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THE EVOLUTION OF MODERN-DAY DRUGS FROM 'DROGUE–MILESTONES, SHORTFALLS AND SCOPE FOR REFORM

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ABSTRACT: The solid drug dosage form, especially the tablet formulations, are made with natural polymer- microcrystalline cellulose (MCC) fibers with many other inorganic agents exclusively to achieve the physical form of the tablet than to enhance the drug efficacy or lowering dosage or frequency of administration. Direct compression is effected directly or after following the procedure of wet granulation. If we explore various digestible fibers from vegetable sources and extract the fibers using the same process as that of MCC, the drug delivery and additional effect of the base can be achieved simultaneously. The review article discusses various ingredients used in tablet formulation and their possible limitations and side effects. Further, the article also elaborates on various physiological, genetic, and tissue-related thrush-holds modifications in the human body *viz*., tachyphylaxis, tolerance, and other changes towards various drugs, and how such modifications pose an additional challenge in the treatment. Such challenges always compel us to look for newer drug molecules where a simple change in the delivery mechanism armamentarium of the tablet formulation may easily address the issue. Target specific delivery of solid drug formulations, especially tablet formulations can be achieved only through timed release and prolonged drug availability than a sudden gush of the drug when formulated with MCC, followed by rapid metabolism or elimination or accumulation of both the drug and the base. The present review article, step by step, narrates the developmental aspects of tablet formulation, advantages, and limitations. Besides the above descriptive account, a clear goal also authors have set to address the above limitations.

INTRODUCTION: Man, in all biological reference points, is also an animal and during early phase of his life (hunter-gatherer, stone age) [1] he was also suffering from very short life expectancy due to predation, natural calamities, diseases *etc*. But the disease due to invisible microbes and other physiological, metabolic, biochemical, anatomical or immunological reasons, he could not comprehend in the early days from the premise of cause and effect [2]. Therefore, he journeyed further to unravel the reasons so that he can devise some solution to his medical problems. That was how his early search for reasons and associated brain development would have taken place.

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Early Inquisitiveness, Beliefs in Mysticism and Spirituality as Cause for Medical Problems: The spirituality and inquisitiveness of the early man should not be looked at from the spectacles of

academic interest, but they were indeed the true stem cells of modern-day science. Since the cause and effect of his problems were unknown to him then, which would have compelled him to hypothesize the existence of an 'unknown' force that was controlling all causes and effects of nature (structure and function of nature) and so shall the life all living being [3].

Divine Worship, Performing Penance and Doing Hymns to Solve Medical Problems: Early man certainly relied upon divine practices such as divine worship, penance, and hymns to solve his medical problems. The Gods in several localities were recognized accordingly to solve different problems, and so were different performances got evolved to deal with different problems [4].

Divine Curse as the Cause of Human Ailments: When solutions become impossible through various instructions of divine persona for certain definite medical problems, a new postulate would have got evolved possibly to justify the defeat as the early wise men would not have been willing to retreat and start a new inquiry. Thus the curse of God would have been integrated into the problem.

The postulate was that the curse of God due to the person's sins mostly in his previous birth, suffering certain medical problems in the present birth [5]. Such a conclusion was stretched further, definitely with undeniable evidence. When the medical problem was of contagious nature, it was forecasted that all those who associate or affiliated with the cursed persons will also suffer from the same medical problem. Hence, the cursed persons must be isolated from society [6, 7]. Tuberculosis, Leprosy, and many other infectious diseases spread to the same family members during close association went strongly in favour of the above postulate as undeniable evidence.

Further dramatization also happened to the above postulate where God's curse to attack a select individual(s) went further to affect the entire community and geographic locality. Best examples were the flowering of bamboo thickets where the nutrient-rich bamboo rice had significantly increased the rat population and the associated spread of rat fever. But the science behind rat fever, where the rat was the main vector, was not known then, and hence the bamboo flowering was taken as the indicator of God's curse, and people used to abandon the village to safe place [8]. During the heavy rainy season, the water stagnation would lead to a high mosquito population and the surge of malaria, which was again considered a divine curse to the entire locality or society [9].

Philosophers as Solution Providers to Medical Problems: When the medical problem becomes obvious and agonizing, and a solution was not available from his proven divine practices, the need for counselors who could provide 'some' wisdom to deal with the real problem, philosophers and spiritual masters, astrologers, *etc*., got emerged [10]. Early philosophers and spiritual masters, instead of focusing too much on the real cause narratives of the problem, have started to force people to believe that both sufferings and kingly life were not totally due to the curse of God but partly due to changes in lifestyle and diet collectively called as 'actions' [11].

