequency of self-medication, commonly used antimicrobial agents, symptoms causing self-medication, sources of inspiration, relation with COVID-19 test results, economic burden involved in self-medication during the outbreak.

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Prevalence, Pattern and Impact of Self Medication of Anti-Infective Agents during COVID-19 Outbreak in Dhaka City

Nasir M^α, Mannan M^σ, Chowdhury ASM^ρ, Zahan T^ω & Perveen RA[¥]

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Outcome measures: Frequency of self-medication, commonly used antimicrobial agents, symptoms causing self-medication, sources of inspiration, relation with COVID-19 test results, economic burden involved in self-medication during the outbreak.

Results: The prevalence of self-medication amid the pandemic of the COVID-19 was 88.33%, and only 179 (28.59%) took medication with doctors' advice and the remaining 447 (71.40%) respondents took the drugs as "self-medication" by other sources. The most frequently used anti-infective drugs during the outbreak were ivermectin (77.15%), azithromycin (54.15%), doxycycline (40.25%). The common symptoms were fever, throat pain, dry-cough, and a total 105 (16.77%) respondents took medications without having any symptoms. Almost 355 (85.33%) had taken medication without doing any test for COVID-19. The causes of self-medication as news of spread, effects, and remedies in media channels, internet, mental stress of lockdown and isolation, insecurity, and panic about the scarcity of drug and healthcare support.

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Conclusion: High risks of developing antibiotic resistance, adverse drug reactions, and financial loss were predictable with the absence of strict regulatory enforcement to protect people and proper utilization resources during the COVID-19 outbreak in Dhaka city.

IMPACT ON PRACTICE

- Self-medication of anti-infective agents during the COVID-19 outbreak is high due to inadequate access to the doctors, easy availability of any drugs without prescription, and remedy of common symptoms.
- Most of the educated citizens having high socio-economic status in Dhaka become stressed due to scarcity of supply as informed by news media, internet, and friends that provoked self-medication of anti-infective agents.
- Unapproved medications for the COVID-19 like azithromycin, doxycycline, hydroxychloroquine and ivermectin were used in self-medication that added unnecessary financial burden.
- Lack of monitoring, surveillance, and regulations in drug dispensing can be a major cause of resistance, organ damage, adverse drug reactions, and interrupted supply chain for high demand during the COVID-19 outbreak in Dhaka city.

I. INTRODUCTION

According to the World Health Organization (WHO), self-medication is explained as "the selection and use of medicines by individuals (or a member of the individual's family) to treat self-recognized or self-diagnosed conditions or symptoms. Reasons commonly adducted for indulgence in self-medication include delayed access to healthcare centers, socio-cultural belief, relatively high cost of hospital treatment, previous experience of treatment of same symptoms, easy availability of drugs, poor regulatory practice, the urgency of feeling relieved, advice from friends and media. The of self-medication is prevalent in most parts of Bangladesh, regardless of socio-economic status and level of education. While this is indisputable, the incidence of self-medication is may be higher in the low or middle-income countries without consulting with qualified health professionals¹. Although the WHO stressed that rational self-medication practice helps in

the prevention and treatment of some minor pathological conditions at affordable cost², otherwise it may cause wastage of resources, resistance to pathogens, and serious health hazards with adverse drug reactions and prolonged morbidity³. In a developing country like Bangladesh, the practice of self-medication may provide an alternative for people as low-cost to avoid the high cost of clinical services, and many drugs dispensed over the counter (OTC) without prescription⁴. But it is gone beyond the OTC drugs and sometimes prescription-only drugs like antimicrobials, sedatives, hypnotics and strong NSAIDs also reported to be dispensed without prescription in few cases.

Moreover, the ratio between doctor and patient in Bangladesh is currently as low that places the country at second position from the bottom, among the South Asian countries, according to the WHO⁵. Besides, some individuals practice out of ignorance, poverty, and generalized hypes.

Dhaka, being the capital and the major economic-hub of the country; it lags in the ratio between healthcare workers compared to other neighboring countries, thus hampering proper and timely healthcare. So, practice of self-medication is almost inevitable as the country has only six doctors, nurses, and midwives for every 10,000 populations, according to the report of health bulletin published yearly by the Health Ministry⁶. Some studies on the general tendency and pattern of self-medication practice of prescription-only drugs among students, and people with or without medical knowledge showed an alarming scenario in Dhaka city⁷.

The outbreak of coronavirus disease-2019 is putting a massive strain on vulnerable healthcare systems in low and middle-income countries like Bangladesh. Inequitable access to healthcare is further widened by the socio-economic gap and sense of insecurity during this pandemic since the beginning of 2020⁸. Besides, the population of higher socio-economic standing is more potential to have access to

better health information, medications and affordability that may lead to self-medication practice in mass. Similarly, people with higher education are reported to have much distress, probably due to high self-awareness and access to mass information network⁹.

The combat against COVID-19 is continuing in Bangladesh, with the highest incidence rate in Dhaka city. The available data by WHO revealed that the highest AR was observed to continue in the Dhaka (2321.7/1,000,000) and was highest (9422.1/1,000,000) from April to June 2020¹⁰. As there is no approved cure for the COVID-19 or a vaccine against SARS-CoV-2, the aim of treatment is focused to manage and reduce symptoms until clinical recovery. Most people (around 80%) are an asymptomatic or mild infections that can be treated at home.

As stated in the National Guideline on Case Management of COVID-19 in Bangladesh, there is no precise, effective treatment for COVID-19; the mainstay of management is early diagnosis and supportive care of symptoms and optimum support for organ function in severe illness. No drug is yet recommended as chemoprophylaxis as there is no quality evidence of efficacy and safety in COVID 19. Though Patients should be managed in hospital settings; however, proper home care may also be advised with mild illness unless rapid deterioration or inability to avail hospital if necessary¹¹. But lack of rapid response, scarcity of hospital beds, absence of private practice, inadequate capacity of testing (RT-PCR), the spread of un-authenticated treatment protocols are putting the citizens in the dilemma of choosing medical advice. Lot of prescription-only drugs like antimicrobials (azithromycin, doxycycline), anti-parasitic (ivermectin), anti-malarial (hydroxychloroquine) are reported to become a shortage in the dispensary and peripheral supply chain throughout the city. Moreover, the risk of a wide range of side effects (Table-I) are also of great concern for undocumented self-medication.

Table-I: List of possible side effects of anti-infective agents used in self-medication during COVID-19

	Mild / common	Severe / rare
Azithromycin	Diarrhea, nausea, abdominal pain, vomiting, headache	Prolong QT interval, Arrhythmia, Hepatic dysfunction, Myasthenia
Doxycycline	loss of appetite, nausea, vomiting, diarrhea, rash, sensitivity to the sun, hives, discoloring of teeth, bloody diarrhea, stomach cramping and pain, fever, dehydration, weight loss	headache, blurry vision, double vision, vision loss, Irritation of esophagus, Anemia, Pancreatitis. pain in upper abdomen, fever, skin reactions, blisters, peeling skin, small purple spots
Hydroxychloroquine	nausea, vomiting, stomach pain or cramps, loss of appetite, weight loss, diarrhea, dizziness, spinning sensation, headache, ringing in ears, mood changes, nervousness, irritability, skin rash, itching, or hair loss.	Bone marrow depression, anemia, aplastic anemia, agranulocytosis, leukopenia, and thrombocytopenia. Hemolysis reported in individuals with glucose-6- phosphate dehydrogenase deficiency, Cardiomyopathy, cardiac failure, prolongs the QT interval, Ventricular arrhythmias, torsade de pointes

Ivermectin	tiredness, loss of energy, stomach pain, loss of appetite, nausea, vomiting, diarrhea, dizziness, sleepiness or drowsiness, itchiness, trouble breathing, swelling of throat or tongue, skin rash	Bronchospasm, hepatotoxicity, seizure
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Because of commonly occurring symptoms of soreness or pain in throat, dry cough, fever, body ache, breathlessness, people started to take medicines without being diagnosed or tested for COVID-19. Besides the risk of misuse or overuse of these drugs may lead to immediate or delayed complications including adverse drug reactions (hypersensitivity, anaphylaxis), drug interactions, malfunction or destruction of vital organs such as the liver, kidney; the practice of self-medication gives a deceitful sense of security, and masking the correct diagnosis. Many countries are using different drugs, but they are not using those as the guidelines and should only be used under the supervision of physicians on a case-by-case basis, not as a general recommendation¹².

Given this high prevalence of self-medication of prescription-only drugs in Bangladesh and its associated adverse socio-economic impact on individuals, and the healthcare service system, supply chain at large. This study is therefore done to evaluate the awareness, pattern and attitude towards self-medication of anti-infective agents among the high socio-economic and educated citizens in Dhaka during the outbreak of the COVID-19 without testing, diagnosis and prescription.

Ethics Approval: None of the authors has any conflict including employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations for this study.

II. METHODOLOGY

Using and relying on the authors' network with people living in Dhaka city, the capital of Bangladesh; this online survey adopted a descriptive non-experimental research design to investigate the awareness and practice of self-medication conducted from April to June 2020, the period during the nationwide lockdown and to surge of number of positive COVID-19 cases. Because it was not feasible to do a community-based sampling survey during this outbreak period, we decided to collect data online by convenience sampling. A structured questionnaire was circulated to complete via clicking the link, connected to Google form. The questionnaire contained a brief introduction on the background, objective, procedure, voluntary nature of participation, declaration of anonymity and confidentiality, and notes for filling in the online questionnaire.

The online questionnaire was developed and validated through the face and content validity techniques, by giving the draft questionnaire to a few of

the citizens with inclusion criteria at Dhaka city, to assess whether the response looks meaningful, well designed and a good measure of the construct to an innocent bystander. The response was used to refine and modify the questionnaire further.

The content validity was done by giving the resultant questionnaire to three independent scholars from the fields of Public Health, Pharmacology, and Social Statistics to assess its appropriateness, clarity, coverage, and relevance to the study.

The reliability of the validated questionnaire was ascertained by test-retest method. The questionnaire was administered twice at two weeks' interval on ten respondents from Dhaka city who practiced self-medication during the COVID-19 outbreak. The responses were compared and the reliability coefficient determined ($r=0.83$). The incorporated draft questionnaire was recast for ambiguity and repetitive questions were struck off.

The cross sectional populations were included with the inclusion criteria as, the adult citizens living in Dhaka city, aged 25 years or more, with the education level of graduation or above, non-medical professionals, having email address, and agreed to participate voluntarily. Respondents having involvement or knowledge on medical background (medical graduates, medical practitioners, nurses, medical researchers, pharmacists) were excluded from finding out the public perceptions, and their responses to take medications without prescription during the COVID-19 outbreak. The frequencies of the response were recorded in the datasheet, and observed according to demographic characteristics, sources of information, clinical symptoms, the status of COVID-19 test results, and cost involvement. The market prices of commonly used medicines as self-medication during the outbreak were calculated to reveal the economic burden caused by COVID-19 driven self-medication practice.

III. RESULTS

Total of 639 participants completed the online survey questionnaire and submitted it with e-mail verification. After excluding 13 respondents, of whom 10 were doctors by profession and three were below the minimum age limit (25 years), the final sample consisted of 626 were valid participants. Among the final sample, 316 (50.47%) respondents were from the age group of 45-54 years, 346 (55.27%) were women, 312 (49.84%) held a bachelor's degree, and 230 (36.74%) engaged in non-civil services. Other demographic characteristics are shown in Table-II.

Table-II: Frequency distribution of respondents by their socio-demographic features

Variables	Frequency	Percentage (%)
Gender:		
Male	282	45.04%
Female	346	55.27%
Age:		
25-34	96	15.33%
35-44	156	24.92%
45-54	316	50.47%
55 +	58	9.26%
Education level:		
Undergraduate	110	17.57%
Bachelor degree	312	49.84%
Master degree	178	28.43%
Doctoral and advanced	26	4.15%
Work status:		
Students	84	13.41%
Civil service	13	2.06%
Non-civil service	230	36.74%
Self-employed / business	184	29.39%
Retired	38	6.07%
Unemployed	77	12.30%

Table-III: Frequency distribution of respondents by use of anti-infective agents

		Number of Respondents	Azithromycin		Doxycycline		Hydroxychloroquin		Ivermectin	
			N	Cost involved (USD)	N	Cost involved (USD)	N	Cost involved (USD)	N	Cost involved (USD)
RT-PCR test	Positive	132	111	490	93	227	84	420	109	160
	Negative	78	20	102	31	76	0	0	55	81
	Not done	416	208	1046	128	313	44	215	319	160
Total		626	339	1638	252	616	128	635	483	710

- Cost involved = Unit price x Daily dosage x Number of days
- Total cost converted from local BDT to USD

Out of 626 respondents, only 73 (11.66%) did not take any medication during the survey period as 12 (1.91%) were negative by rRT-PCR test for COVID-19 and 61 (9.74%) did not test. The remaining 132 respondents (21.08%) was found positive test results for COVID-19.

The most frequently used prescription-only drug among the respondents were ivermectin (77.15%), azithromycin (54.15%), montelukast (43.13%), calcium supplements (41.37%), doxycycline (40.25%), and hydroxychloroquine (20.44%) respectively. The frequency of taking the prescription-only drugs among the respondents who were not even diagnosed by the rRT-PCR positive results, was reported higher with ivermectin (76.68%) and azithromycin (50.0%) as shown in Table-III.

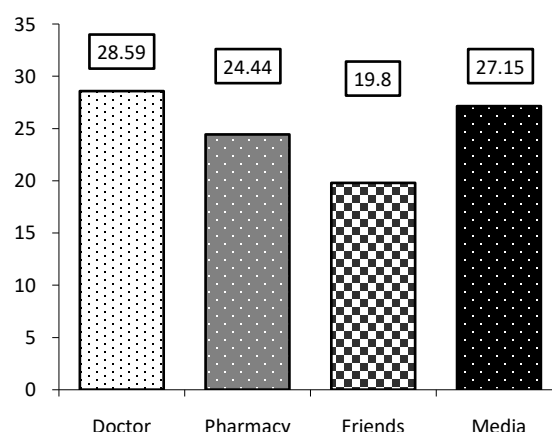


Figure-1: Distribution of respondents taken medication according to source of advices

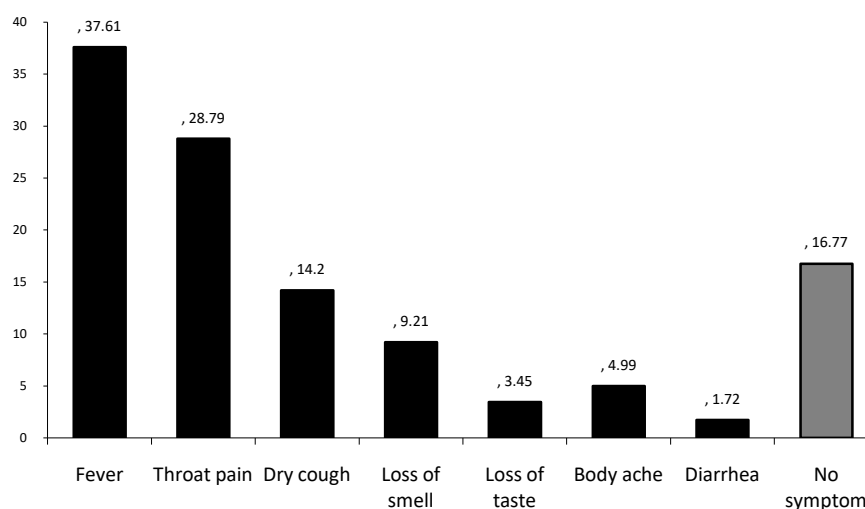


Figure-2: Distribution of respondents taken medication according to symptoms

Among the respondents, only 179 (28.59%) took medication with doctors' advice and remaining 447 (71.40%) respondents took the drugs, as "self-medication" by the other sources like friends/family, pharmacy/dispensary and media/internet as shown in Fig-1.

A total of 105 (16.77%) respondents took medications without having any symptoms, and the remaining 521 respondents, common symptoms for which the respondents took medications were fever (37.61%), throat pain (28.79%), dry-cough (14.20%), loss of smell (9.21%), loss of taste (3.45%), body ache (4.99%), and rarely diarrhea (1.72%) respectively as shown in Fig-2.

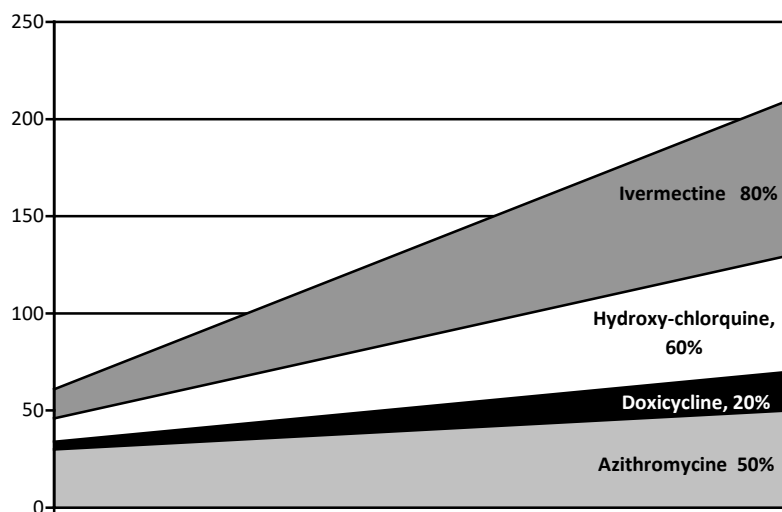


Figure-3: Raised price of the anti-infective agents during COVID-19 outbreak

The market price of the anti-infective agents was higher than the retail price as shown in Fig-3. Azithromycin raised almost 37%, hydroxychloroquine 18%, doxycycline 12% and ivermectin 7%, respectively.

IV. DISCUSSION

To the best of our knowledge, this is the first online survey in Dhaka city evaluating the pattern and frequency of self-medication practice of prescription-only drugs in the COVID-19 outbreak (April to June 2020) in Bangladesh. As the survey population was well-educated adults from different working status, the respondents' participation was expected to represent the sincerest and accurate scenario of the defined survey population.

An almost equal proportion of males and females participated in the study and most of them (50.47%) belonged to the age group of 45-54 years. The highest number of respondents (49.84%) were graduates (Bachelor's degree), and the lowest with doctoral degrees (4.15%). Only 2.06% respondents were from civil service and the rest were from non-civil service (36.74%), self-employed, or business (29.39%) living in Dhaka city at the time of the COVID-19 pandemic.

Among 626 survey population in Dhaka city who had taken medication for COVID-19, only 132 (21.08%) were documented as positive and 78 (12.45%) as negative by RT-PCR test. The rest of 416 (66.45%) had never done the test, but almost 355 (85.33%) had taken medication without doing any test for the COVID-19. This finding could be due to having additional distress due to high self-awareness of their health, as reported by Roberts T. et al. among people with higher educational status⁹. Having self-medication without detecting COVID-19 among a large number of respondents could also be due to feeling of insecurity influenced by the availability of local medical resources,

efficiency of the public health system, and prevention and control measures taken in pandemic situation¹⁷.

