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# Experimental Pharmacology Series

**What is Experimental Pharmacology (Ex-Pharm) Series**

This is a computer assisted learning (CAL) software containing various programs which simulate animal experiments in Pharmacology. These programs can be used to demonstrate effect of drugs on different animals systems. The package is user friendly, highly interactive and full of animated sequences which make simulation appear realistic. The current version of Experimental Pharmacology (Ex-Pharm) Series Software consists of following computer simulated experiments:

**Experiments List**

01-05. Experiment on effects of various drugs (Mydriatic, Miotic and Local Anaesthetic) on rabbit's eye.
- 01 - Epinephrine
- 02 - Atropine
- 03 - Ephedrine
- 04 - Physostigmine
- 05 - Lignocaine

06. Study of analgesic activity with the help of "Tail Flick Apparatus" (Analgesiometer).
07. Study of analgesic activity with the help of "Hot Plate Apparatus" (Analgesiometer).
08. To study analgesic activity by "Writhing Test".
09. Study of "Antihistaminic drugs/Anti allergic" drugs by mast cell stabilization method with help of "Histamine Chamber".
10. Study of "Muscle Relaxant" activity with the help of "Rota-Rod Apparatus".
11. Study of "CNS Depressants & Stimulants" Using "Actophotometer".
12-14 . Study of drugsz acting on CNS (Including Anxiolytic Activity) using following modules
    a. Elevated Plus Maze Method
    b. Pole Climbing Method
    - Evaluation of Anti Psychotic Drugs
    - Evaluation of Sedative Drugs
15. Study of anticonvulsant activity using "Electro Convulsiometer".
16. To study PTZ induced convulsions in mice.
17. Study of effect of hepatic microsomal enzyme inducers on the phenobarbitone sleeping time in mice.
18. To study the action of strychnine/ anaesthetic on frog neurons (excitability).
19. Test for pyrogens using rabbits.
20. Effect of drugs on isolated guinea pig ileum (in vitro).
21. To study respiratory depression effect on rabbit.
22. Study of stereotype and anti-catatonic activity of drugs on mice.
23. Experiments on thyroid and antithyroid drugs - The effect of thyroxin, TSH and propylthiouracil on metabolism.
24. Experiments on blood sugar - The effect of insulin (hypoglycemic activity) and alloxan on blood glucose.
25. Study of anti-inflammatory activity using carrageenan induced paw oedema method
26. Study of diuretic activity using metabolic cage

27-30. Experiments on amphibian nerve-muscle (sciatic nerve and gastrocnemius muscle) preparation.
27. Recording of Simple Muscle Twitch
28. Effect of Temperature
29. Effect of stimuli of increasing frequency.
30. Effect of stimuli of increasing strength.

31-38. Experiment on effect of various drugs on isolated frog's heart. (DRC- Dose Response Curve)
31. Epinephrine
32. Norepinephrine
33. Isoprenaline
34. Calcium chloride
35. Propranolol
36. Acetylcholine
37. Potassium chloride
38. Atropine sulphate

39-53. Experiments on effect of different drugs on dog BP & heart rate.- Virtual Practice- Effects of drugs on the dog BP and heart rate.
39. Epinephrine (Adrenaline)
40. Norepinephrine (Noradrenaline)
41. Isoprenaline 42. Acetylcholine 43. Histamine
44. Ephedrine 45. Phentolamine 46. Propranolol
47. Atropine 48. Cimetidine 49. Carotid Occlusion
50. Central Vagus
51. Peripheral Vagus.- Effects of vasopressor and vasodepressor with appropriate blockers.
52. Virtual Practice- Reversal action of adrenaline on blood pressure and heart rate.
53. Virtual Practice- Reversal action of acetylcholine on blood pressure and heart rate.

54-55. Experiments on "Lagendorff's Apparatus".
- Effect of coronary vasodilators on isolated heart
- Effect of parasympathomimetics

56. Experiment on bioassay of histamine on the ileum of guinea pig.

57-60. Bioassay of acetylcholine on the isolated rectus abdominis muscle of frog
(a) By Matching Method (b) By Interpolation Method
(c) By 3 Point Method (d) By 4 Point Method.

61-64. Bioassay of oxytocin on the isolated rat uterine horn by following methods
(a) By Matching Method (b) By Interpolation Method
(c) By 3 Point Method (d) By 4 Point Method.

65-68. Bioassay of serotonin on the isolated rat fundus strip by following methods
(a) By Matching Method (b) By Interpolation Method
(c) By 3 Point Method (d) By 4 Point Method.

69. To record the DRC and to determine the pD2 value for acetylcholine on frog rectus abdominis muscle.
70. Determination of pD2 value of histamine on guinea pig ileum.
71. Determination of pD2 value of serotonin on rat stomach (fundus part) strip.
72. Determination of pA2 Value of prazosin using rat anococcygeus muscle (by Schilds plot method)
73. Study of anti-ulcer activity - using pylorus ligation method.
74. Evaluation of effect of acetylcholine (spasmogens) using rabbit jejunum.
75. Evaluation of effect of different drugs on ciliary motility.
76. Evaluation of effect of saline purgatives on frog intestine.