From the prefixed acceptance of how our life was shaped and destined by an invisible force to man's attempt to know 'why' and know 'how', had set a new trajectory and man started to deviate into another stream of thoughts to know and search of 'what' would really solve his problems. There began the germination of early medical science, and the dialogue was more towards health and health problems (diseases) than anything else; the medical science got its seeds in the human mind to later grow and expand as what we see today as the advanced medical science [12].

Health Care Practices of Early Man: From offerings to God, performing special worship systems to psycho counselling, man has started to use and explore various natural resources available around him to solve/address some of his health problems [13]. The use of herbal preparations, minerals, metals and several animal-based products all started to occupy his health care space [14]. Ayurveda, Unani, Homeopathy, Traditional Chinese Medicine (TCM), etc., are examples of the above theorization [15].

Designing of Ancient Healing Recipes to Achieve Target Specific Delivery: The ancient healing and folk health practices like Ayurveda, TCM, Homeopathy, Unani, *etc*., clearly tells about

various dosage forms of their preparations such as decoction prepared directly from herbs in water, preparation of the same in oils or in wax to deliver slow-release, in milled form as churna or the calcination, ashing process to dispense the recipe as bhasma or ashes *etc*. [16].

Trekking the Historical Annals to Trace the Inventor of Drug and Modern Medical Science: The word drug originates from the French word 'drogue', which means 'dry herb'. Since collective efforts was happening in different parts of the world simultaneously to solve human ailments and also the possibility of exchange and integration of the wisdom and experiences was also occurring in bits and fragments, we must admit that the history had not left any strong evidence of how by whom and when the modern medicine evolved [17]. Because medical science evolved alongside mysticism and spirituality, the demarcating line even today remains evanescent [18].

Various Dosage Forms of Modern Day Drugs: The modern-day drugs are prepared in different dosage forms such as solid, semi-solid, liquid, powder, and injectable forms [19].

Solid preparations are further classified into

a) Dry powder for topical application.

b) Capsule.

c) Tablet.

d) Dry powder for syrup conversion.

The semi-solid preparations cover creams and lotions. Under the liquid category, tonics, syrups, alcohol-based topical preparations *etc*., are defined.

Distinct and Distinguished Drug Dosage Forms The Real Milestone in Modern Medicine: Depending upon the nature of the disease, the characteristics of the drug, treatment frequency, and duration, convenience, and also to achieve high compliance possibility, different drug dosage forms have arrived. In the case of pediatric use, suppositories have been developed with wax as excipient or base [20]. Among various dosage forms, solid dosage forms offer higher usage ease, compliance, and convenience [21]. The solid dosage forms are highly defined in their strength, and therefore the concentration of the drug to be taken at different time intervals remains accurate. Further, the solid dosage forms, either tablet or capsule, are quite portable even during travel [22].

Limitations and Advantages in Capsule versus Tablet Drug Dosage Form: At the patients' end, both the tablet and capsule would appear the same from the usage per se.

But scientifically, both these forms are different and also can vary vastly in therapeutic effect [23].

Advantages of Capsules:

- Active drug without base is possible.
- Hard gelatin shell will offer oxygen barrier benefits.
- Photosensitive sensitive drugs can be capsules.
- Capsule shell can be opened to get the drug directly.
- Capsules offer less gastrointestinal irritation.
- Odour and taste can be masked fully.
- Oil and fat-soluble nutrients also can be capsules.

Advantages of Tablets:

- High acceptance and elegant to look.
- Desired size, shape, and appearance are possible.
- Scored tablet facilitates the user to limit the dosage.
- High-cost advantage.
- All age group and geography accept chewable tablet form.
- Controlled release/ timed release of the drug is possible.
- Dissolution control for quick, delayed, or extended-release can be achieved through excipient selection.

Disadvantages of Capsules:

- Bulky materials can result in a large capsule size.
- Ingredients can interact with capsule shell.

- Limited fill weight based on capsule volumes.
- Variation in fill volume is known to occur.

Disadvantages of Tablets:

- Potentially poor disintegration in the GI tract unless properly controlled for disintegration.
- Granulation technique can add heat/moisture to components.