The rate of self-medication of antimicrobial agents like azithromycin (54.15%), doxycycline (40.25%) was found much higher during the outbreak of COVID-19 comparing to 21% and 25% for azithromycin and doxycycline before the pandemic as reported by Chowdhury N et al¹³. Azithromycin was the fifth-highest percentage of people with self-medication throughout the previous years, whereas it became the most common antibiotic during the present pandemic. On the other hand, ivermectin being the anti-parasitic agent, was self-medicated by 77.15% of the respondents. This might be due to the nationwide broadcast of an experience by a team of Bangladeshi physicians, and Bangladesh Medical College Hospital (BMCH) claimed as "outstanding results" in 60 patients with COVID-19 patients all of whom recovered in a combination with ivermectin and doxycycline¹². This attempt was made on the outcome of an in-vitro study reported as a single treatment by ivermectin is capable of ~5000-fold reduction of viral load at 48 hours in cell culture¹⁴. Self-medication of this drug was found highest (483/626) among the respondents irrespective of test results by RT-PCR. Though the drugs like chloroquine, hydroxychloroquine and azithromycin, was recommended in the treatment protocol of the Covid-19 patients in Bangladesh, according to the "National Guidelines on Clinical Management of Coronavirus Disease-2019" published in the health directorate's website¹¹; hydroxychloroquine was used much less (20.44%) than any other antimicrobials without prescription. This could be due to mass publicity and sharing of news in national and international news and social media as the drug can cause hazardous abnormalities in cardiac rhythm in the COVID-19 patients, and should be limited only in clinical trials or hospitals with adequate facilities to monitor any cardiac

complications, warned by FDA in a safety communication briefing globally¹². The overall the prevalence and dominance of self-medication of antimicrobials in low and middle-income countries were reported around 39% in previous studies before the COVID-19 pandemic^{15,16} but was outrageously higher (88.33%) in Dhaka city during the pandemic.

Considering the sources or advice for medication, only 179 (28.59%) respondents followed or consulted with doctors and rest by media or internet (27.15%), pharmacy or dispensary (24.44%), and friends or family (19.8%). This finding was very much similar to the previous studies that reported the high prevalence of self-medication (including antimicrobials) since people could obtain any drugs from the pharmacies without prescription even in the distant areas of the country¹⁸. Moreover, during a pandemic, people struggle to cope with constant news of the spread and effects of COVID-19 on news-media, social-media, internet without having adequate forms of social support and access to doctors as a result of lockdowns and self-isolation^{8,19}. Most of the respondents (37.61%) took antibiotics as self-medication for fever during Covid-19 outbreak, followed by throat pain (28.79%), dry cough (14.20%), whereas almost 16.77% respondents had no symptoms whatsoever. Having inappropriate antimicrobials, and supplementary medications (zinc, calcium, Vitamin-D) without prescription is associated with the risk of drug interactions, masking symptoms of underlying diseases, and most importantly, the development of antimicrobial resistance^{20,21}.

Prices of essential COVID-19 medicines have increased 4% globally since February 2020, as reported by Gustav Ando in Life Science Research and Analysis. Although there is no specific treatment for Covid-19, the drug administration in Bangladesh started working in advance to increase the production of some supportive medicines²². Despite the availability of essential drugs, the increase demand in major cities for self-medication of azithromycin raised almost 37%, hydroxychloroquine 18%, doxycycline 12%, and ivermectin 7% respectively. The total amount of buying those medicines in response to COVID-19 situation had an unnecessary financial burden on the people in Dhaka. Overall economic hardship in low and middle-income countries have to cope with the added expenditure that could be avoided by strict regulatory surveillance on self-medication and dispensing without prescription.

Although there is no approved specific medication to prevent or treat COVID-19, this online survey among the educated adults with high socio-economic standings revealed that a high prevalence of self-medication of prescription-only drugs was persistent during the outbreak in Dhaka city. Unsolicited news of spread, effects and remedies in media channels, internet, mental stress of lockdown, and isolation, insecurity, and panic about the scarcity of drug

and healthcare support might has triggered up the practice self-medication. Psychological distress levels were also influenced by availability of local medical resources, prevention and control measures²³. There is sufficient evidence of increasing resistance to antibiotics in Bangladesh resulting from irrational and misuse of antibiotics, where sales of antibiotics are not restricted at any level²⁴. Unopposed access to buy antibiotics and its injudicious use might provoke a long-term burden of drug-resistant strains with problems of under and over-dosage, treatment failure and severe adverse effects on vital organs. It also results in delays in care seeking, which results in paradoxical economic loss due to delayed diagnosis, and irrational treatment²⁵. Bangladesh is already in the burden of a lower ratio of healthcare workers and a supply support system, with a high rate of community-transmission of COVID-19 and requires effective and efficient enforcement of regulation against free display and sales of drugs without prescription and individuals duly authorized.

V. CONCLUSION

The pattern of medication, including self-medication, is an important health indicator, which reflects the degree of supply utilization, and regulatory enforcement of healthcare services within a community. Immediate acceleration of health education campaigns, strict legislations on dispensing drugs and increasing the quality, and access to healthcare are the important interventions that might change the people's health-seeking behavior²⁶. The pandemic situation of COVID-19 is likely to sustain for years and it will have a huge socio-economic and psycho-social impact on people's lifestyle and behavior, as predicted by the WHO, and epidemiologists from different regions. Therefore, a vast nationwide survey and surveillance should be done on self-medication of the mass population to protect them from the potential risks, overuse shortage and irrational financial burden during the COVID-19 outbreak.

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Nanocomposites:- A Recent Overview

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Abstract- Nanocomposites are substances that incorporate nanoparticles (0.5-5% by weight) into a matrix of standard material, which enhances the mechanical strength, toughness including thermal or electrical conductivity and other properties. Nanocomposites are versatile in terms of their applications such as anti-corrosive, healing of bones, sensors, environmental protection, packaging, wastewater treatment, and diagnosis of tumors and other diverse uses. They may be fabricated by blending nanofillers with a polymer to produce a composite. The current trend of processing is by polymerizing monomers. Nanocomposites serve as sustainable solutions to curb global issues. Evaluation is performed on properties such as mechanical, thermal, dispersion, and toxicological. Some marketed products of nanocomposites include InMat (coating), FiltekZ350 XT by 3M (tooth fillers), chitosan/organic rectorite nanocomposite films (bactericidal activity), graphene oxide/Carboxymethylcellulose (targeted drug delivery of anti-cancer drug doxorubicin), MD¹ Flex, NanoClean MD¹, PlactiveTM (Antimicrobial nanocomposites) and NovaProTM (Tooth fillers). This article discusses about Nanocomposites—their types, preparation methods, recent research and applications.

Keywords: Nanocomposites; classification; preparation; reinforcement; applications; health-care; engineering.

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Abstract- Nanocomposites are substances that incorporate nanoparticles (0.5-5% by weight) into a matrix of standard material, which enhances the mechanical strength, toughness including thermal or electrical conductivity and other properties. Nanocomposites are versatile in terms of their applications such as anti-corrosive, healing of bones, sensors, environmental protection, packaging, wastewater treatment, and diagnosis of tumors and other diverse uses. They may be fabricated by blending nanofillers with a polymer to produce a composite. The current trend of processing is by polymerizing monomers. Nanocomposites serve as sustainable solutions to curb global issues. Evaluation is performed on properties such as mechanical, thermal, dispersion, and toxicological. Some marketed products of nanocomposites include InMat (coating), FiltekZ350 XT by 3M (tooth fillers), chitosan/organic rectorite nanocomposite films (bactericidal activity), graphene oxide/Carboxymethylcellulose (targeted drug delivery of anti-cancer drug doxorubicin), MD¹ Flex, NanoClean MD¹, Plactive™ (Antimicrobial nanocomposites) and NovaPro™ (Tooth fillers). This article discusses about Nanocomposites—their types, preparation methods, recent research and applications.

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I. INTRODUCTION

In the world of material science, 'composites' are those types of materials that are prepared employing two or more substances - termed as matrix and reinforcement substances, which show distinct properties at the macro level, but upon combination yield materials with behaviours/ properties unlike those of the components arising from their synergism. What was envisioned and predicted in the 1960s by the physicist Richard Feynman about nanotechnology is now seeing a new era in the material science in the form of nanocomposites. A Nanocomposite is a framework for nanoparticles that are incorporated to improve a specific property of the material. In the present era, the perception of acquiring design uniqueness and property combinations that are not found in conventional composites, are obtained by using nanocomposites. Nanocomposites can be developed from a versatile materials from polymers to bacterial celluloses and nanoparticles. The applications of nanocomposites are overwhelming and encompass engineering sectors, health care, environmental protection to name a few.

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The market value for nanocomposite materials is projected to grow from USD 4.1 billion in 2019 to USD 8.5 billion, by 2024¹. Extensive research too is being carried out on the materials and the applicability of the nanocomposites, thus making them to have a significant impact on the global economy.

II. CLASSIFICATION

Over the decades, progresses in the nanocomposites have been extensive. They have been made from different kinds of materials. The nanocomposites may be classified on the following basis:-²

- i. *Based on the source/origin*
 1. Natural Nanocomposites
 2. Synthetic Nanocomposites
- ii. *Based on the filler particle dimension*
 1. Three dimensional nanocomposites
 2. Two dimensional nanocomposites
 3. One dimension nanocomposite
- iii. *Based on the matrix*
 1. Ceramic based nanocomposites
 2. Metal based nanocomposites
 3. Polymer based nanocomposites
 4. Elastomeric nanocomposites
 5. Dendrimer nanocomposites
 6. Bionanocomposites
- i. *Based on the source/origin:-*
 - a. Natural Nanocomposites:- They are materials occurring in nature like bone and wood. The components include organic substance for eg. cellulose, chitin, collagen, and proteoglycans, and mineral phases like calcium carbonate, hydroxyapatite, and silica. Bone for example is an organic-inorganic mixture of with collagen as the organic substance and hydroxyapatite as the inorganic counterpart.
 - b. Synthetic Nanocomposites:- In the last three decades, endeavors were made for the creation of artificial nanocomposites. Thus these come under the class of synthetic nanocomposites. Eg. Metal and ceramic nanocomposites. Others include polymeric and elastomeric systems. Research continues in artificial ceramics, polymers and their composites to provide microstructure almost like those of biomaterials.² The synthetic nanocomposites are discussed further under the classification based on the matrix substance.

ii. *Based on the filler particle dimension:-*

A particle is a three dimensional entity. Like any other nanosystem, nanocomposites too can be classified based on number of dimensions of the particle that are within the nanometer range. There are three types.

1. Three dimensional nanocomposites or Iso – dimensional nanocomposites

When all the three dimensions of a particle fall in the range of nanometers, they are called iso-dimensional nanoparticles. Spherical silica particles obtained by *in-situ* sol-gel methods are isodimensional.

2. Two dimensional nanocomposites

For a nanocomposite, when two of its dimensions are in the order of a nanometer scale while the third is larger, it leads to formation of elongated structures like nanotubes and whiskers. E.g. Carbon nanotubes (CNT) and polysaccharide whiskers are two dimensional nanoparticles.

3. One dimensional nanocomposite

For a particle, if there is only one dimension in the nanometer range, while the others are in larger dimensions, the filler is in the form of sheets. E.g. Polymer-layered nanocomposite crystal. These materials are almost exclusively produced by the intercalation of a polymer (or a monomer subsequently polymerized) within the collection of layered host crystals.²

iii. *Based on the matrix:-*

1. Ceramic based nanocomposites

In this sort of composites, ceramic makes up the fundamental piece of volume, for example, a compound of oxides, bromides, nitrides, and silicides. As a rule, the sophomore part of nanocomposites involves metal. Examples of ceramics incorporated are: - $\text{Al}_2\text{O}_3/\text{SiO}_2$, $\text{Al}_2\text{O}_3/\text{SiC}$, $\text{Al}_2\text{O}_3/\text{CNT}$, $\text{Al}_2\text{O}_3/\text{TiO}_2$, SiO_2/Ni . Typically the two segments (metal and ceramic) are finely scattered in one another to evoke specific nanoscopic properties. These blends develop their optical, corrosion resistance, electrical, magnetic properties, including tribological and protective properties. The ceramic matrix consists of Aluminum oxide (Al_2O_3) or Silica carbide (SiC) framework. After the addition of a low amount of (about 10%) silica carbide particles of suitable size and hot pressing, the aluminum oxide lattice gets fortified. Numerous techniques have been developed for the fabrication of ceramic matrix nanocomposites.³ They include combining reinforcement with the powdered matrix followed by pressing, slurry processes, and vapor deposition methods. Computer-Mediated Communication (CMC) scanning may be used in medical devices, implants, structural loading components, surfaces for wear or friction, automobile, aerospace, and power generation applications (engines, turbines, etc.). The merits of

ceramic nanocomposites are their improved mechanical properties, thermal stability, flame retarding nature, higher chemical resistance and high electrical conductivity. The demerits are that due to the high processing temperature manufacturing is complex, and hence, the processing is expensive; they are susceptible to thermal cracking.⁴

2. Metal based nanocomposites

Metal matrix nanocomposites (MMNC) allude to substances composed of malleable metal or alloy matrix in which such nanosized strengthening substances are structured in the form of a sphere i.e., fullerene, tube, i.e. CNT and sheet, i.e. graphene. Due to their excellent mechanical properties and chemical stability, the interest in reinforcing MMNCs with nano-Carbon (nano-C) materials has developed rapidly. Both metal and ceramic features are combined.⁵ Example of metals used are:- $\text{Fe-Cr}/\text{Al}_2\text{O}_3$, $\text{Ni}/\text{Al}_2\text{O}_3$, Co/Cr , Fe/MgO , Al/CNT , Mg/CNT .³ While synthesizing metal nanoparticles, nanofluids made of metals, thin-film with metal nanoparticles and polymers are used. Polymers act as reducing agents, capping agents, and suspending agents during the preparation. They also can be used as a substrate or binders for metal nanoparticles.² Metal nanocomposites are applied in solar cells, and conductivity improved electronic circuits, sensors, and biosensors especially for sensing of viruses and malignant growth molecules. Versatile utility is evident from the work on polymer-metal nanocomposites. When Cu/Ag nanoparticles are incorporated into polymers like polyvinyl alcohol, improvement in antibacterial properties can be seen.⁶ The merits of metal nanocomposites are their higher strength density and higher modulus density. While the demerits are higher cost of some physical systems, and complicated fabrication methods for fiber reinforced system.⁷

3. Polymeric matrix composites

Polymer matrix composites (PMCs) contain a blend of continuous or short strands of fibers bound together by the natural polymer matrix. Examples of Polymers incorporated are:- Thermoplastic/thermoset, polymer/layered silicates, polyester/Titanium dioxide (TiO_2), polymer/CNT, polymer/layered double hydroxides.³ Reinforced plastics and advanced composites are the two categories of polymer matrix composites. When contrasted with metal nanocomposites, they embrace many fascinating properties such as superior corrosion and exhaust resistance. Most advanced PMCs nowadays are made by a laborious method known as lay-up. The synthesis of polymeric matrix composites involves placing sequential layers of impregnated polymer fiber tapes on a mold surface, followed by heating to cure the lay-up into the associated integrated structure.⁸ The merits of polymer nanocomposites are superior mechanical

properties, promising electrical conductivity, noise damping, corrosion resistance, low permeability of fluids, light weight, low filler content, and ease of manufacturing. While the demerits are non-uniform distribution, high viscosity, and formation of agglomeration.⁹

There are classified into four types based on their reinforcements:-¹⁰

- i. Nanoclay-reinforced nanocomposites:-
- ii. Carbon nanotube-reinforced nanocomposites:-
- iii. Nanofiber-reinforced nanocomposites:-
- iv. Inorganic particle-reinforced nanocomposites:-

i. *Nanoclay – reinforced nanocomposites*

In recent years, research has been directed from the microcomposites towards clay polymer nanocomposites.¹¹ Nanocomposites show improved mechanical, electrical, and thermal properties compared to the bulk materials and composites that are reinforced with micro-sized particles and fibers. Typical materials classified in this category have at least one dimension measuring smaller than 100 nm. Clay being a natural mineral, it is being used in fabrication as it is cheap and abundantly available. During synthesis, reinforcement of clay nanocomposites with two dimensions at two varied length scales can be acquired with microfibers or particles to obtain hybrid composites. Functional properties, for example, thermal or electrical conductivity, can be achieved additionally with high mechanical properties. Muscovite, phlogopite, smectics are some clay minerals. Epoxy, polystyrene, polypropylene, polyurethane, nylon, and polyethylene are commonly used polymers as a matrix for clay/polymer nanocomposites. The merits of clay-polymer nanocomposites are high tensile strength, flexural, and thermal properties. While the demerits are that homogenous dispersion is hard to achieve in nanoclays. The density of nanoclay is higher than the polymer matrix; therefore, higher nanoclay contents lead to heavier composites with lower tensile strength.¹² They are sub-classified into three types²:-

- a. Conventional composites
- b. Intercalated nanocomposites
- c. Exfoliated nanocomposites

a. Conventional composites:- The structure of clay nanolayers in conventional composites (separate phase) is maintained when combined with the polymer, but the polymer is not intercalated into the clay structure. Consequently, the clay fraction plays little to no practical part in these composites and serves solely as filler for economic considerations.

b. Intercalated nanocomposites:- A single (or occasionally more than one) extended polymer chain intercalates between the layers of silicate, resulting in a well-ordered multilayer morphology made of alternating polymeric and inorganic layers.

c. Exfoliated nanocomposites:- An exfoliated or delaminated structure is obtained when the silicate layers are entirely and uniformly dispersed in a continuous polymer matrix. Extensive polymer penetration, resulting in silicate layer disorder and subsequent delamination, creates exfoliated structures consisting of single 1-nm thick silicate layers suspended in the polymer matrix.²

ii. *Carbon Nanotube-reinforced nanocomposites*

Though polymers are simple to handle than metals and ceramics, they are not as sturdy or rigid. Their mechanical properties can be enormously enhanced by incorporating fibers with strong Young's modulus. The resulting polymer composites are a crucial class of lightweight materials with outstanding mechanical properties. Unlike micron-sized particles and short fibers used in traditional composites, CNTs allow polymers to be reinforced at the molecular level. This imparts significantly higher effect on the mechanical properties. With longer fibers as in CNT, the interface between the fiber and the matrix will be sturdy making the reinforcement to be efficient.¹³

iii. *Nanofiber-reinforced nanocomposites*

Carbon nanofibers (CNFs) are a particular type of vaporized carbon fibers that fill the physical properties gap between conventional carbon fibers (5-10 μ m) and carbon nanotubes (1-10 nm). The reduced nanofiber diameter provides a greater surface area with fiber surface quality. Usually, the CNFs are not concentric cylinders; the length of the fiber can vary from about 100 μ m to several cms and the diameter is between 100 - 200 nm. The most common form of the CNF is the truncated cone. Other forms of CNF include cone and stacked coin shapes.