77-78. Determination of acute irritation of a test substance.
- Skin irritation (Including edema formation)
- Eye irritation *In addition to above mentioned interactive experiments, modules are provided for following:

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80. Blood withdrawal techniques.
81. Methods of anaesthesia & euthanasia.
82. Animals used in experimental pharmacology.
83. Instruments used in experimental pharmacology.
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# INDEX

## ARTICLES



**Material and Methods**: This section may be divided into sub-sections if it facilitates better reading of the paper. The research design, subjects, material used, and statistical methods should be included. Results and discussion shall not be drawn into this section. In human experimentation, ethical guidelines shall be acknowledged.

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# The Role of Interferon in Modern Medicine: Clinical Applications and Therapeutic Potential

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**Abstract:**
Interferon (IFN) is an antiviral substance that was discovered in 1957. Interferons are multifunctional cytokines widely used in clinical settings as an anti-viral drug. Interferon (IFN)-α and -β are produced by virus-infected cells; IFN-γ is produced as a primary response of T lymphocytes to mitogenic stimulation. Any type of IFN is a (glyco) protein with a molecular weight of about 20,000 kDa. IFNs act by binding to cell surface receptors and triggering activation of IFN-responsive genes, probably via specific base sequences located in the 5′ non-coding region of such genes, resulting in changes in cell function. The advance in the basic research of IFN has revealed the action mechanism of its antiviral effect at a molecular level and provided wide clinical applications. IFN is known to have various biological activities including antiviral effects, anti-tumor effect, Hepatitis, Multiple sclerosis and Granulomatous diseases etc. IFN is considered to exert its action by not only directly inhibiting viral proliferation, but also stimulating cytotoxic T cells, natural killer cells, and macrophages.

**Key words**: Interferon, Types of IFN, Clinical Application

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**INTRODUCTION:**

Interferons were the first family of cytokines to be discovered. In 1957, British virologist Alick Isaacs and The Swiss researcher Jean Lindenman, at the National institute for medical Research in London did an experiment using chicken cell cultures. Found a substance that interfered with viral replication and was therefore named Interferon. Nagano and kojima also independently discovered this soluble antiviral protein.[1]

In 1957, Alick Isaacs (1921–1965) and a post-doctoral Swiss student, Jean Lindenmann, were studying the phenomenon of "viral interference"—the ability of one virus to inhibit the replication of another virus.[2]

In 1986, 29 years after the discovery of interferon, the development of genetic engineering enabled the production of large quantities of high-quality interferon. This allowed for its widespread application in both research and clinical settings, which ushered in a new era for interferon.[3]

Milestones in interferon research up to the year 2000 are summarized in table 1.

**Table 1: Milestones of interferon research**[3,4,5,6]

| Years | Important events |
|---|---|
| 1957 | Virus-induced IFN |
| 1964 | IFN-mediated antiviral protection of mice |
| 1967 | Non-viral IFN inducers: ds RNA |
| 1969 | IFN-antitumor activity in mice |
| 1970 | IFNs: a family |
| 1973 | Clinical trials with impure IFNs |
| 1975 | IFNγ (immune IFN) |
| 1976 | IFN has antiviral effect in HBV-infected humans; Immunological effects of IFNs |
| 1977 | Human antitumor effects |
| 1980 | Purification, cloning, sequencing of IFN-α1, IFN-α2, IFN-β; Endothelial cell motility |
| 1981 | Clinical MS effects; Recombinant IFN cancer clinical trials |
| 1982 | IFN-γ cloned |
| 1983 | IFN gene promoter; First ISG cloned (2-5A synthetize) |
| 1984 | ISG promoters |
| 1986 | IFN-α2 FDA approval for hairy cell leukemia |
| 1987 | IFN anti angiogenic effects |
| 1988 | IFN-γ receptor cloned |
| 1989 | IRFs identified |
| 1990 | IFN-α2 FDA approval for HCV; Clinical pegylated IFN; IFNα receptor cloned |
| 1992 | STAT family of transcription factors; JAKs/STATs cloned |
| 1993 | IFN-β FDA approval for MS |
| 1995 | IFN-γ receptor complex crystal structure |
| 1997 | Toll receptor cloned |
| 1998 | Hundreds of ISGs |
| 2000 | Proval IFN-γ FDA |
| 2001 | Toll-like receptor 3 shown to recognize double-stranded RNA |
| 2003 | the discovery of a third type of interferon, IFN-λ |
| 2004–2005 | Cytosolic helicases RIG-I and MDA5 can trigger IFN production in response to double-stranded RNA or RNA viruses |
| 2013 | the discovery of another type of interferon, IFNL4 |
| 2017 | was made of amino acid and complementary DNA sequences of ovine trophoblast protein-1 (oTP-1), later renamed as interferon-tau (IFNτ) |






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(31.11±0.12-39.52±0.44 m. Pas). This low viscosity is not suitable for topical application. So, prepared nanosponges were added to the gel matrix using different combinations of polymers to improve the viscosity. F4 was chosen as an optimized formulation—the *ex vivo* permeation data along with CLSM photographs showed penetration into deeper tissue. Further, antifungal activity with a zone of inhibitions for all prepared gels were found effective against fungal strain.