List of Excipients used in Tablet Dosage form: Several excipients are used in the formulation of the solid dosage form of modern-day drugs and which are Lactose, directly compressed starch, hydrolyzed starch, Microcrystalline cellulose, Diabasic calcium phosphate dihydrate, Calcium sulphate dihydrate, Mannitol, Sorbitol, Sucrose, Dextrose, natural gums such as Acacia, HPMC, HPC, natural protein – Gelatin, PVP, Sodium alginate, Magnesium stearate, croscarmellose, Crospovidone, Sodium starch glycolate, *etc.* [24-30]. Some excipients are used largely to achieve binding of the tablet formulation during compression or granulation and to give mechanical support to the dosage form. The disintegrants are used to release the drug at the gastrointestinal level. In contrast, glidants, lubricants, and anti-adherents are used during the compression stage to achieve a uniform and even flow of the formulation.

Magnificent and Miserable faces of Modern Medical Science: Although every development may give its best to us but will demand its price, subtly proving the universal law that there is no loss, there is no gain. The infectious diseases mostly may warrant only short-term medication, *i.e.*, until the elimination of the pathogen. In contrast, the non-communicable or auto-immune diseases warrant the use of the drug for lifelong [31-35].

Necessarily the high frequency and prolonged duration of the drug usage is bound to cause the following medical problems such as:

1. Drug resistance by the etiological agent.
2. Tolerance and Tachyphylaxis.
3. Wide range of side effects due to accumulation.

Drug resistance by the etiological agent is attributed more due to the genetic exchange between drug-exposed microbes in the hospital site vis-à-vis the newly infected microbe [36]. Indiscriminate antibiotic use, use of the drug less than the required dose, the duration of use, and the antibiotics' wrong choice collectively contribute to drug resistance among various pathogens [37-40]. Below is a summary of some drug-resistant microbial pathogens encountered by the modern medical world. Methicillin-resistant *Staphylococcus aureus (MRSA), Vancomycin-resistant Staphylococcus aureus* (VRSA), Drug-resistant *Streptococcus pneumonia*, Vancomycin-resistant *Enterococcus* (VRE), Multi-drug resistant *Pseudomonas aeruginosa*, *Clostridioides difficile,* Carbapenem-resistant *Enterobacteriaceae* (CRE), Multi-drug resistant *Mycobacterium tuberculosis* (MDR-TB), Multidrug-resistant *Acinetobacter*, Drug-resistant *Neisseria gonorrhoeae*, *S*taphylococcus epidermidis (coagulase-negative staphylococci, CoNS), Drug-resistant Campylobacter, Fluconazole-resistant Candida, Extended-spectrum Beta-lactamase producing Enterobacteriaceae, Drug-resistant nontyphoidal Salmonella, Drug-resistant Salmonella Serotype Typhi, Drug-resistant Shigella, Erythromycin-resistant Group A Streptococcus, Clindamycin-resistant Group B Streptococcus, *etc.* [41-50].

Milestones and Shortfalls in Drug Formulation to Address Emerging Drug-Resistant Pathogens: Although several attempts to prevent drug resistance were focused more on the active pharmaceutical agent, no significant development has been attempted on the delivery system, especially the excipient armamentarium of the formulation. Nanotechnology has been attempted effectively, but the toxicity and other limitations [51] greatly undermined the benefit of nanotechnology. Rapid absorption, accumulation, and cumulative effects of nano-sized drug particles posed a challenge to our health care system. Although the nano technology enables the drug delivery to achieve effectively in the bacterial and fungal cells, the same effect in mammalian cells heavily limits the benefit of such technology due to potential accumulation and poor elimination [52]. Antibiotics mostly those pose potential limitation in use due to microbial resistance; need re-look at how the

excipient design, dose-release-time-elimination per se, frequency and treatment duration reduction, *etc*., All the above can be achieved through innovation at the excipient level. Botanical fiber/polymer technology may offer a solution to the problem of drug resistance if explored scientifically because herbal fibers, in general, are compatible with the human system and may contribute positively to the gastrointestinal ecosystem; the rate of metabolism of the fibers also can be regulated and thereby the release pattern of the drug can be modified/timed or mutilated, tailored and tutored to achieve both efficacies and to prevent drug resistance. Suppose the drug load is regulated so that the microbe cannot escape and cannot employ the inherited genetic mechanism to develop resistance. In that case, the problem of drug resistance can be avoided at least partially. Therefore, the revolution at the excipient level is necessary and urgent.

Problem of Drug Tolerance and Tachyphylaxis: The tolerance of human cells/organs or the system in toto can be classified into two sub-types: acquired tolerance and innate tolerance [53].