iv. *Inorganic particle-reinforced nanocomposites*

Particles of nanometer size were made from different organic-inorganic particles, and these impart improved properties to the composite materials. Specific particles have been used to prepare nanocomposites of polymer / inorganic particles including Metal (Al, Fe, Au, Ag, etc.), Metal oxides (ZnO, CaCO₃, TiO₂, etc.), Nonmetal oxide (SiO₂) and SiC.¹⁰

4. *Elastomeric nanocomposites*

The elastomeric nanocomposite is a cross-linked elastomeric polymer with nanoparticles dispersed inside the rubber matrix. The nanoparticles contribute reinforcement and offer some functional features to the pristine rubber.¹⁴ Artificial rubbers have greater designing properties than naturally obtained elastomers. Nitrile Butadiene hydrocarbon Rubber (NBR) nanocomposite is created by the co-polymerization of vinyl cyanide particles in NBR by an emulsion method. Graphene Oxide (GO) and Carbon Black (CB) are used in Elastomeric nanocomposites. They are the most common fillers for natural and artificial rubber composites, particularly in the tires industry and

in a few automotive components. Some methods of preparing elastomeric nanocomposites are direct combining method, in-place chemical change, and solution combining technique.¹⁵ These nanocomposites are lighter in weight, their cost is lower due to lesser percent of fillers are necessary, offer good barrier properties, flame retardation, better thermal, and dimensional stability.¹⁶

5. Dendrimer nanocomposites

Dendrimers are monodisperse macromolecules built with the most significant degree of manufacturing control. Branching and connecting units are present in the nerve-fiber along with a small molecule or a core compound, forming either round dendrimers or rod like macromolecules. The physical and synthetic properties of particles and atoms vary enormously depending on the mass property of the materials.¹⁷ Dendrimers are composed of combinations of core types such as Ethylenediamine (EDA), Diaminobutyl (DAB), Polyamidoamine (PAMAM) and Polypropylimine (PPI) and different surface residues such as amine, carboxyl, and alcoholic groups.¹⁸ These dendrimer surfaces will be made compatible with several organic and inorganic materials. The core region can accommodate molecules for nano-level storage and delivery. Dendrimer metal nanocomposites are created by reactive encapsulation. Metal ions are pre-organized by the dendrimer; thereafter, immobilized in/on the polymer molecule. The size, shape, and surface practicality are determined and constrained by the nerve fiber macromolecules, by the chemistry of the preorganization and by the method used for immobilization. These materials have the optical and physiological properties of the guest molecules and the solubility and compatibility of the host. The interior or the exterior may either be hydrophilic or hydrophobic.

Dendrimers could interact strongly with versatile surfaces. Interaction with metal demonstrated dendrimer hybrid nanocomposites. Dendrimer templated nanoparticles show distinctive physical and chemical properties because of the atomic/molecular level dispersion of inorganic guest(s) among a dendrimer host. Alcohols, hydrazine, sodium borohydride, or sodium are utilized as reducing agents for the metals. Copper nanoclusters are one example. They are strongly distinguished through UV-visible absorption at short wavelengths. The presence of copper nanocomposites or little spheres are indicated by the single spectral bands of 250 nm.¹⁷ The merits of dendrimer nanocomposites are their excellent electrical, magnetic, and catalytic properties; increased strength and chemical reactivity compared to the traditional macro- and micro-materials. But they also have a potential for toxicity.¹⁹

6. Bionanocomposites

Nanocomposites that contain commonly occurring polymers (biopolymer) with an inorganic nano entity are called bionanocomposites (BNCs). They are also referred to as nanobiocomposites, green composites, or biohybrids. BNCs have been widely used in the field of biology, material sciences, and nanotechnology. They are biocompatible and biodegradable. Carboxymethyl cellulose, chitosan, alginate, gelatin, guar gum, pectin are the polymers commonly employed. Biomedical technologies such as tissue engineering, bone repair, dental applications, and controlled drug delivery employ BNCs.²⁰ The merits of bionanocomposites are their biodegradability and thermal properties. But they are expensive and difficult to synthesize.²¹

III. PREPARATION OF NANOCOMPOSITES

Nanocomposites may be produced employing the methods given below.

- i. In-situ polymerization
- ii. Solution casting
- iii. Co-precipitation
- iv. Melt intercalation
- v. Electro spraying
- vi. Template synthesis
- vii. Electrospinning
- viii. Latex technique
- ix. Supercritical fluid method

i. *In-situ polymerization*

In this strategy, the nanoparticles are mixed priorly with the monomer arrangement or monomeric fluid. Initiators are used for polymerization - heat, radiation, or other methods. Ceramic nanocomposites, bionanocomposites, polymer nanocomposites, clay-polymer nanocomposites, elastomeric nanocomposites are prepared by this method.^{3,20,22,23,24} Because of low monomer thickness, the uniform blending of particles in the monomer using high shear blenders is much easier to achieve. Also, the low consistency and high diffusivity bring about a higher pace of monomer dissemination into the interlayer region. The solvent undergoes evaporation ultimately. Through the combination of response conditions and surface changes, it is conceivable to control nanocomposite structurally. The preparation of nanocomposites by *in-situ* polymerization is depicted in Fig.1.²⁵

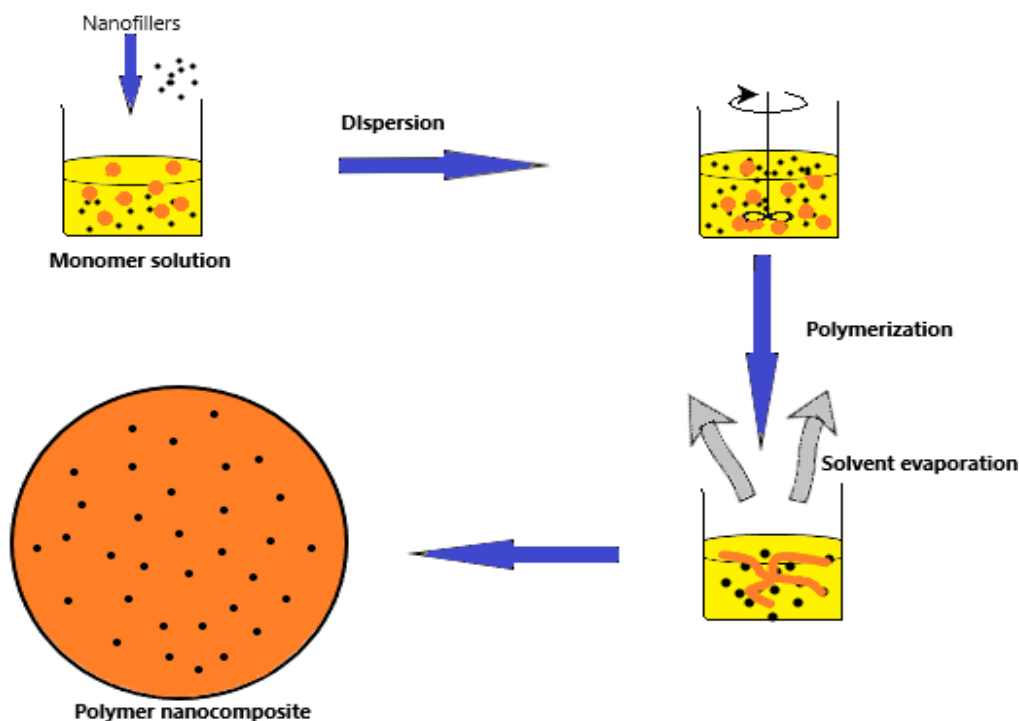


Fig. 1: In-situ polymerization method for preparation of Nanocomposites ²⁵

ii. Solution blending method

In this method a solvent or solvent mixture is used to dissolve or disperse the filler nanoparticles. The polymer or pre-polymer is taken in a suitable solvent. Based on the solvent system, solution intercalation may occur between the polymer and filler. The polymer has to be soluble in the solvent and the clay or phyllosilicate filler materials must swell and disperse. The phyllosilicate is typically dissolved/ swollen in the solvent. Polymeric solution is separately prepared. These two solutions are blended. Absorption of the polymer chains occurs on the nanoparticles. The nanoparticles agglomerate again when the solvent is expelled. Through this technique, few exfoliated nanocomposites are synthesized. The product cost is high, as this method requires an enormous amount of solvent. The choice of appropriate solvent relies on the types of polymers used to prepare nanocomposites, restricting the applicability of this method. Some polymers employed include polyethylene oxide, polyvinyl acrylate, and polyacrylic acid.² Bionanocomposites, clay-polymer nanocomposites, and elastomeric nanocomposites are prepared by this technique.^{20, 22, 24}

iii. Co-precipitation

Metal oxide nanoparticles, mixed metal, or metal ceramics nanocomposite and also different types of metal nanocomposites such as metal-metal oxide, oxide-oxide, and oxide-matrix are prepared by utilizing the co-precipitation method. A homogenous solution of ions is obtained, when precursors such as inorganic salts are dissolved in water. Such salts begin to precipitate as hydroxides or oxalates once the critical

concentration of the species is reached, followed by nucleation and growth phases. The solution's pH, temperature, and concentration of salt are responsible for the size and shape of particles. The calcination to change hydroxides into oxides with a definite crystalline structure occurs after precipitation, filtration, and washing. The precipitation medium employed is sodium hydroxide, ammonia, ammonium hydroxide, sodium carbonate, etc. To prevent agglomeration, surfactants are used because of which the particle size has been affected. Affordable, water-based reaction, flexibility, mild reaction conditions, size control, basic, and simple are the advantages of this method.²⁶ Ceramic nanocomposites may be prepared by this process.³

iv. Melt intercalation

This approach represents an easy way to synthesize nanocomposites. Nanoparticles are blended with a molten polymer, rather than using a solvent. Solvents are not being used in this method. It provides a financially enticing route in creating compound nanocomposites. By this method, a wide variety of polymer/clay nanocomposites have been synthesized using nylon 6, polypropylene (PP), and polystyrene. However, care must be taken to fine-tune the surface chemistry of the coated salts. It plays a crucial role in the delamination / dispersion of the sample. It is important to disperse the clay particles in the molten polymer. For non-polar polymers, e.g. PP, a polar compatibilizer such as maleic anhydride-modified PP (Polypropylene- Maleic Anhydride) is commonly added to improve the compatibility of PP and clay. This is the dispersion of clay nanoparticles. Nanofiber Polymer / CNF (Cellulose Nanofiber) nanocomposites have also been formulated

using this process. It is necessary to apply shear stress to disintegrate and disperse nanoparticles; therefore, it must be regulated at an acceptable level. The characteristic properties of nanocomposites formed by this method rely on two main factors, i.e., processing conditions and enthalpy interaction between polymer and nanoparticles. The only drawback of this strategy is that bound biopolymers are degraded by either the mechanical cutting force or the temperature applied throughout the process that results in degradation due to the cleavage of the compound chains and, subsequently, a decrease in the relative molecular mass in the clay-supported nanocomposites softening process. For example, high shear sustained over long periods of time is required for the scraping of platelets. However, such high and prolonged shearing will contribute to the degradation of bound polymers.²

The melt intercalation approach has enormous benefits in comparison to both polymer intercalation solution and in situ intercalation polymerization. The two reasons are: Firstly, it is environmentally friendly since there are no organic solvents implicated, and furthermore, it is compatible with industrial processes such as extrusion and injection molding. The process for this method is simple as it involves annealing (statically or under shear), a mixture of the polymer and layered silicate above the softening point of the polymer. Bionanocomposites, clay-polymer nanocomposites, elastomeric nanocomposites are prepared by this technique.^{20,22,24} The preparation of nanocomposites by melt intercalation is depicted in Fig.2.²⁷

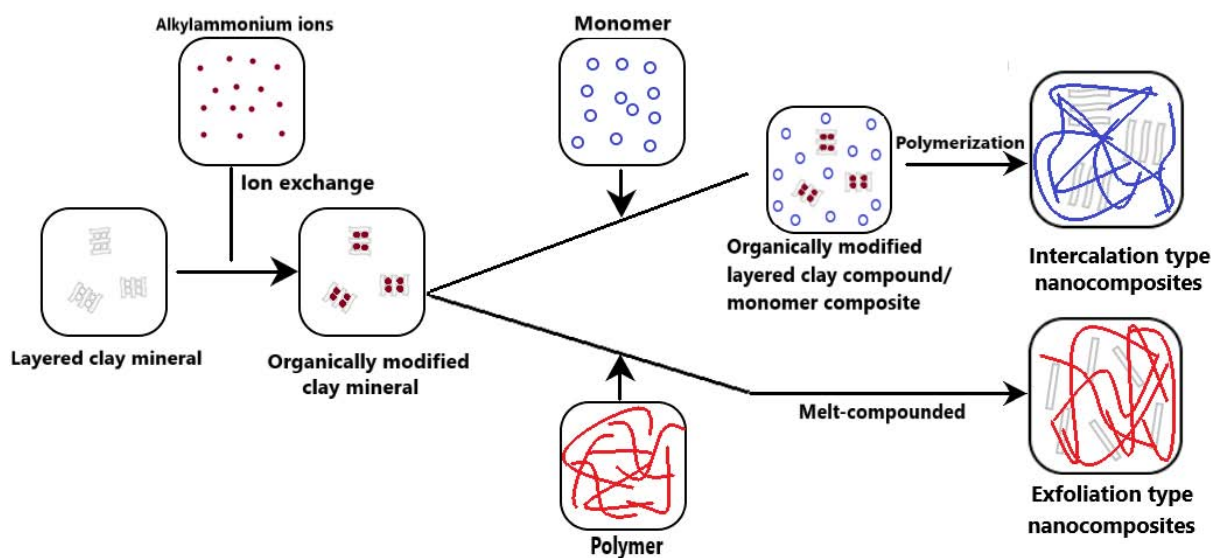


Fig. 2: Preparation of Nanocomposites by melt intercalation method ²⁷

v. Electro spraying method

In electro spraying method the constituents of the nanocomposite are in liquid form (solution/dispersion). Small and closely mono-disperse particles are formed when the solution or suspension of nanoparticles is sprayed. Potential difference between nozzle and collector plate lead to deposition of the droplets on the plate. The droplet size can be maintained typically by maintaining the flow rate of the liquids or by changing the voltage of the droplet charge applied to the nozzle. Coagulation is prevented by self-dispersing charged aerosol. This method finds application in areas concerning drug delivery, diagnostic and therapeutic biomedical imaging, implant coating, and tissue engineering. Ceramic nanocomposites are prepared by this process.³ The preparation of nanocomposites by electro spraying is depicted in Fig.3.²⁸

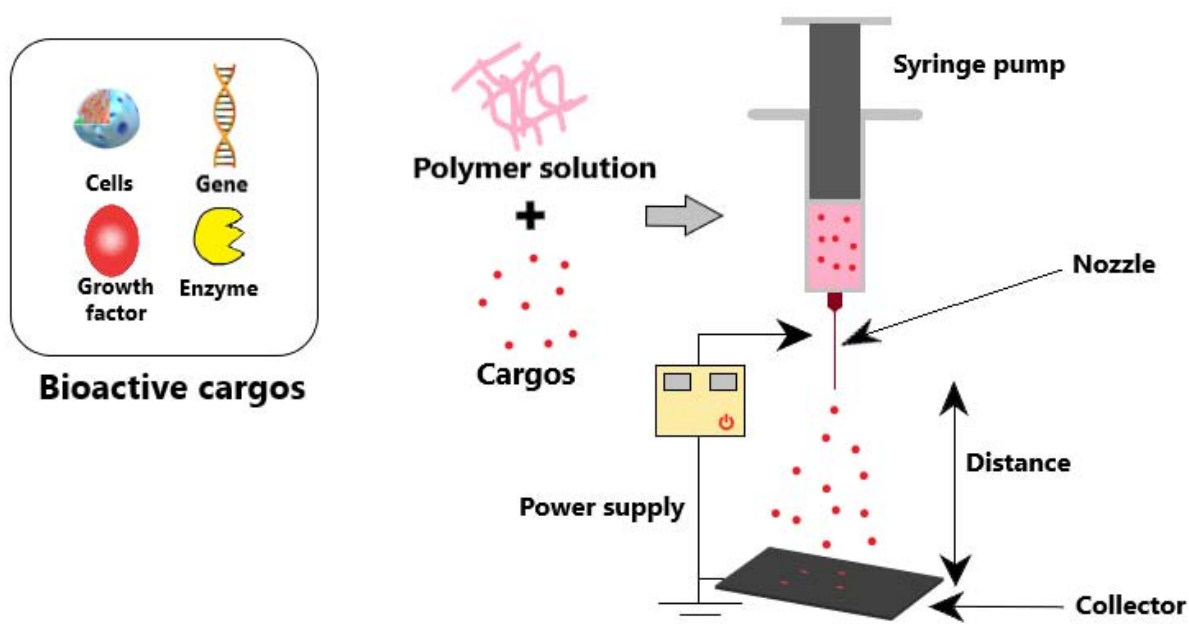


Fig. 3: Nanocomposite preparation by electro spraying method ²⁸

vi. Template synthesis

A template, in general terms may be stated to be a form, mold, or pattern used as a basis or lead to making something. In this method of preparation of nanocomposites, a template is employed upon which the nanomaterial is built upon or developed. The templates can be naturally occurring - nanominerals, biological molecules, cells, and tissues; and synthetic materials surfactants, porous materials, micro and nano particles, etc. Those templates which have a rigid structure are termed as hard templates and those that do not have are termed as soft template. These systems are simple, vital, and applicable for large scale production.²⁷ A variety of non-silicon-based mesoporous materials, such as solid or hollow aluminum oxide, titanium oxide, aluminum phosphate microspheres, mesoporous carbon pellets may be used as templates. The choice of design is crucial for preparing nanomaterials. There are possibilities of contamination due to side products, as it largely requires water-soluble polymers.²⁹ Polymer nanocomposites, bionanocomposites, are prepared by this technique.

vii. Electro-spinning technique

Electro-spinning is the latest and the most preferred method to prepare nanocomposites. During electro spinning, the blend of a polymeric solution is drawn through a syringe and high power voltage is being applied to the polymeric solution by an alligator clip attached to the syringe needle. The volt is accustomed to 15kV. The polymer is administered through the blunt needle end, utilizing the syringe pump to regulate the flow rate of the solution. The fibers are collected on an electrically grounded foil of aluminum

mounted to the tip of the needle at 15 cm vertical. A few process parameters for optimization include polymer concentration, voltage applied, distance between syringe tip and collector foil, solution flow rate, etc. Polymer nanocomposites, metal-based nanocomposites are prepared by this method. The preparation of nanocomposites by electro spinning is depicted below in Fig.4.³⁰