In a simple sense, the acquired tolerance occurs in response to prolonged drug exposure. But the innate tolerance is genetically determined where prior drug exposure may be completely absent. The best examples of innate tolerance are the microbe Leuconstoc sp. to vancomycin, and relatively high tolerance of amphotericin in specific populations are the best examples of innate tolerance [54].

The acquired tolerance of our system to certain drugs is the precursor to tachyphylaxis, and the acquired tolerance is further classified into

1. Pharmacokinetic tolerance is where the system is persistently exposed to certain drugs, which has increased the rate of clearance mechanism of such drugs. The best example is the clearance of ethanol by CYP450 enzymes [55].

2. Pharmacodynamic tolerance where the persistent exposure of the drug results in the production of adaptive homeostatic response, which in turn down-regulates the receptor or the second messenger systems are dampened. This would collectively diminish the pharmacological effect of the drug [56].

3. Receptor down-regulation is another type of drug tolerance where sustained exposure to the drug degrades the receptor either by direct inactivation or endocytosis [57].

4. Receptor deactivation is when the receptor protein is phosphorylated due to sustained exposure. Nicotine receptor to nicotine serves as the best example of the above (Huganir *et al.*, 1987) [58].

5. Receptor subunit modification means the modified receptor complex is selectively allowed to express, diminishing drug sensitivity. GABA-A receptor to benzodiazepines (Littleton, 2001) is the best example [59].

6. Receptor refractory period is a transient period of tolerance where correction is possible post-withdrawal [60].

7. Second messenger change is when the post-receptor dual messenger system is deactivated, for example, β-2-agonists (Haney *et al.*, 2005) [61].

8. Drug target depletion is a process where the key molecule is used up in drug action. Therefore the disease will have diminished activity until the key molecule is re-synthesized or regenerated. Presynaptic noradrenaline depletion due to ephedrine therapy is the best example of the above [62].

9. Physiological tolerance is the effect of the drug where the receptor responses remain the same, but the physiological adaptive mechanism may restore homeostasis, reducing the drug effect. Vasodilator antihypertensive drugs and their distal action on cardiac function and associated blood pressure is the best example for the above [63].

10. Learned tolerance, behavioural tolerance, and conditioned tolerance are other types of acquire tolerance mechanisms our body develops towards drugs on prolonged use.

Besides the above, sensitization does occur towards certain drugs, which is nothing but the reverse of tolerance or intolerance [64]. The amphetamine group of drugs produces such conditions. Similarly, cross-tolerance is also quite common, where the body system develops tolerance to a class of drugs where the exposure is limited only to one of them. The nitrate group of drugs often produces such response [65]. Like tolerance mechanism, the term tachyphylaxis has not been defined in an absolute sense until this date.

In the 14th edition of Katzung, tachyphylaxis is defined as "when the responsiveness diminishes rapidly after administration of a drug, the response is said to be a subject of tachyphylaxis. Peck and Hill have defined tachyphylaxis as "a rapid decrease in response to repeated doses over a short time period". Goodman and Gilman have defined the term tachyphylaxis as a "stat such that the effect of continued or repeated exposure to the same concentration of a drug is diminished" [66-68].

The Key Characteristics of Tachyphylaxis are

1. Repeat administration.
2. Same dose.
3. Diminished physiological effect.
4. Develops over a short period of time.
5. Not dose-dependent (a larger dose of the drug may not restore the effect).
6. Rate-sensitive (requires frequent dosing).

List of Medical Conditions / Drugs That Produce Tachyphylaxis:

a) **Indirect sympathomimetics:** Both Ephedrine and Metaraminol would displace noradrenaline from vesicles; tachyphylaxis occurs due to repeated use because noradrenaline is depleted from the vesicles [69].

b) **Amphetamines:** Methylphenidate use in ADHD-affected children over 3-4 hours is known to cause depletion of neuro-transmitters [70].

c) **Nitroglycerin:** Tachyphylaxis develops over hours of infusion due to mechanisms that nobody seems to be able to agree upon but which are thought to be multiple. Some combination of "pseudo tolerance" with vascular remodeling and physiological tolerance due to counteractive endogenous vasopressors is implicated, but some aspects must also be due to "true" tachyphylaxis because there is cross-tachyphylaxis among different nitrates has been observed [71, 72].

d) **β-2 agonists:** "rapid onset of tolerance" is described, particularly with bronchodilator effects. This develops after 1 dose and takes a week to resolve [73].

e) **Nicotine:** tachyphylaxis develops after a single dose, which occurs by incompletely understood mechanisms. Weirdly, the degree of tachyphylaxis has some sort of regional variability in the brain [74].

f) Non-nitrate vasodilators, e.g. prazocin are subject to tachyphylaxis effects not because of receptor effect but mainly because of the development of a vigorous and counterproductive sympathetic regulatory response vasodilation [75].