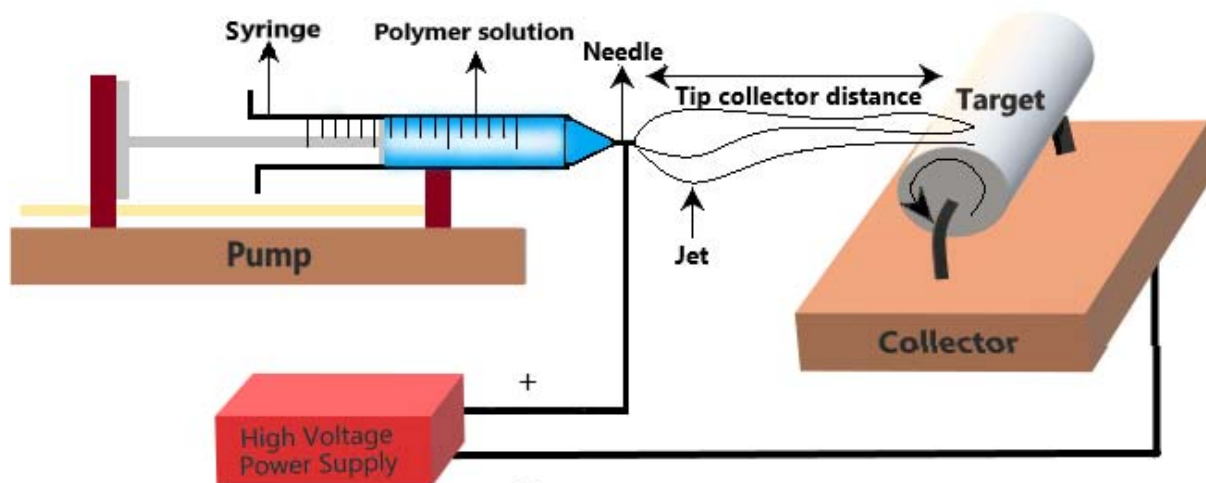


Fig.4: Electro-spinning technique for Nanocomposite preparation³⁰

viii. Latex technique

This approach is used in the elaboration of elastomeric nanocomposites. Elastomeric nanocomposites were obtained by coagulating the latex of elastomers like Styrene-Butadiene Rubber (SBR), styrene-vinyl pyridine-butadiene with an aqueous clay suspension. The clay material employed may be bentonite dispersion in water (4%), aqueous sodium montmorillonite clay suspension (2%). Subsequently, an aqueous dispersion of the curing agent was applied, and pre-vulcanization of the latex-clay mixture was performed yielding the nanocomposite. A 2% sodium montmorillonite aqueous suspension and SBR latex were combined and coagulated in an electrolyte solution (1% calcium chloride or 2% sulphuric acid). Upon washing and drying, the SBR-nanocomposite was obtained. Vulcanization was done in a two roll-mill.²⁴

ix. Supercritical fluid method

Supercritical fluid technology has been used in preparation of polymer/metal-polymer nanocomposites.³¹ One newer study includes preparation of the glossy CaCO_3 -polymer nanocomposites in the presence of a polymer by

introducing CO_2 as a supercritical fluid into an aqueous system of calcium ions. Supercritical CO_2 was used to facilitate the mineralization for the development of a CaCO_3 -polymer nanocomposite with a controlled three-dimensional shape. In general, a combination of poly vinyl alcohol (PVA), Ca-acetate, and poly acrylic acid (PAA) was poured into a mold; the mold was placed into an autoclave and CO_2 was introduced to the polymer matrix leading to formation of CaCO_3 -polymer nanocomposite. Laser Raman spectroscopy and electron transmission microscopy revealed that the resulting nanocomposite consisted of widely scattered nanoparticles of CaCO_3 and had excellent mechanical properties. Its flexural strength was superior to the flexural disabilities of CaCO_3 provided by hot hydrothermal pressing method. Polymer nanocomposites are produced by this process.³²

IV. RESEARCH AND APPLICATIONS

Nanocomposites have become versatile materials in many domains of life. Their utility is diverse. The current research thrust and applications of nanocomposites are given in Table 1.

Table 1: Various applications of nanocomposites

SL no.	Property/ Application	Remarks / Nanocomposites used
1.	Rheological Properties	The influence of solvent, organic filler, CNTs, inorganic fillers, pulp fibers, micellar system, nanoparticles, etc on the rheological property of nanocomposites has been evaluated. Hybrid nanocomposites can be made from natural or synthetic fibers and/or both are utilized. Hybrid nanocomposite rheological property has been found to depend on fiber content, fiber length, fiber orientation, fiber-to-matrix bonding, fiber configuration and filler. Some materials studied include Triglycidyl Ether Trimercapto Ethanol Phosphorus (TGETMEP) and 4,4-diaminodiphenyl benzene (MDA). Some fillers employed were Tri Sodium Phosphate (PTS) and Titanium oxide (TiO_2) ³³ .
2.	Targeted drug delivery	Targeted drug delivery to cancer tissue has been studied employing nanocomposites. Doxorubicin in glioma, methotrexate in osteosarcoma are some examples. Doxorubicin has been formulated with graphene oxide and ferrosferic oxide ($\text{GO}/\text{Fe}_3\text{O}_4$) conjugated along with lactoferrin for targeting. Methotrexate was delivered to human osteosarcoma cells via Magnesium- aluminum double hydroxide coated on Silicon dioxide nanodots ³⁴ .

3.	Controlled drug delivery	Release rate control of drugs like metformin, propranolol, aceclofenac etc, has been achieved by biopolymer based nanocomposites. Chitosan has been studied. Nanocomposites have been prepared employing aminopropyl silane along with polyethylene glycol/ polypropylene glycol, magnesium silicate, and locust bean gum respectively for the mentioned drugs ³⁴ .
4.	Wastewater treatment	Nanocomposites consisting of nanomaterials like zero valent metal nanoparticles, metal oxide nanoparticles (TiO ₂ , zinc oxide), carbon nanotubes have been used the treatment of wastewater. Silver nanoparticles have antimicrobial activity and aid in water disinfection while the zero valent metal nanoparticles aid in removal of organic and inorganic pollutants ³⁵ . The nanocomposites may aid purification of wastewater due to their interactions with pollutants either through chelation, absorption, ion exchange, etc.
5.	Bone tissue engineering	These artificial bone graft substitutes are utilized to satisfy bone integration and regeneration of bone <i>in-vivo</i> . Hydroxyapatite nanowire/collagen elastic porous nanocomposite were studied ^{36,37} . The mechanical properties and cell attachment efficiency were assessed in detail. Polymers were broadly used in tissue engineering. However, polymer cannot attain mechanical behavior comparable to bone. Polymer nanocomposites proved to be a viable solution for repairing defects in bones. Another work includes graphene based nanocomposite scaffold incorporated into a fibrin hydrogen for bone repair. ³⁸
6.	Gas barrier and food packaging	Nanocomposites exhibit versatile properties and find application in w Overall barrier performance can be increased, by the proportion of incorporation of the filler, and the amount of clay within the chemical compound ³⁹ . Due to obtaining a characteristic barrier, extended interest in nanoclay composites in food packaging, each versatile, and rigid. Packaging of processed meats, cheese, cereals. Exploration into new nanocomposites for food packaging include studies on nanocomposite made with chitin and bamboo nanofibers where no solvent has been used and so is a green synthesis ⁴⁰ , microbial polyhydroxybutyrate (PHB) based graphene nanocomposites for potential food packaging applications ⁴¹ , zein films with zinc oxide (ZnO) and ZnO- magnesium quantum dots based nanocomposite is found to have UV barrier properties. ⁴² Extensive work has been reported on chitosan based nanocomposites for food packaging applications.
7	Construction of automobile Fuel tanks.	The solvent transmission has been reduced in polyamides by using nanoclays. Due to incorporation of nanoclays vital decrease in fuel transmission through polyamide-6/66 polymers. Due to which, extended intrigue is currently being appeared in these materials as each fuel tank and components for cars ⁴³ .
8	Textile industry	The polymer/CNT nanocomposites find applications in textiles for flame retardation, electromagnetic shielding, for dye removal and as sensors. Non-conducting polymers such as epoxy, nylons, polyesters, etc. and intrinsically conductive polymers like polyaniline, thiophene, and polypyrrole have been used in textiles incorporating carbon nanotube ⁴⁴
9	Anticorrosives	Corrosion is the deterioration of a material due to exposure to the environment and is a global problem. the use of coatings and corrosion inhibitors are the common strategies to overcome corrosion. Polymeric coatings with incorporation of nanofillers show better inhibition of corrosion. Montmorillonite, CNTs, Single-walled CNT, Double-walled CNT, Multi-walled CNTs, Functionalized CNT are some nanofillers ⁴⁵ . Organically Modified Fluorohectorite in Polyetherimide (PEI) nanocomposite's matrix been studied for anticorrosion coat material. ⁴⁶
10	Agriculture	To reduce the burden of fertilizers and pesticides, nanocomposites are used. Misfortune in soil diversity and resistant development against pests and pathogens are the consequences of using chemical fertilizers in excess. Water treatment, pest control and detection, agriculture productivity. ⁴⁷
11	Nervous tissue engineering	For addressing the issue of regeneration of peripheral nerve injury (PNIs), nanocomposites supported with silk fibroin (SF) reinforced gold nanorods (GNR) were fabricated and studied GNR nanocomposites had a better cellular attachment, proliferation, and growth with no toxicity, compared with bulk SF scaffold. ⁴⁸
12	Cosmetics	Cosmetic industry has seen studies involving the use of nanocomposites. Ag-TiO ₂ nanoparticles show enhanced antibacterial property than TiO ₂ alone. A novel Nanocomposite was made employing ZnO, TiO ₂ and Ag TiO ₂ /Zn ₂ TiO ₄ /Ag which could be beneficial in development of sunscreen cream with high protection ⁴⁹ . Antiaging functionality has been found due to UV protection and water retention capacity of Quaternized carboxymethyl chitosan/organic montmorillonite nanocomposite and was suggested as a new cosmetic ingredient. ⁵⁰
13	Electrochemical nanosensor	Against conventional spectroscopic or chromatographic methods for estimation of biomolecules/ drugs, novel electrochemical sensors based on nanocomposites were developed. Nanocomposite surface is coated with Molecular Imprinting Polymer (MIP) which has cavities for the analyte molecule. Graphene / graphene oxide and silver nanoparticles were studied. ⁵¹ Photoelectrochemistry platform based on N-doped graphene/TiO ₂ nanocomposite has been developed as sensor for antioxidants capacity assay. ⁵²

14	Dental applications	Dental filling technology finds potential application for nanocomposites. Poly methyl methacrylate nanocomposites reinforced by nanoparticles of Titanium dioxide and Calcium aluminate have been studied for mechanical and tribological properties. ⁵³ other dental applications include fabrication of core and post systems and dental brackets, dental restorations like inlays, onlays, veneers, and crowns. the liquid crystalline epoxy nanocomposite resin made of bisphenol epoxy resin have been used for orthodontic brackets with improved microhardness. ⁵⁴ another filling materials studied includes MCM-48 mesoporous silica nanocomposites with hydroxyapatite. ⁵⁵
15	Solar cell	Either to harvest solar energy or to assist charge transfer process, both organic and inorganic nanocomposites have been successfully integrated into the solar cells. A novel superparamagnetic core-shell nanocomposite of poly(<i>m</i> -aminobenzenesulfonic acid) (PABS) and Fe ₃ O ₄ was synthesized by <i>in-situ</i> polymerization. The power conversion efficiency of the novel nanocomposite was found to be 660% higher than TiO ₂ and Aluminum based material using the same polymer. ⁵⁶ Silver/Graphene oxide/TiO ₂ ternary nanocomposite based photoanode approach has been studied to develop highly-efficient plasmonic dye-sensitized solar cells which showed 6% enhancement in power conversion ⁵⁷ .
16	Aerospace engineering	Given the possibility of combining the desired properties, nanocomposites are improving their role in aerospace applications and have scope for future space missions. Multi walled carbon nanotubes (MWCNT) have been used with a variety of polymeric materials to prepare nanocomposites suitable for aerospace applications. MWCNT/ Polyetherimide nanocomposite has been prepared by melt dispersion. ⁵⁸ MWCNT/Epoxy nanocomposite has been prepared by a novel spray coating process. The effects of the process parameters on the morphology and on the electrical properties of the nanocomposite films were investigated ⁵⁹ .
17	Luminescent materials	A new class of fluorescence materials have been synthesized which will find application in sensor systems. Ternary nanocomposite of high fluorescent polyaniline (PANI)/2-acrylamido-2-methylpropanesulfonic acid (AMPSA) capped silver nanoparticles (NPs)/graphene oxide quantum dots (GOQD) (PANI/Ag (AMPSA)/GO QDs) have been synthesized by <i>in situ</i> chemical oxidative polymerization of aniline. It showed high and stable emission peak at 348 nm. This may be used in optical sensing and biological imaging ⁶⁰ .
18	Antibacterial- Novel nanoantibiotics Antimicrobial photodynamic therapy Bacterial cellulose based NC	Many nanocomposites have been reported to have antibacterial action. The antibacterial action has been put to various applications as in water purification, in fisheries and aquaculture, etc. Bacteria that multidrug resistant are posing serious threat to therapy of various diseases. In the health care, graphene nanoplatelets /Cr ₂ O ₃ nanocomposites (GNPs/Cr ₂ O ₃) have been reported as a potential nanomedicine. This nanocomposite had excellent growth inhibition against <i>Pseudomonas aeruginosa</i> and <i>Staphylococcus aureus</i> . ⁶¹ Silver nanoclusters/rose bengal nanocomposite (AgNCs/RB) have been developed and evaluated as an antibacterial agent with functional response to light. <i>Streptococcus mutans</i> , <i>Porphyromonas gingivalis</i> and <i>Aggregatibacter actinomycetemcomitans</i> have been studied. The bacterial turbidity was found to be significantly reduced by the use of the novel nanocomposite. The activity has been attributed to activity silver ions as well as generation of ¹ O ₂ species due to photoexcitation. ⁶² Bacterial cellulose (BC) based The nanocomposites have been developed. The nanocomposite film was synthesized by incorporating Graphene Oxide-CuO nanohybrids into BC matrix through homogenized blending. displayed better antibacterial activity against gram-positive than gram-negative bacteria. BC/GO-CuO nanocomposites showed higher antibacterial activity than BC/CuO. ⁶³

V. CONCLUSION

The versatility of nanocomposites in terms of the exhaustive combinations of materials and their far outreaching applications in all the domains of life makes them a segment of science drawing much attention for future expansion. The present market exists in the areas of Packaging, Automotive, Electronics and Semiconductors, Coating, Aerospace & Defence, Energy, Others (Marine, Biomedical, Industrial)¹. In addition to the market for the constituents of nanocomposites like CNT, Graphene, clays, etc.,

commercialization has progressed in products like InMat (coating)⁶⁴, FiltekZ350 XT by 3M (tooth fillers)⁶⁵, chitosan/organic rectorite nanocomposite films (Bactericidal activity), graphene oxide/ Carboxymethylcellulose (targeted drug delivery of anti-cancer drug doxorubicin)⁶⁶, MD¹ Flex, NANOCLEAN MD¹and PLACTIVE (Antimicrobial nanocomposites),⁶⁷ NovaPro™ (Tooth fillers)⁶⁸. Tremendous progress is evident in science of nanocomposites. with improvement in material from simple binary system to ternary and hybrid systems; in fabrication technologies from spray coating to ink jet printing. Though

nanocomposites have been popular for a long time yet the potential in newer materials, design and fabrication methods, characterization and applications and has great scope for future development.

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Nanotechnology and Chitosan Nanoparticles in Veterinary Medicine

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Keywords: nanotechnology, veterinary medicine, chitosan nanoparticles, wound healing.

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Nanotechnology and Chitosan Nanoparticles in Veterinary Medicine

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Abstract- Nanotechnology is the new interesting field of science that enables us to use agents of extremely tiny sizes below 100 nm in novel applications. Although advent of nanotechnology in veterinary medicine isn't similar as in human medical settings, but this field has been a recently attracted veterinary researcher. Here, we review the recent papers dealt with the uses of nanoparticles in variety of applications in particular chitosan nanoparticles.

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1. INTRODUCTION

The skin is the largest organ in our body that provides a protective covering for the body besides its other physiological and defensive functions[1]. One of the most common skin pathologies is wound that defined as any break and disruption of the normal cellular and anatomical or functional continuity of the skin [2, 3]. Wound is a multifactorial disorder and it could be caused by physical, chemical, electrical or microbial causes[2]. Returning of skin to normal structure and replacement of destroyed or damaged tissue by newly produced tissue is called wound healing. Wound healing is a physiological and complex process established by four continues and overlapping phases (hemostasis; inflammation; proliferation, and tissue remodeling)[4, 5].

There are no lines of demarcation between the four previously mentioned stages that can be detected on the clinical or cellular level. The main goal of wound healing is to speed the recovery and restore the normal anatomical structure and function of the injured part with minimal scarring [6]. These steps involve multiple cellular and molecular events tightly controlled by numerous growthfactors, chemokines, and cytokines. In addition to the dynamic relationship between skin and microbiome (skin flora), that is another major contributor to the outcome of the wound healing process[7]. Signaling networks involving the interleukin (IL) family and growth factors are required to coordinate cell-cell and cell-extracellular matrix (ECM) interactions, that are essential to fully wound healing[8, 9].

The program of healing process can be interrupted by numerous factors which are classified into local factors (oxygenation, woundinfection, foreign body, venous sufficiency, wounded part, depth, local tension, and pressure) and systemic factors (age, gender, sex hormones, stress, ischemia, diseases, obesity, medications, alcoholism, smoking, immunocompromised conditions, and nutrition)[10, 11], Fig (1). Here in our paper, we highlight the variable applications of nanotechnology in veterinary medicine such as animal production, reproduction, diagnosis and treatment, nanovaccines, drug delivery, Nanosensors, and wound healing. Also, Chitosan nanoparticles were separately discussed.

Nanotechnology is a rapidly developing branch of science that studies the synthesis, structure, and dynamic of the atomic and molecular nanometer (maximum diameter of 100 nm) of nanoparticles [12]. Nanoparticles are synthesized by size reduction using either top-down methods such as milling, high-pressure homogenization and sonication or bottom-up processes such as reactive precipitation and solvent displacement [13]. The size and shape are key determinants to the biological efficiency of nanoparticles, by influencing active substance delivery (carrier circulation), penetrability (either directly through cell membranes or through phagocytosis), and cellular responses (receptor recognition) [14, 15]. The convergence of nanotechnology with medicine has been adding new hope in the therapeutic and pharmaceutical fields through a new discipline known as nanomedicine. This is the way for the development of novel materials and for the treatment of several pathologies [16].

a) Nanotechnology in Veterinary Medicine

Nanotechnology application in veterinary medicine is still relatively innovative. Recently, the nano-applications are already used in the veterinary medicine, animal health, production, breeding, reproduction, and nutrition [17], Fig(2).

1. Diagnosis and Treatment

In veterinary medicine, there is little definition of an animal's condition until clinical symptoms are detected. Infection can be substantially spread in the herd until disease is diagnosed. Nanotechnology may be effective method in critical clinical diagnoses because of this property[18].

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Biochips can be used for diagnosis of animal diseases. A Biochip (or microarray) is a device typically made of hundreds or thousands of short artificial DNA strands that are accurately deposited on a silicon circuit. Biochips can also be used to trace the source of food and feeds to detect the presence of animal products from different species as a means to locate the source of pathogens a response to public health threats as avian flu and mad cow disease [19]. Using biochips, biological samples such as blood, tissue and semen can be instantaneously analysed and manipulated [20]. Nanoshells can be injected into the animal's to locate tumour cells. The nanoparticles release an attached drug at the tumor site to destroy the cancer cells. These nanoparticles are made from ironoxides [21].

Nanoparticles were used to target toxoplasmosis and human immunodeficiency (HIV) virus, *Staphylococcus aureus*, tuberculosis (TB), *Brucella abortus*, anthrax, *plasmodium vivax*, *plasmodium malariae*, hepatitis B (HBV) virus, influenza virus [22-24], *Listeria monocytogenes* [25], SARS-CoV [26]. Also it has a role in reduction of aflatoxin as in use of nanosilver which used in treatment of experimental aflatoxicosis in broiler chickens. In other study revealed that supplement of nanosilver to diet containing aflatoxin could diminish the inhibitory effects of aflatoxin [27]. Also, gold nanoparticles and gold-based test strip have been used for the rapid detection of infectious bursal disease (IBD) virus antibodies in chickens [28], foot-and-mouth disease (FMD) virus [29], pathogenic bacteria [30], bluetongue virus [31], specific bacterial contaminants in chicken, such as *S. typhimurium* and *S. enteritidis* [32], antibacterial effect against *Bacillus Calmette-Guérin* (BCG) and *Escherichia coli* [33], haptoglobin in mastitic milk of bovine [34], diagnosis of viral infections in pigs [35], rapid detection of *Mycoplasma suis* in porcine plasma [36], and bacterial toxins [37]. Mastitis is common multifactorial disease that affects high-yielding animals primarily cows and is usually caused by *Staphylococcus*, *Streptococcus*, and *E. coli*, which leads to economic consequences for reducing the yield of milk [38, 39]. Zinc oxide nanoparticles (ZnO-NPs) have been found to be effective against bacterial biofilms inside the udder tissue such as *S. aureus* and *E. coli* [40, 41]. ZnO-NPs is more sensitive to detect cancer biomarkers and used in diagnostic and therapeutic purposes in common neoplastic conditions of animals such as lymphoma, cutaneous cancer, transmissible venereal tumor, and equine sarcoids [42-44].

In experimental studies applied by [45] on recent and infected wound in veterinary field by application of chemical and green synthesized ZnO NPs, they concluded that NPs having excellent antimicrobial healing effect with minimal scarring especially in green synthesized ZnO NPs. Also, Nanoparticles could be used in mass treatments of

ectoparasites facilitating the drug-parasite interaction. Nanoparticles are used for improvement of the effectiveness of phytotherapeutic products such as the antiparasitic silver nanoparticles using *Cissus quadrangularis* against *Hippobosca aculeata* and *Rhipicephalus* (Boophilus) microplus [46]. The nanoshells facilitate the target of the parasite improving the treatment of parasites and it can be useful in the study of host-parasite as biosensors. Nanodevices can allow the diagnostic of parasite in herds allowing veterinarians to suggest a correct health management [47].

2. Nanovaccines

Nanotechnology provides different forms of veterinary nanovaccines such as: recombinant *Bacillus anthracis* spore-based vaccine, influenza virus vaccine, *Helicobacter pylori* vaccine, *Tetanus toxoid*, *Bordetella pertussis* vaccine, Rota virus capsid vaccine and *Bovine parainfluenza* type 3 vaccine. The mucosal immunity is developed following intranasal administration of influenza virus vaccine and both IgG and IgA immune response are developed following the oral administration *Bovine parainfluenza* type 3 vaccine.

Also chitosan nanoparticles (CS NPs) were prepared with *Leishmania* superoxide dismutase and subcutaneously injected as recombinant *Leishmania* SOD vaccine. Also, intranasal (*pneumococcal* antigen A vaccine and *Streptococci equi* vaccine) or pulmonary (TB vaccine) vaccines were nano-based. Also, gold nanoparticle-based vaccine were developed against FMD, Newcastle disease, influenza virus, or herpes simplex virus 2, and also vaccines of African horse sickness virus (AHSV) [48-50].

3. Drug Delivery

The nanoparticles play an important role in drug delivery as they can carry drug and genes to the target site. The drug delivery systems have important effects on absorption, distribution, and excretion rate of drugs or other substances in the body [6]. Liquid vitamins that were prepared by nanotechnology are available for poultry feed and their nanosized are designed to pass through the gastrointestinal tract and deliver the vitamins or other nutrients directly in the bloodstream and therefore increase their bioavailability. NPs mask undesired tastes and improve the nutrient dispersibility and durability of the feed. In addition, they decrease the need to use preservatives [51]. In animals, smart drug delivery systems allow antibiotic use in amounts less than possible. Also, smart delivery systems can perform processes such as its ability to decide the regulation in the process of delivery of drug or its ability to make the drug addition according to the need, and the perception of chemicals in the site. Smart delivery system decrease the antibiotic usage and the treatment cost in farms [52].

4. Nanosensors

Nanosensors are miniature devices that can be used for diagnosis of biological material or tissue samples [53]. It has been used in several biomedical applications in veterinary medicine including animal health for diagnosis of some microbial pathogens-diseases [54, 55] and for animal production, especially the delivery of controlled quantities of drugs into breeding animal beverages. Nanosensors used for prevention of bovine tuberculosis [54] and early diagnosis of subclinical Ketosis (SCK) that is essential for management of dairy cattle health [56]. Detection of *Mycobacterium bovis* using nanosensors in infected cattle via breath allowed for real-time cattle monitoring [57]. In addition, the sensors can be used to measure body temperature, antibiotic detection, detect their sweat constituents, observation of behavior, movement, and stress via the implantation on animals [55].

5. Animal production and Food sector

By experimental studies applied by [58] on New Zealand White rabbits fed on nanoparticles; they showed increased weight gain at the fattening period. Similar beneficial production effects have been reported by [59] and [60] in chicken experiments. As the excellent results to an additive which improves the sanitary status of animals. So, the beneficial effect of nanoparticles used in animal production was most frequently observed in such parameters as weight gain, average daily gain, or improvement of the feed conversion rate (FCR) value [61]. As well, the nanomaterials that have been digested and shed in the feces can be used for fertilization in pastoral soil.

Nowadays, the nanomaterials are used for meat production as ingredients or additives in the food. They enhance the taste and reduce the use of fat, salt, sugar, and preservatives. Reducing the salt level is especially important and presents a great challenge for meat industry because in spite of advantages, use of salt consequently increased risk of cardiovascular disease since it is linked to hypertension [62].

6. Animal reproduction

Management of breeding is an expensive and time-consuming problem for dairy and swine farmers [19]. There are various applications of nanotechnology in the field of animal reproduction which optimize the general reproductive performance at its different stages starting from the diagnosis and treatment of reproductive disorders and detection of estrus till managing reproductive problems such as retained placenta [63]. Also, the NPs can also be used for sustained release of reproductive hormones [64].

Currently, Nanosensors also used to diagnose genital tract infectious diseases, metabolic and hormonal disorders, and even for the detection of estrus [65, 66]. Similarly, a nanotube implanted under the skin, it is bind and detects the estradiol antibody at the time

of oestrus by near infrared fluorescence and the change in level of estradiol in the blood can be measured [19].

b) Chitosan Nanoparticles (CS NPs)

Chitosan Nanoparticles (CS NPs) is an excellent example of nanomaterials which included in all stages of wound healing [67]. CS NPs showed an increased activity than its parent chitosan [68] due to its increased surface to volume ratio [69]. Chitosan is a natural and biodegradable polysaccharide composed of $\beta 1 \rightarrow 4$ linked N-acetylglucosamine and derived from the alkaline deacetylation of chitin which is the principal component of the cell walls of some fungi and the exoskeleton of insects, crustaceans [70, 71], mollusks [72], yeast or green algae [73].

1. Synthesis

CS NPs consists of three functional groups, including an amino group and primary and secondary hydroxyl groups. CS NPs can be cross-linked with glutaraldehyde, glyoxal, and terephthalaldehyde, producing hydrogels that can be used in different applications such as organ transplants, restoring organ function, gene delivery, and targeted therapy [74, 75]. so, chitin and chitosan are manufactured commercially in large scale [76]. In its crystalline form, chitosan is normally insoluble in an aqueous solution above pH 7; however, in diluted acids (pH 6.0), the protonated free amino groups on glucosamine facilitate solubility of the molecule. Chitosan preparations of various molecular weights (50–2,000 kDa), degrees of deacetylation (30–95%), and further molecular derivatization patterns allow extensive adjustment of mechanical and biological properties [77].

CS NPs can be synthesized using either “bottom-up” or “top-down” approaches and/or a combination of both procedures [78]. CS NPs are synthesized through numerous “bottom-up” approaches such as polymerization of CS with methacrylic acid (PMAA) to make CH-PMAA NPs, or through a reverse micelle medium or microemulsion methods [79]. Top-down approaches such as milling, high-pressure homogenization, and ultra-sonication are also applied for the synthesis of these nanomaterials [80]. Many methods have been employed for the syntheses of CS NPs, but five methods are presently available. They are ionotropic gelation, microemulsion, emulsification solvent diffusion, polyelectrolyte complex, and reverse micelle method [81], Fig (3). Out of this, the most widely used methods are ionotropic gelation and polyelectrolyte complex. These methods are simple and do not apply high shear force or use organic solvents [82].

2. Biomedical applications

Chitosan nanoparticles have great commercial value due to its high nitrogen content and other physiochemical properties like biocompatibility, adsorptive ability [69], biodegradable [72],

anticholesterolemic, fungistatic, noncarcinogenic, remarkable affinity to proteins, stimulation of healing, tissue engineering scaffolds, and drug delivery [83-85]. In addition to, hemostatic activity, anti-infection activity, property to accelerate wound healing [86], allergenicity, and bioactivity make it a very attractive substance for diverse applications as a biomaterial in the biomedical, food, and chemical industries [87, 88]. Other chitosan properties are low toxicity, availability, low cost, permeability to oxygen, and ease of chemical modification [70, 89, 90]. The biodegradation rate of chitosan samples is the highest at a temperature of 36°C and is characterized by a relatively prolonged induction period, which is shorter at higher temperatures. The smaller the molecular weight of chitosan, the shorter the induction period [91].

3. Drug Delivery

Separated reports are available on the use of combinations of antibiotics and chitosan and its derivatives as antimicrobials. Decker *et al.* proposed a synergistic chlorhexidine/chitosan combination for improved anti-plaque strategies [92]. Tobramycin is one of the antibiotics which is reported to show synergistic action with chitosan in planktonic culture of *Pseudomonas aeruginosa* [93]. Bioadhesive and antimicrobial properties of chitosan and its derivatives are effective in antimicrobial drug delivery control, release of Chlorhexidine and Nystat in oral preparations [94, 95], release of ampicillin [96], drug delivery system for Ofloxacin [97] in ophthalmic preparations, and gastrointestinal-release preparations for Tobramycin sulfate [98].

4. Antimicrobial and antifungal activities

CS NPs are present in many forms such as beads, powders, gels, sponges, tubes, fibers, and films [99-101], hydrogel [102], and biofilm [103]. These forms facilitate the antibacterial and wound-healing activity of CS NPS. Chitosan nanoparticles were shown to have significant bactericidal effects on different types of bacteria and no cytotoxic effect on mouse fibroblast cells [104]. Their antimicrobial effects against a broad range of gram positive and gram-negative bacteria as well as fungi were reported [105-107]. Archana, D., *et al.*, reported in an experiment on a wound in rats the antimicrobial and wound-healing activity of chitosan [67]. Although several studies have shown that chitosan exhibited higher antibacterial activity against gram-positive bacteria than gram-negative bacteria, while some other studies have shown that gram-negative bacteria as more susceptible than gram-positive [108, 109], many works have demonstrated that there is no significant difference between antibacterial activity and bacterial species [110].

Studies have reported the antibacterial activity of CHNP against *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus mutans*,

Salmonellatyphimurium, *Salmonellacholeraesuis*, and *Pseudomonasaeruginosa* [107, 111]. Antifungal activity of CHNP has also been reported against *Aspergillusniger*, *Fusariumsolani*, *Rhizoctoniasolani*, *Collectotrichumgloeosporioides*, *Candidaalbicans* [68, 112]. Chitosan's antibacterial efficacy also depends on multiple factors both intrinsic and extrinsic. Intrinsic parameters comprise the molecular weight and degree of deacetylation of parent chitosan, nanoparticle size, and concentration. The extrinsic factors involve pH, temperature, reactive time and so on [113].

The CS NPS size is an important factor which affects its antimicrobial activity, as the decrease in size at lower concentrations is due to decreased viscosity causing better solubility of chitosan in acetic acid solution and resulting in better action of chitosan [114].

However, deacetylation degree, positive charge content, and other factors including molecular weight can affect the antibacterial activities of chitosan [115], as the molecular weight has a stronger effect on the antimicrobial activity compared to the degree of acetylation [108, 116, 117]. It has been reported that decreasing the molecular weight of chitosan may increase its binding affinity to the membrane due to improved mobility, attraction, and ionic interaction [118], though a proper antibacterial activity can be obtained only when the molecular weight is larger than 10 kDa [119]. In acid, the antimicrobial activity was shown to increase with increasing molecular weight [116], while the antimicrobial activity changed at pH 7.0 [115].

The most prevalent proposed antibacterial activity of chitosan is by binding to the negatively charged bacterial cell wall causing disruption of the cell thus altering the membrane permeability [120, 121], followed by attachment to DNA causing inhibition of DNA replication and subsequently cell death [121]. Another possible mechanism is that chitosan acts as a chelating agent that selectively binds to trace metal elements causing toxin production and inhibiting microbial growth [122]. For instance, chitosan composites have shown antiviral activity against H1N1 influenza A virus [123] and Human cytomegalovirus (HCMV) strain AD-169 [123, 124].

5. Wound healing

The application of nanotechnology in the field of wound healing gave way to the manufacture and innovation of many bandages, which in turn speed up healing with the least possibility of scarring. [16]. From our point of view, the good selection of suitable nanomaterials for different wound types can play the main role in wound healing and tissue remodeling. The nanomaterials used in wound healing are classified into two categories: (1) nanomaterials that exhibit intrinsic properties beneficial for wound treatment and (2) nanomaterials included in drug delivery [125, 126]. An ideal material should be able to protect wounds against microbial interactions [127].

An experimental study performed by Chandika, P., *et al* [128] documented that chitosan increased wound healing rates in mice. N-acetyl glucosamine (NAG) present in chitin and chitosan is a major component of dermal tissue which is essential for repair of scar tissues [129]. Chitosan's positive surface charge enables it to effectively support cell growth [130] and promotes surface-induced thrombosis and blood coagulation. Free amino groups which are present on the chitosan membrane surface may form polyelectrolyte complexes with acidic groups of the cellular elements of blood [86]. Chitosan promotes the dermal regeneration during skin reconstruction by regulating the deposition and accelerating the arrangement of thin collagen fibers. It also modulates fibroblast activation, sustaining the regeneration of the extracellular matrix while stimulating cell proliferation and migration (i.e. the formation of granulation tissue) and enhancing wound healing [131].

Natural products-derived biomaterials can provide materials with greater complexity and composition, and in order to mimic the extracellular matrix (ECM) conditions of the wound and to provide a scaffold for the fibroblasts for collagen deposition, ECM-based therapies have gained popularity [132].

Studies suggest that chitin and chitosan promote the migration of polymorphonuclear and mononuclear cells and accelerate the reformation of connective tissue and angiogenesis (necessary for the arrival of repair cells such as fibroblast)[133]. In recent studies, chitosan has been used to deliver bioactive molecules, basic fibroblast growth factor[86] and human epidermal growth factor[134] were encapsulated in this biomaterial; electrospun nonwoven nanofibrous hybrid mats based on chitosan and poly[(L-lactide)-co-(D,L-lactide)] were produced; [135] chitosan dressing incorporating a procoagulant (polyphosphate) and an antimicrobial (silver); [85] and chitosan acetate bandages were used as a topical antimicrobial dressing for infected burns[83].

II. CONCLUSION

Nanotechnology is a rapidly developing branch of science that could be applied in various aspects with different actions. Although advent of nanotechnology in veterinary medicine isn't similar as in human medical settings, but this field has been recently attracted veterinary researchers. We conclude that the field of nanotechnology in veterinary medicine is a promising field in different disciplines; surgery, pharmacology, vaccinology ... etc.

Conflict of interest

No conflict of interest.

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FIGURE LEGENDS

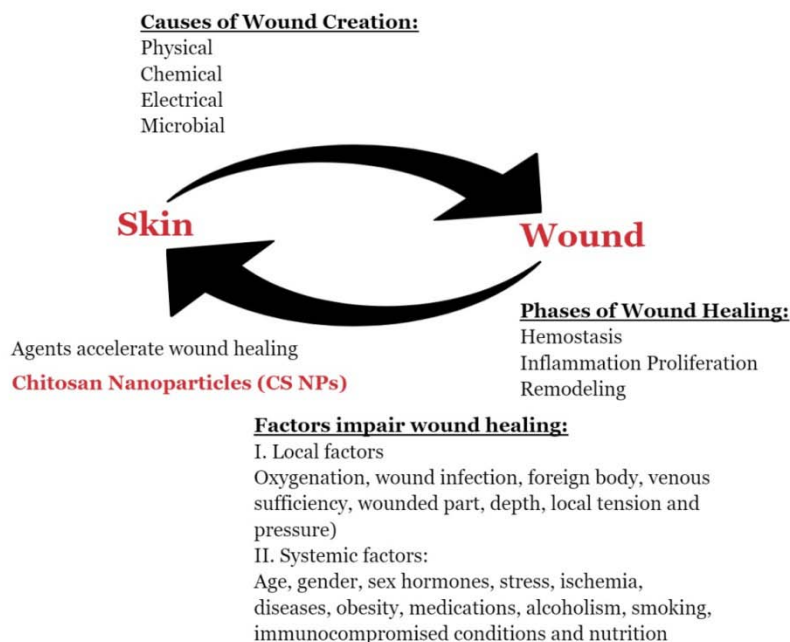


Fig. (1): Showing the normal stages of the wound healing.