Posology: Although Posology has been an evolved science dealing in detail about how medicines are to be dosed for human or veterinary use [76], but has unitarily focused much on the active pharmaceutical agent than the excipient. Posology dwells much into age, gender, body weight, climatic factors, time of administration *etc*., not much has been explored about how the excipients or the backbone system of the solid dosage form can be exploited to deliver the drug effectively and avoid or limit the obvious limitations such as tolerance and tachyphylaxis.

Side-Effects of Drugs as a Shortfall and Scope for New Invention: Several drugs are known to produce serious and severe side effects to the human system, although they may heavily offer remedial benefits to the given medical problem. Drug loss in the visceral system by not appropriating the target site, unwanted accumulation, radiating effects, *etc*., contributes to side effects of the drugs. Common side effects are constipation, skin rashes or dermatitis, diarrhea, dizziness, drowsiness, headache, insomnia, severe

gastric irritation, *etc*. Certain drugs produce severe side effects such as the emergence of suicidal tendencies, abnormal heart rhythms, internal bleeding, cancer, adrenal axis, *etc.* [77].

The most common causes of drug-induced side effects are

a) Drug-drug interaction where, for example, aspirin interacts with warfarin and increases bleeding and bruising [78].

b) Drug-food interaction, for example, the statin group of drugs, would reduce cholesterol levels. The common antifungal drug, Griseofulvin, requires a fatty meal for proper absorption and otherwise may not be absorbed properly [79].

c) Drug-herb interaction is quite common; for example, antidepressant medications often react with St.John's Wort and, in turn would, elicit hyperactive mood in people who suffer from bipolar disorder [80, 81].

Remodelling of Drug Formulation is Need of the Hour and Not Necessarily New Active Pharmaceutical Agents: Most of the drugs invented so far for several medical conditions in the allopathic system of medicine are quite effective and all most all details about their pharmacokinetics, toxicity, mutagenicity, generation toxicity *etc*., are well known. The inevitability of the drugs to save the life of patients is also well known and the science has only very limited option than allopathic drugs. However, the side effects and other medical complications due to certain drugs and at the same time the requirements of such drugs in the therapy of certain diseases for long-term usage definitely warrant new research in remodelling the drug formulation than innovating new therapeutic molecules.

Why Don't we Trace and use Drugue (Dried – Herbs) in Modern Day Drug Armamentarium to Mitigate the Shortfalls: The term drug has evolved from the French word drogue, which refers to dried-herbs [82] essentially authenticate the use of herbal-based preparations to treat several diseases in the ancient times. With the arrival of synthetic chemistry, knowledge about molecular structure, chemical synthesis, *etc*., had begun, replacing the herbal preparations completely from allopathic medical science. However, several excipients, predominantly the microcrystalline cellulose, are a polymer prepared from herbal sources and used as the most common binder in the tablet dosage form. Herbal fibers, herbal proteins, *etc*., can be explored to deliver the drug where the true-bio-delivery system for modern-day drugs needs to be developed.

The bio-delivery system (pro-drug) may help us to reduce toxicity, dosage, frequency of use, physio-chemical and bio-pharmaceutical obstacles, and increased pharmaco-kinetics. Natural Chemistry, pharmacognosy, and synthetic chemistry need to work together to address the shortfalls of modern medical science, and also the use of botanical space needs to be increased.

CONCLUSION: The present review article enumerates various stages of solid drug formulations and the list of base ingredients under the broad title 'excipients' used in tablet formulation. Also has clearly given thrust to research and innovation to identify and study newer base materials from safe vegetable sources as an important future dimension in drug development. Digestible fibers offer enormous health benefits.

If such digestible fibers are used, the tablet drug delivery we can achieve effective and offer the base's additional benefit. Further, the use of several inert agents can also be avoided. Such formulations alone may answer tolerance, tachyphylaxis, and other short-term side effects of various drugs in the future. The review also concludes on how we can minimize the drug load and frequency of usage through slow and sustained release from the base by making the base a mosaic system. The time has come, the base also needs to be treated as 'drug' to increase the pharmacological benefit of the drug.

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