Fig. (2): Showing applications of Nanotechnology in Veterinary Medicine.

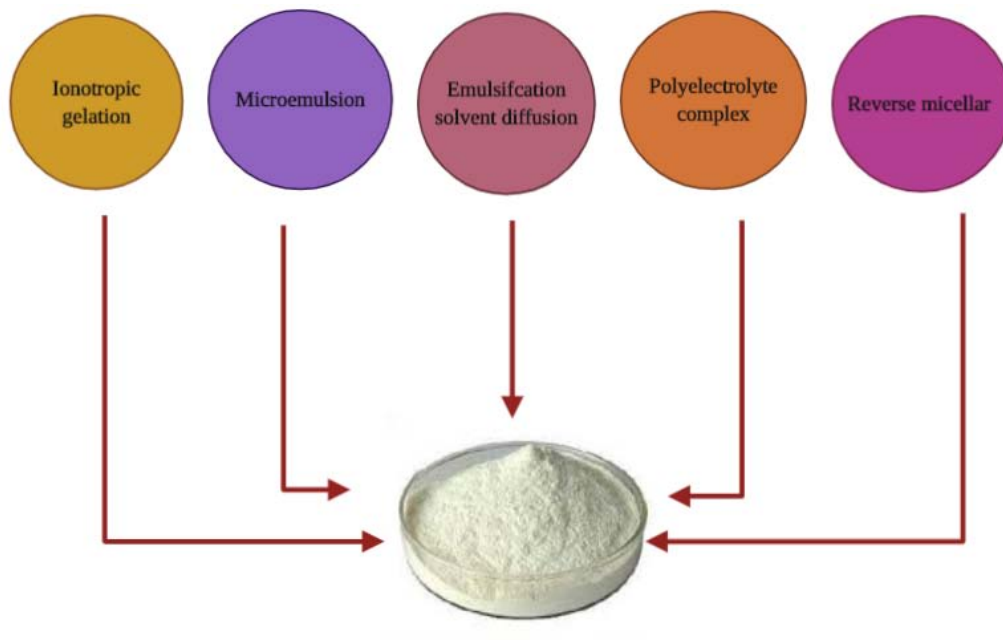


Fig. (3): Different methods of Chitosan nanoparticles synthesis.

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Non Conventional Approaches for Management of Drug Addiction and CNS Disorders

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Abstract- Addiction is a serious and widespread disorder that has devastating consequences for individuals and society. However, the existing treatment for addiction is moderately effective at best. In recent years, the researchers have renewed their interest in the effectiveness of classic hallucinogens for clinical uses such as treating addictions and other behavior-related health issues. In the present work, we tried to review both pharmacological mechanisms of actions and the recent researches done on the use of classical hallucinogens in treating addiction. Also, some selective review related to other relevant researches was done, for suggesting prospectus of future research. The classic hallucinogen showed extraordinary record for safety in clinical research. Also, with the limited understanding of the clinically important impacts of classic hallucinogens, there are many opportunities for future research which may contribute novel knowledge and help in treating addiction. This review provides the scientific literature related to the use of classic hallucinogens and the related mechanism of action of psychedelic in treating drug addiction.

Keywords: addiction, natural psychedelics, hallucinogens.

GJMR-B Classification: NLMC Code: V 55



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1. INTRODUCTION

Addiction can be defined as a relapsing and chronic illness that is characterized by the obsessive seeking of drugs and its continued use regardless of its harmful effects. [1]. . Addiction totobacco, alcohol, and other drugs is the main reason for disability and death globally[2].

Most addictive drugs facilitate the dopamine function in the CNS [3]. The mesolimbic dopamine system was considered as their primary target of addictive drugs. The mesolimbic dopamine system starts in the ventral tegmental area (VTA), It projects to accumbens nucleus, hippocampus, amygdala, and the prefrontal cortex) Addictive drugs can be classified broadly into three classes based on their specific molecular target and cellular mechanisms for activating the mesolimbic system. 1st class targets the Gio protein-coupled receptors, The cannabinoids, opioids, hallucinogens, and Jama-hydroxybutyric acid (GHB), exerts their action via this pathway 2nd class interacts with ion channels or ionotropic receptors, they include dissociative anesthetics, alcohol, nicotine, benzodiazepines, and some inhalants. And the 3rd class interacts with dopamine transporter includes amphetamines, cocaine, and ecstasy. These three classes of drugs loosely map onto three distinct cellular mechanisms to increase dopamine levels. The first is the direct stimulation of the dopamine neurons (e.g., nicotine). The second mechanism is the interference with the reuptake of dopamine or the promotion of non-vesicular release (e.g., amphetamines). The third mechanism is indirect, whereby the drugs inhibit γ-aminobutyric acid (GABA) neurons that act as local inhibitory interneurons (e.g., opioids) [4].

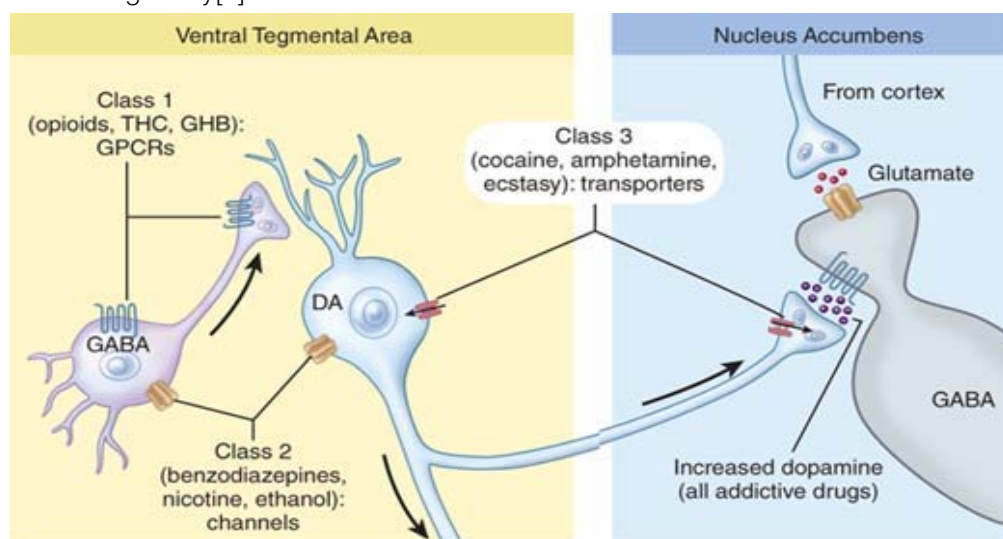


Figure 1: Neuropharmacology classification of addictive drugs by primary target[4].

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II. LIMITATIONS OF CURRENT TREATMENTS FOR ADDICTIONS

Several pharmacological and behavioral treatments have been developed that target specific aspects of addiction. However, the effects of most currently available treatments remain disappointingly not optimal [2]. Therefore, there is an increasing interest to search for new medications and revolution in the management of addiction. In this context, natural products represent a wealthy resource. The objectives of the current review are to summarize the progress in utilizing natural products in the management of addiction.

a) Methodology

Searching PubMed 2009-2019, for herbal medicine, natural products, nutraceuticals, special emphasis was given for use of Psychedelic, or psychoactive substances for management of addiction. The results are summarized below.

b) Results

History and definition of Psychedelic substances

Psychedelics are psychoactive compounds whose primary action is to alter the cognition and perception by affecting the neurotransmitters of the brain. Interestingly they are not likely to produce dependence nor addiction. The recent history of these compounds began with the isolation of mescaline, the psychoactive alkaloid produced by the peyote cactus, by Heffter in 1898, and the discovery of the effects of LSD by Hoffman in 1943.

The pharmacological effect of these compounds have been studied in a wide range of animal models [5].

c) Structure and chemistry

A-indoleamines include indolealkylamines such as dimethyltryptamine (DMT), psilocybin, lysergic acid diethylamide (LSD). B-phenylalkylamines include mescaline [6]. (Update the structure, chemistry, clear figures).

d) Characteristic features

Many natural PSY possesses features that might encourage research regarding their utility as an anti-addiction drug: [2].

- 1) Absence of the addictive effects.
- 2) Their molecular target support anti-addiction effects.
- 3) Their psychological effects changes in behavior and personality which is persisting likely to participate in natural addiction recovery

e) Clinical studies

Clinical trials utilizing Natural PSY have been recently reviewed. These compounds vary widely in their structures, and pharmacological profile but all relatively

non-addictive, and exhibited similar subjective effects' [2].

1. LSD & psilocybin

A meta-analysis of data on LSD as a treatment for alcoholism from the 1950s to 1960s showed its beneficial effect on alcohol abuse. A clinical trial demonstrated the effectiveness of psilocybin on smoking cessation and found that 80% of patients were smoke-free 6 months after receiving two or three doses of psilocybin along with cognitive-behavioral therapy (CBT). Another study demonstrated the utility of psilocybin as an adjuvant in the management of alcoholism. (psilocybin-assisted psychotherapy.). These studies highlighted the preliminary efficacy of natural PSY in the treatment of depression, anxiety, addiction. They are thought to exert their main effect via partial agonist or agonist activity at the serotonin 2A (5HT_{2A}) receptors [7]. [8].

2. DMT (Ayahuasca)

Ayahuasca is a decoction prepared using two plants: *Psychotria Viridis* and the vine of *Banisteriopsis caapi*. The 1st contains DMT (which is destroyed in GIT by MAO) and the 2nd contains (MOA inhibitor) beta-carboline alkaloids and harmala alkaloids (tetrahydroharmine, harmaline, and harmine). This combination allows DMT to be effective orally [9]. [6]

Several animal studies using ayahuasca demonstrated its include antidepressant effect [10]. [11], anti-addictive properties in an animal model for alcoholism [9, 12].

Studies in humans to demonstrate the utility of Ayahuasca— assisted therapy showed promising results. An old study showed its efficacy in the management of alcoholism Halpern et al. (2008)- Reported remission of drug or alcohol abuse or dependence, Fabregas et al. (2010)- demonstrated lower several drugs of abuse and improved psychological status Thomas et al. (2013)-, demonstrated Statistically significant reductions in cocaine use. And Improvements in some psychological parameters or quality of life

Regular ayahuasca users frequently reported a decrease in consumption of cocaine, alcohol and other addictive drugs long-term use of ayahuasca are not related with loss of cognitive function ayahuasca do not cause its tolerance and also marked it to have an inadequate dependence potential.

Ayahuasca increases the levels of stress hormones prolactin and cortisol in the blood. It may cause moderate increases in systolic (SBP) and diastolic blood pressure (DBP) was observed, with minimal change in heart rate. Ayahuasca's use for healthy individuals seems to be practically safe in the context of physiological effects. The side effects commonly observed with ayahuasca use are vomiting and nausea, which is related to the dose [13].

3. Ibogaine

Ibogaine is an indole alkaloid with psychoactive effect, it is an active constituent of an African rainforest shrub *Tabernanthe iboga*. Its efficacy in the management of addiction is well documented, surprisingly after a single dose. However, ibogaine's serious toxicity that leads to fatality is one of the major causes of concern. [14].

Efficacy should be more clear

Pharmacokinetics

Ibogaine is metabolized into Noribogaine (O-desmethylibogaine or 12-hydroxyibogamine) by CYP2D6 with exhibit genetically based variable metabolizing capacity. The half-life of noribogaine is longer than ibogaine. (about?) [15, 16].

Mechanism of action

Ibogaine and noribogaine are thought to act via several pathways. They are an agonist of κ - and μ -opioid receptors and an antagonist of the N-methyl-D-aspartate (NMDA), glutamate and nicotinic acetylcholine receptors, [17].

Adverse effects Ex-Vivo and animal model

Studies in animals demonstrated serious toxicity, including cerebellar damage and abnormal cardiac function [15].

Ibogaine showed neurodegenerative effects in the rats in high doses with excitotoxic effects on Purkinje cells in the cerebellum. Dose lower than 25 mg/kg did not exhibit neurotoxicity. Besides noribogaine may be less neurotoxic than ibogaine [16].

In our opinion, the dose used in human is not likely to cause neurotoxicity. Support by data or ref

In human cardiomyocytes, the therapeutic levels of ibogaine and noribogaine significantly decreased the action potential repolarization. Therefore their use may evoke cardiac arrhythmia. A genetically based alteration in certain cardiac (hERG) potassium channels which is blocked by ibogaine predisposes the patient for serious QT interval prolongation, serious arrhythmias, and sudden cardiac arrest (Fig 1). Cardiac toxicity to noribogaine is thought to be similar to ibogaine [18].

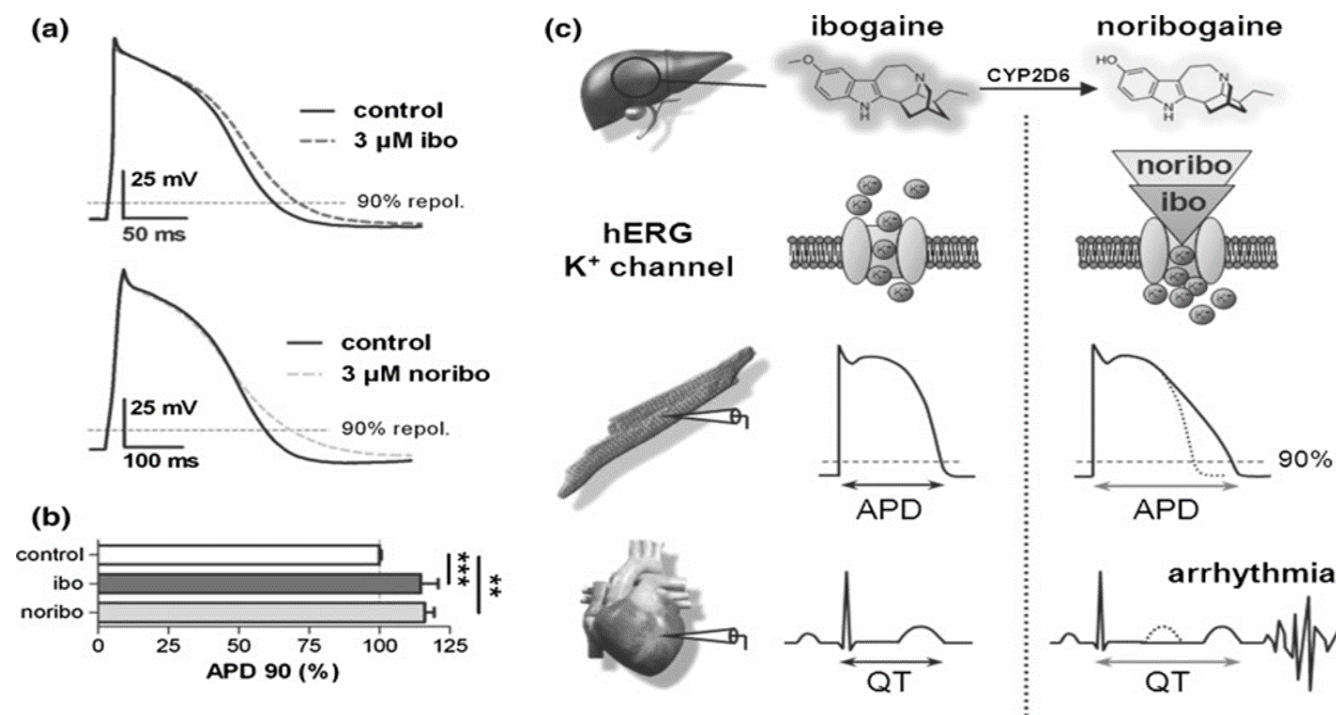


Figure 2: Ibogaine and noribogaine impair the electrophysiology of the human heart [18]

Report fatalities in human & drug interaction [16].

4. Salvinorin A

Salvinorin A is an active constituent of sage, *Salvia divinorum*. Structurally, it is not an alkaloid. It does not affect the 5-HT_{2A} serotonin receptor, [19].

Mechanism of action

Salvinorin A is acting as a selective agonist of the kappa-opioid receptor (KOR). It retains its anti-addictive property of traditional kappa-opioid receptor agonists with many enhancements such as decreased side effects. Many studies showed that salvinorin A can modify the dopaminergic pathway via decreased

dopamine levels in the caudate-putamen and dopamine neurotransmission levels in the dorsal striatum, basically by regulating the release of dopamine instead of its uptake [19, 20].

Lake of studies on human & limitations

At present, there are no studies regarding the therapeutic usage of salvinorin A on humans. Its intense hallucinatory effects (accompanied by dissociation, dysphoria, and motor effects) represented a major limitation of its use in humans [19].

Pharmacokinetics

It is metabolized by CYP450 and has a very short half-life of about 75 min [20].

f) Non psychedelic natural products

Thymoquinone (TQ)

It is one of the main bioactive ingredients of *Nigella Sativa*, family Ranunculaceae. TQ possess protection against oxidative stress, inflammation, and infections. and, neuroprotective effect. It exhibited beneficial effects against toxin-induced neuroinflammation and neurotoxicity [21].

In the animal model, TQ attenuated the development of tramadol tolerance and dependence. El-Shamy et al. (2013) A study also reported that *Nigella sativa* possesses the ability to modulate neurotransmitters release and reuptake (dopamine, serotonin, gamma-aminobutyric acid, and acetylcholine and gives a beneficial effect on the decrease of drug tolerance [22].

Safety and limitation of Psychedelics

A comprehensive study of risk and safety matters was described by Johnson and colleagues [23]. Here we abstract a brief description.

1. Potential adverse effects

Classical hallucinogens may be used in unsafe ways, but they normally do not impose addiction. Psychosis, though it is rarely observed in medical places. classical hallucinogen has very minimum physiological toxicity.

No evidence of neuropsychological deficits or damage of organ the most important concern was the anxiety and fear, [24] [2].

2. Safeguards against risks

Screening for a history of psychiatric behavior; administration under medic observation and availability of measures for the management of any cardiovascular abnormality may improve the Risk/ benefit ratio. [2, 23]

III. CONCLUSIONS

Using some natural psychedelics for example DMT for management of drug addiction is a very promising approach and research should be encouraged to optimize their clinical utilization. More work needs to be done on mechanisms of action, e.g., psychological mediators and persisting psychological change, neuroimaging studies of persisting effects, other biomarkers, and the possible role of genetics in moderating response to psychedelics should be manipulated. Conclusively, as all the drugs have some associated risks, constant care of safety for the patient is important, including the optimization of screening, preparation, debriefing, and follow-up sessions.

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Marketing/Promotional Initiatives by Pharmaceutical Companies – “Doctor’s Perspective”

By Mr. Nadiminti Rajesh Kumar & Dr. Sajid Alvi

Abstract- The study was aimed to obtain the current perception of the different specialties of doctors about the promotional/engagement initiatives established and implemented by the Pharmaceutical firms. The objective was to understand the need gaps and doctor’s preferences in the area of promotional/engagement initiatives, by conducting face-to-face interviews.

Analysis of Sales force/ Sales Representatives effectiveness was also a part of the project. This was an attempt to understand the relationship between the sales representatives and the physicians, which weights to influence the prescription generation. The preference of the physician towards the traits of a Sales Representative where identified. The behavioural and professional characteristics of the representatives were the area of focus. This feedback was employed to improve the approach by the representatives towards the Physicians.

Keywords: e-detailing, Pharmaceutical promotion.

GJMR-B Classification: NLMC Code: QV 701



Strictly as per the compliance and regulations of:



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Another part of the research was to take the feedback of the physicians on Digital Initiatives that are being adopted actively in the pharmaceutical world. These include:

- The shift from a VISUAL AID to E-DETAILING for detailing of the product.
- Introduction of engagement apps for the Physicians – Speciality specific, Knowledge sharing apps.
- Social media campaigns for spreading awareness, launches etc.

Keywords: e-detailing, pharmaceutical promotion.

I. INTRODUCTION

The paper was aimed to understand the need gaps and the potential opportunities that are available in the marketing/promotional initiatives for the medical fraternity. This was done by conducting a primary market research which involved face-to-face interviews with the physicians of different specialities. 11 specialities of doctors were chosen to have holistic and a representative result/feedback. Along with the initiatives the doctors were asked to give feedback on the performance and effectiveness of sales representatives, where the doctors preference of how sales reps should approach the doctors could be mapped. Feedback on the digital initiatives, the technology based advancements in the engagement approaches by the pharmaceutical companies.

II. LITERATURE REVIEW

Many countries have measures in place to limit advertising by pharmaceutical companies. In India, the direct to user/consumer advertisement i.e. “Patient” is not allowed according to the law. Hence the promotion and advertisements are channelized towards the doctors, as they have a direct relationship with the patients. The Pharmaceutical firms communicate and send the message about their products to the Patients Via Doctors. This is accounted as “Marketing to health-care providers”.

- Marketing to health-care providers takes three main forms: activity by pharmaceutical sales representatives, provision of drug samples, and sponsoring continuing medical education (CME).
- The pattern has evolved witnessing a shift from these traditional initiatives to the new age digital initiatives.
- However, a blend of traditional practices and the newer initiatives pertaining to the technology and advancement is the most practised and followed in the pharmaceutical system.
- Pharmaceutical companies have their distinct customers: “DOCTORS”, hence every pharmaceutical firm engages the physicians with a host of promotional tools.
- The basic intent behind these tools is to build a long term relationship with the doctors in order to ensure continuous business and support from the doctors towards their firm.
- While the companies make efforts and positively influence doctors, such initiatives highly encourage doctors to prescribe their drugs marketed by their sales representatives.
- Companies use various tools viz. gifts for personal/clinical use/academic use, scientific education programs, collaboration for clinical studies or patient awareness, detection camps and sponsorships.
- Based on feedback collected from doctors, company would plan and channelize investment and efforts and therefore streamline the entire customer relationship management process.

III. OBJECTIVES OF THE RESEARCH PAPER

- The overall research objective was to gather feedback from doctors on current promotional tools

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and various doctor engagement activities undertaken by pharmaceutical companies.

- To identify the various types of scientific/non-scientific engagement initiatives, which activities appeal to the medical fraternity and identify top companies associated with every type of engagement initiatives
- To identify need gaps/opportunities in terms of doctor engagement initiatives which doctors would want pharma companies to undertake
- To assess the quality of sales representatives and identify attributes on which doctor's evaluate sales reps. Identify top companies basis the quality of sales reps

- To find out the feedback on digital means of engaging and communicating with doctors: i.e. e-detailing and other digital promotional activities.

IV. TARGET SELECTION

- The market research was conducted in Hyderabad and Pune. The motive was to have a good representation from the parts of India, and have a more representative feedback.
- The territory that I covered was the South & Western India, namely Hyderabad and Pune.
- The sample size considered and covered in Hyderabad- Total : 103

Hyderabad											
Specialty	Cons. Phy	Cardio	Psycia	Neuro	Ortho	Gastro	Dermat	Paed	Gyneac	Chest	Opthal
Number	17	12	12	5	13	6	12	6	12	4	4

PUNE											
Specialty	Cons. Phy	Cardio	Psycia	Neuro	Ortho	Gastro	Dermat	Paed	Gyneac	Chest	Opthal
Number	10	6	7	9	6	6	6	6	9	9	11

- The sample size considered and covered in Pune- Total: 85
- Overall Face-to-Face interviews conducted with the physicians in Hyderabad and Pune accounts to 188.

V. RESEARCH METHODOLOGY

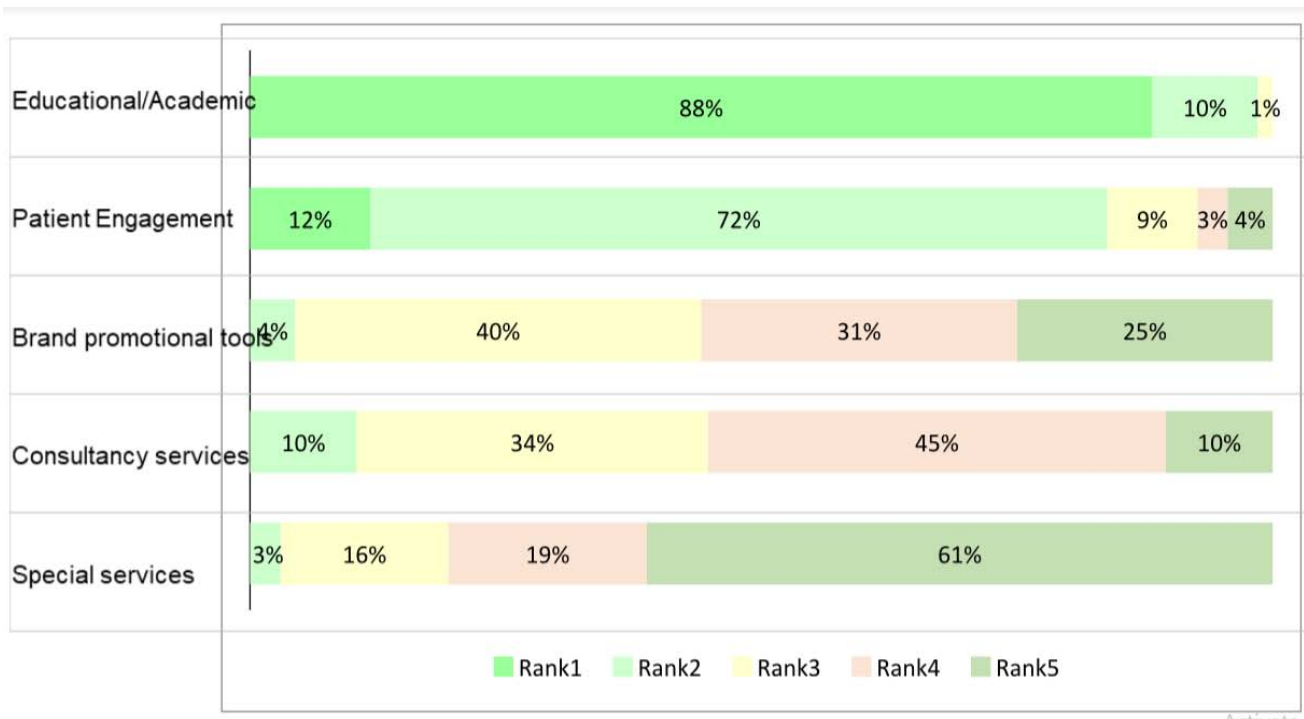
- Type of research: Exploratory and Descriptive
- Research design: Qualitative and Quantitative
- Target Customers: Consultant Physicians, Cardiologists, Chest Physicians, Dermatologists, Gastroenterologists, Gynaecologists, Neurologists, Orthopedicians, Ophthalmologists, Paediatricians, Psychiatrists.
- Sample size: 188 Doctors

- Type of questionnaire: A structured questionnaire was prepared having closed and open ended questions.
- Data collection method: Face-to-Face interviews with the doctors.
- Data analysis tool: MS Excel
- Territory covered: Mumbai and Pune
- Tools used for research:
 1. Primary data: Primary data was collected from doctors through structured questionnaires. It is original, authentic and serves the purpose of the project.
 2. Secondary data: Secondary data was collected from literature, articles and internet.

VI. DATA ANALYSIS

I: Feedback on Overall Promotional Engagement Initiatives

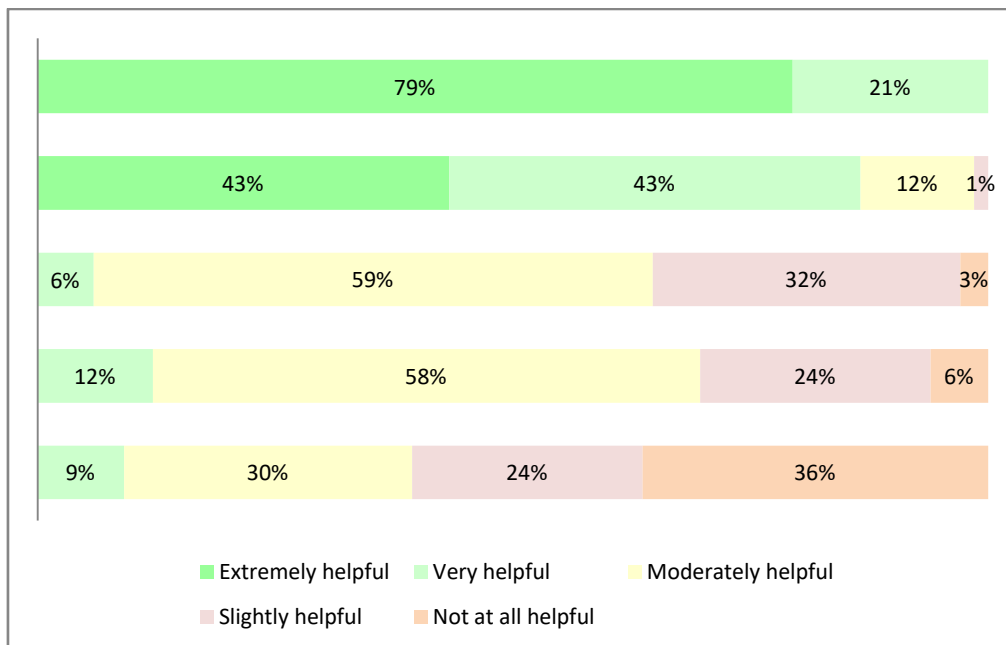
Considering the different kinds of tools/initiatives that pharma companies engage you with, what is your opinion about importance of each (Rank order 1 to 5)?



Interpretation:

- From the above picture it can be inferred that, Educational/Academic initiatives are the most preferred initiative accounting to 88% (Ranked 1) and Patient Engagement initiatives are perceived as most important by 12% of the doctors. The Consultancy services stand at 10% followed by Brand promotional tools are ranked most important by 4% of the doctors and finally Special services are marked as important by 3% of the doctors.

Which initiative influences your prescription behavior the most (Kindly tick the most relevant option)?



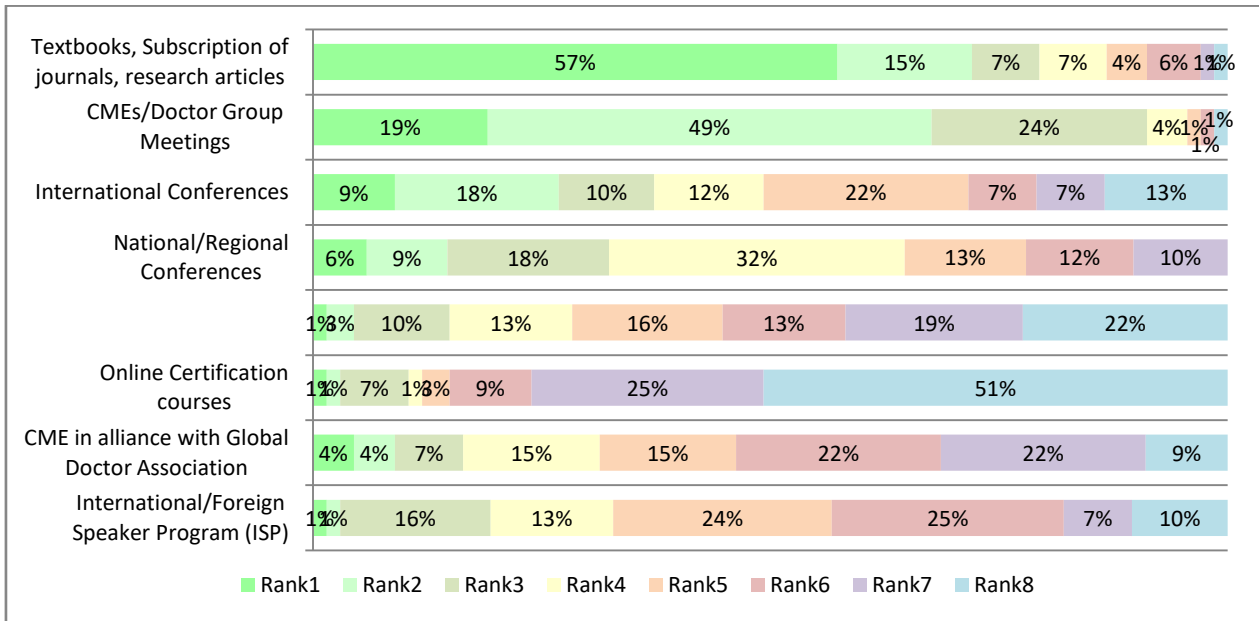
Interpretation:

While in terms of usefulness of the initiative, again Educational initiatives and Patient Engagement appear to be most influential initiatives. 79% of the physicians consider the educational/ academic initiatives the most useful and thereby play a role in influencing the prescription and 43% of physicians consider patient engagement initiatives most useful. The Consultancy services are considered as most useful initiative by 12% of the doctors. The Special

services are perceived as the most important by 9% of doctors and finally the Brand promotional tools are considered as most useful by 6% of doctors.

Section II: Feedback on Educational/Academic Service

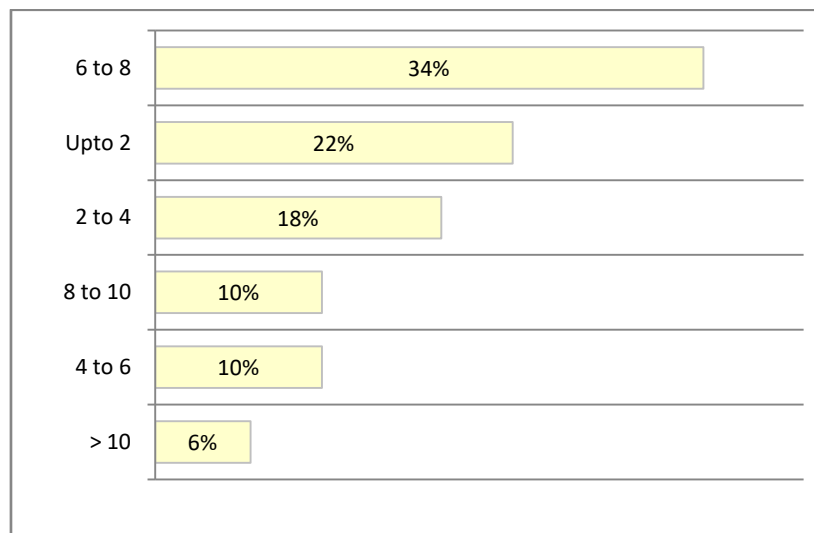
1. Considering the different kinds of tools/initiatives that pharma companies engage you with, what is your opinion about importance of each (Rank order 1 to 8)?



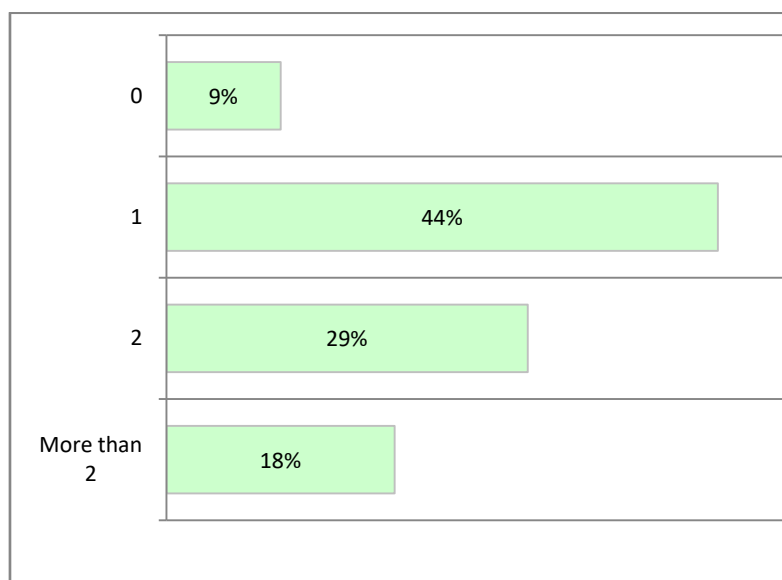
Interpretation:

- The usefulness of the initiatives towards the up gradation of the knowledge has seen highly fragmented response pattern. In Edu./Academic initiatives, Textbooks, Subscription of journals, research articles(57%) and CMEs/Doctor Group Meetings(19%) are considered most important to upgrade scientific knowledge. If the top two ranks are considered as the parameter, The Edu/academic initiatives are considered as most important to upgrade the scientific knowledge accounting to 72% of the physicians and followed by CME's with 68% of the doctors. The International conferences were considered as most useful by 27% of the doctors. Followed by national conferences and other online initiatives.
2. Talking about CMEs, how many invitations do you receive for a CME per week? Out of those invitations, how many do you prefer to attend?

CME's Invitation per month:



CME'S attended per month by the physicians:

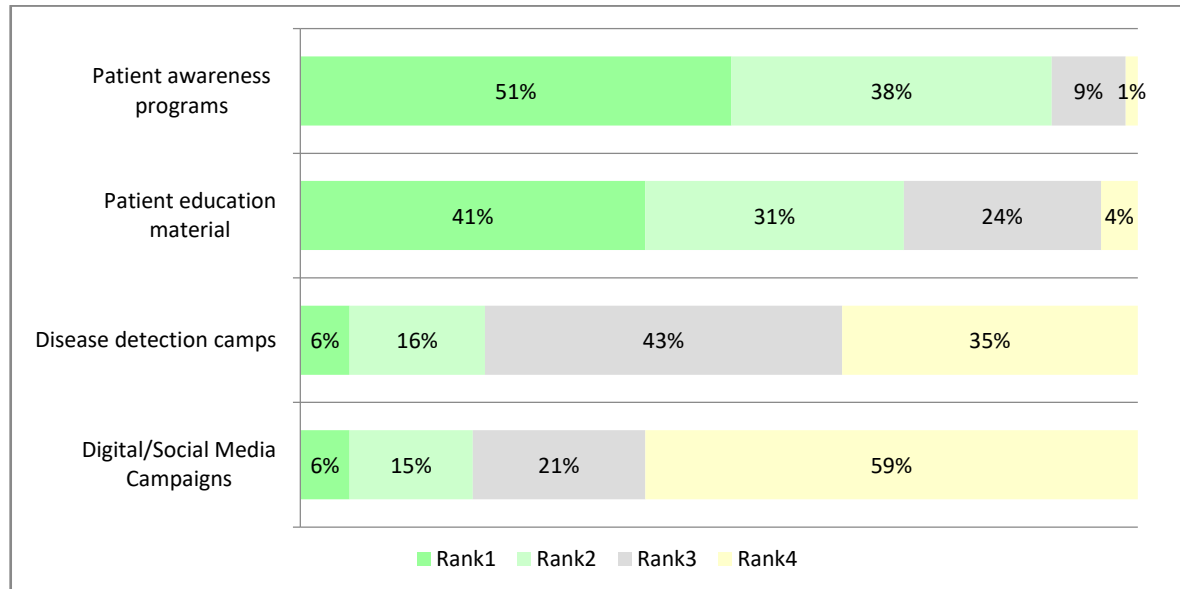


Interpretation:

- If the graphs are seen carefully it can be observed that, 34% of the doctors receive around 6-8 invitations to the continuous medical education, 22% of the doctors get at least 2 invitations per month. But, only 44% of the doctors attend only 1 CME out of the host of invitations they get. 9% of doctors choose NOT to attend any CME.

Feedback on Patient Engagement Initiatives:

- Doctor, amongst the Patient Engagement Activities, according to you which initiative is important to build your connect/influence the patients? (Rank in an order of 1 to 4 for each)

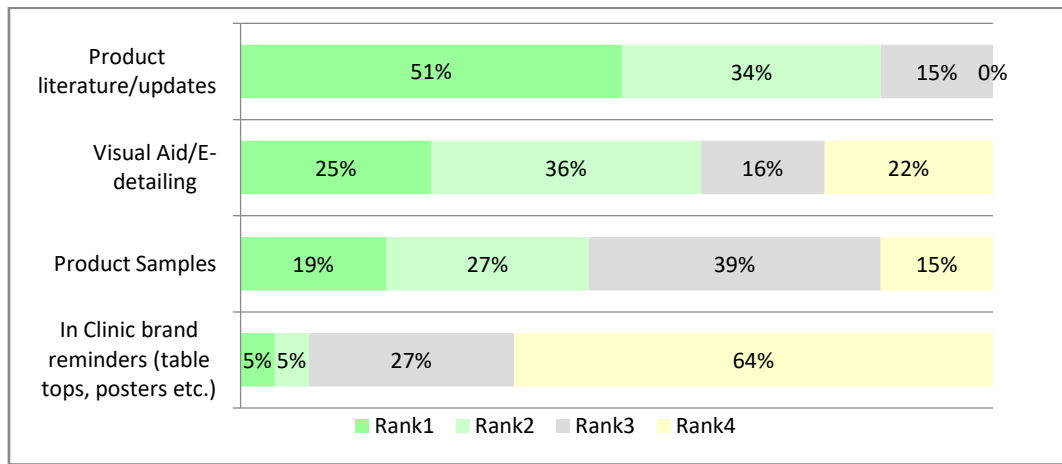


Interpretation:

- Among the Patient Engagement initiatives, Patient Awareness programs (51%) and Patient Education material (41%) are considered most important to build connect/influence the patients. The Disease detection camps and Digital/social media campaigns have bagged 6% each.

Feedback on Brand Promotional Tools:

- Amongst the various brand promotional tools which tool helps you recall the brand name the most (rank in an order of 1 to 4 for each)?

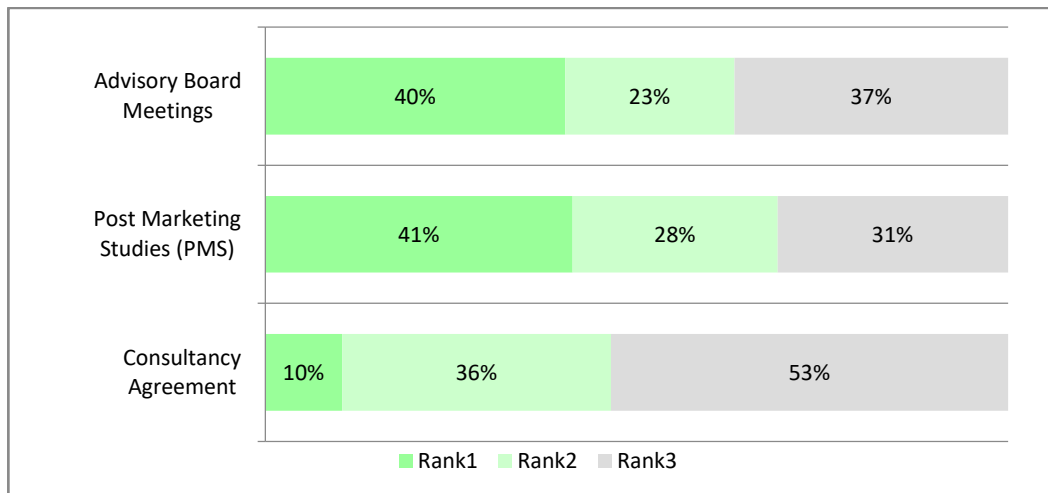


Interpretation:

- Product literature was perceived as Clinical updates: regarding the drugs and studies on it about various types of reactions, efficacy etc. The Clinical updates (51%) are considered most useful to recall brand name, followed by 25% of Visual aid/e-detailing, 19% of Product samples, 5% of Clinical brand reminders.

Feedback on Consultancy to Pharma Companies

- In Consultancy to Pharma Companies given a choice, which initiative would you prefer the most? (Rank in an order of 1 to 3 for each).

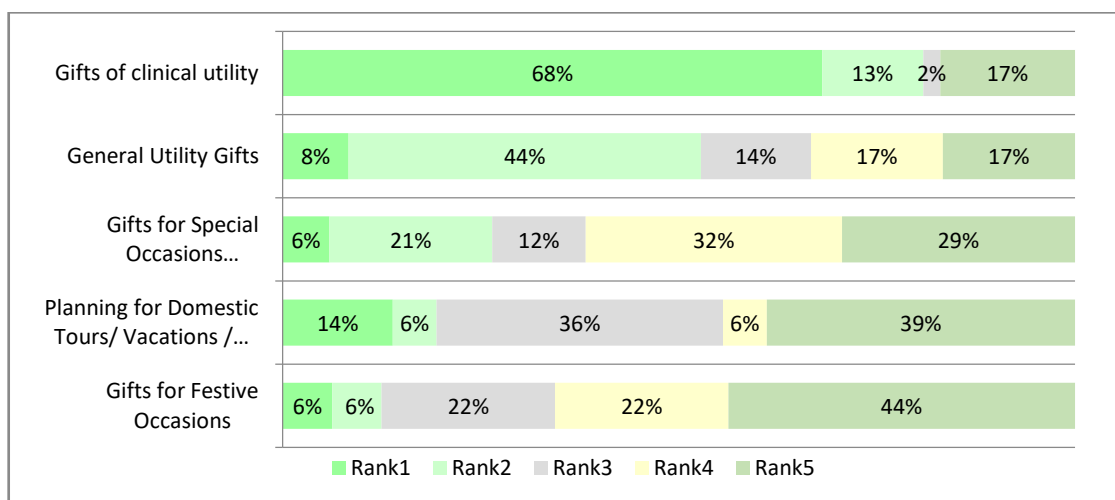


Interpretation:

For Consultancy services, PMS (41%) most preferred followed by Advisory Board meetings (40%).

Feedback on Special Services:

- Doctor, amongst the various Special Services which initiative is the most preferred by you? (Rank in an order of 1 to 5 for each).

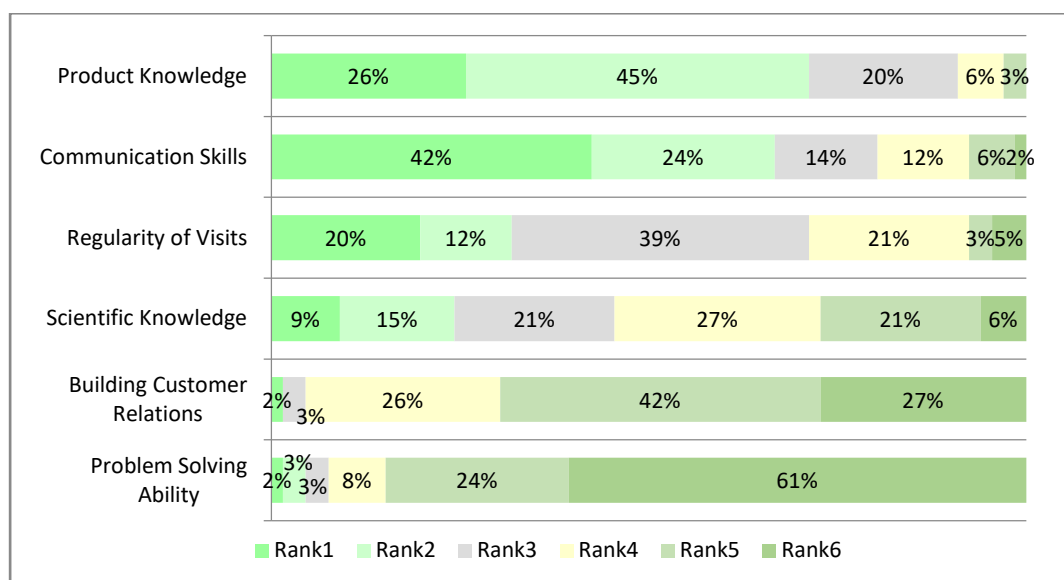


Interpretation:

68% Doctors prefer gifts of clinical utility, followed by 14% of them preferring planned tours and vacations. 8% of them prefer Gifts for general utility. 6% each for Gifts for special occasions and festive occasions.

Feedback on Sales Representatives

- Amongst the various factors to assess the sales reps, which factors do you consider most important (rank in an order of 1 to 6 for each)?



Interpretation:

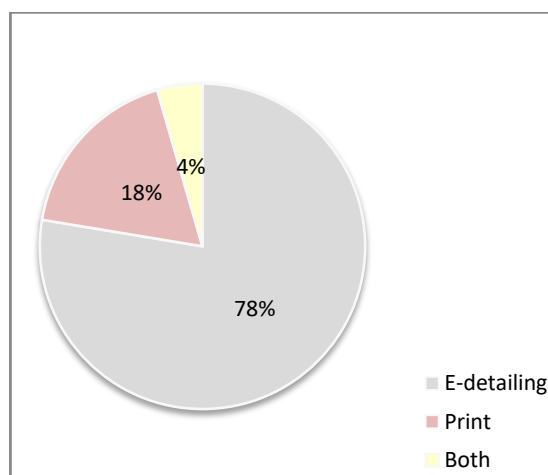
The doctors perceive Communication skills (43%) followed by Product knowledge (26%) as most important factors to assess sales representatives.

20% of the physicians perceive regularity of visits the most important.

9% of them expressed that scientific knowledge as a important parameter. 2% building customer relations and 2% problem solving ability.

Section VIII: Feedback on Digital Initiatives

- With the emergence of technology-based alternatives pharma companies have started engaging with you through various digital means of communication. One of the most popular being E-DETAILING using a tablet device. Which medium of detailing would you prefer the most?

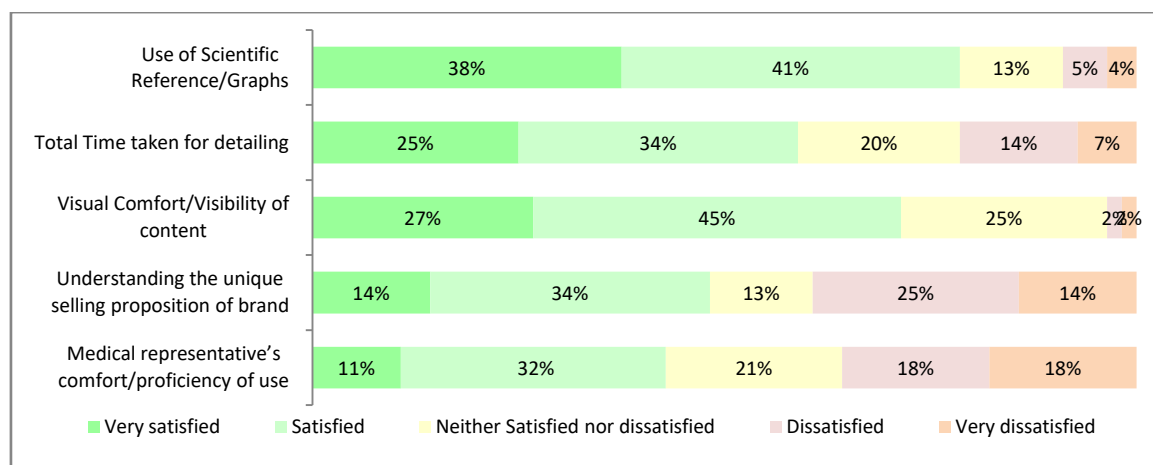


Reasons for preferring e-detailing over print
Eco-friendly/Saves paper
Saves Time
Visually effective
Easy to understand
Informative references available
Convenient
Informative
Graphically explanatory
Technical advancements
Informative graphs available

Interpretation:

More than 3/4th of the doctors preferred E-detailing over Print medium.

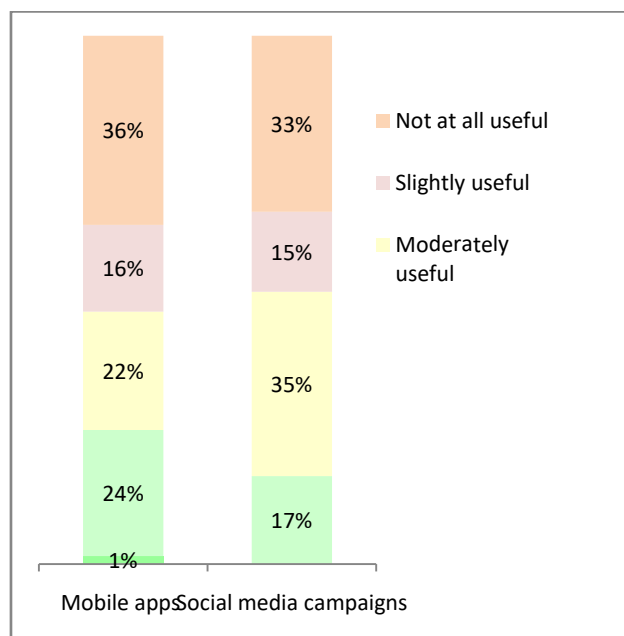
9. Compared to the traditional detailing, can you give us a satisfaction score for E-Detailing on the following parameters, (1 is least satisfied and 5 is most satisfied).



Interpretation:

E-detailing scored lower on Rep's comfort and understanding unique selling proposition of the brand.

10. How useful are the various mobile apps and various social media campaigns launched by pharma companies?



11. What kind of mobile applications do pharma companies engage you with? Can you name and describe any such app which you found most useful in your professional/clinical experience?

Mobile apps names recalled by the doctor
Medscape App
Medline
mobile App by -Sun Pharma, Glenmark, Intas, Zydus, Cipla, Abbott, Femme Health, Aresto, Nestle, USV
Knowledge Genie App
Up to date App
1 mg App
CiplaMed App
Pastest App
Epocrates App
NbN2 App

12. What are your expectations from a knowledge sharing app in your clinical practice?

Expectations from Knowledge sharing app
No time for mobile applications/Not prone to use apps
Apps with regular updates on Drug
Apps with Drug Details: MOA, side effects, contraindications
Apps which are User Friendly
Apps which include Patient awareness and knowledge
Apps Which gives Scientific Knowledge Update
Apps with Drug Details
Apps with Disease specific information
Apps which give access to latest Journals/research articles
Would prefer Google, E-mails and SMS for updates

Insights

After a comprehensive research and analysis about the various promotional/engagement initiatives involved in the sector of marketing and advertisement done to the health-care providers, it is observed that:

1. Among all the initiatives, Edu./Academic initiatives have taken the majority of importance followed by Patient engagement initiatives. However, other services like special services didn't get a considerate importance.
2. In the Education/Academic initiatives, the top initiatives like Textbooks, Subscriptions of journals, research articles and CMEs/DGMs are perceived relatively more important.
3. Around 78% of Physicians receive more than 2 CME invitations per month, while only 44% of the doctors attend 1 CME.
4. At patient level, Physicians prefer more of patient awareness programs, and less disease detection camps.
5. To recall brand names, Clinical Updates are most helpful, followed by Visual aid/ E-detailing, while In-clinical reminders tools are the least preferred.
6. Among the consultancy services, PMS is the most preferred initiative.
7. Sp. Services tools like clinical and general utility gifts are mostly preferred.
8. For Sales reps factors, communication skills is ranked the most important factor.
9. ~75% of Physicians prefer E-detailing over print detailing.

10. Very few Physicians find mobile apps and social media campaigns useful, however most are not able to recall/name any of the apps or campaigns.

VII. RECOMMENDATIONS

1. Within Education/academic initiatives, Latest Journals subscriptions and research articles should be provided regularly to ensure continuous literature up gradation.
2. To ensure participation at CMEs, plan CMEs at convenient time and venue. CMEs should be based on academically advanced or new topics with eminent speakers. Also CMEs/Conferences with accreditations and credit points are doctor's choice.
3. At Patient level, focus on awareness programs and patient Education material should be considered.
4. Among the brand promotional tools, focus should be emphasized on regular clinical updates. Moderate amount of brand reminder tools should be provided to the physicians.
5. Consultancy services should be done more effectively, focusing on advisory board meetings and PMS. Awareness and exposure to the consultancy agreements should be done in order to engage and attract the interested physicians.
6. E-detailing being the preferred medium, improve the proficiency of the sales reps for e-detailing.
7. Mobile apps for doctors can be launched with regular drug updates, apps with access to complete drug information and access to latest journals.

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21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium through which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

INFORMAL GUIDELINES OF RESEARCH PAPER WRITING

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear: Adhere to recommended page limits.



Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.



The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.



Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."



Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

THE ADMINISTRATION RULES

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BY GLOBAL JOURNALS

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Topics	Grades		
	A-B	C-D	E-F
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring



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