## Conclusion

The findings conclude that the prepared nano gels have potent antifungal effects that need exploration for research in future studies in clinical trials. All the prepared herbal gels are in good condition till today (November 2024). Carbopol-934 gelling agent showed promising results and avoided side effects like skin, eye irritation and environmental hazards to aquatic animals. CLSM photographs for the *ex vivo* permeation study suggested that the formulation could penetrate deeper tissues and was effective for topical delivery.

## Acknowlegedments

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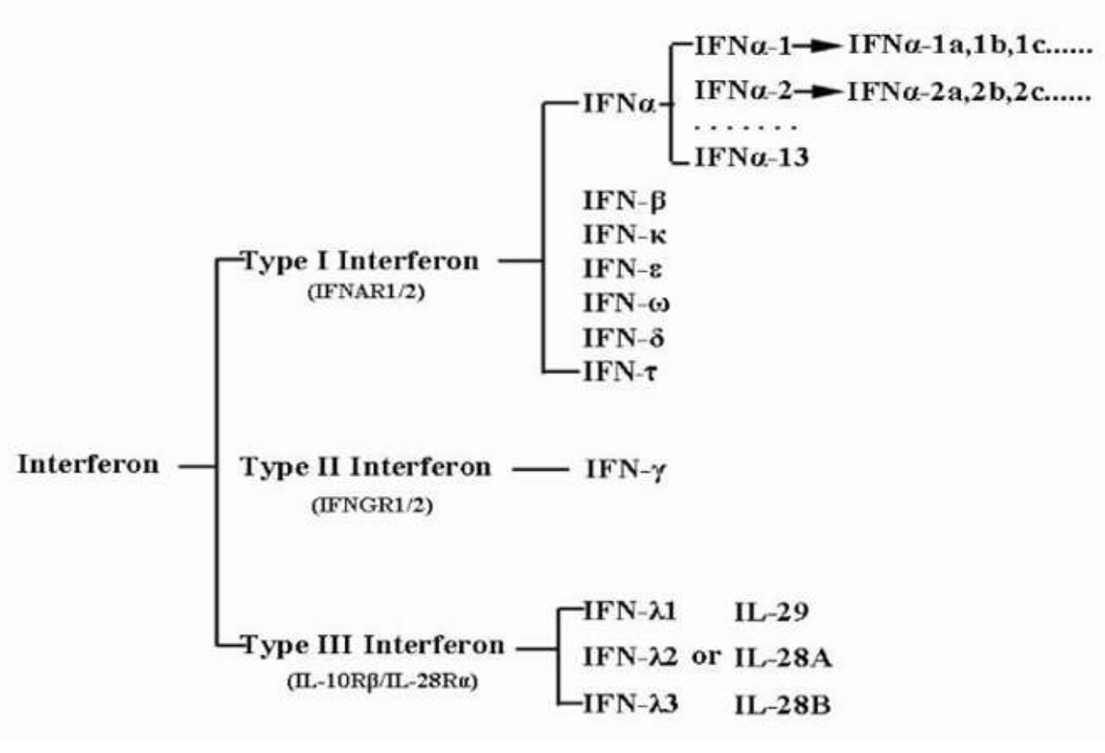
## CLASSIFICATION OF INTERFERONS:

**Based on the type of receptor**

Based on the type of receptor through which they signal, human interferons have been classified into three major types. [3,7,8]




## TYPES 1 IFNS:

They are mainly involved in the innate immune response against viral infections. They come in 13 sub types namely IFNA1, IFNA2, IFNA4, IFNA5, IFNA6, IFNA7, IFN8, IFNA10, IFNA13, IFNA14, IFNA16, IFNA17, IFNA21.[9]During most viral infections, the immediate host response is characterized by an induction of type I IFN. These cytokines have various biological activities, including anti-viral, anti- proliferative and immunomodulatory effects. After induction, they bind to their IFN-α/β receptor, which leads to downstream signalling resulting in the expression of numerous different IFN-stimulated genes. These genes encode anti-viral proteins that directly inhibit viral replication as well as modulate immune function.[10] These genes are found together in a cluster on chromosome 9.IFN-α is also made synthetically as medication in hairy cell leukemia. The International Non-proprietary Name (INN) for the product is interferon alfa. The recombinant type is interferon alfacon-1. The pegylated types are pegylated interferon alfa-2a and pegylated interferon alfa-2b.[11]

## TYPE 2 IFNS:

In general, interferon-beta (IFN-β) is the main subtype made by fibroblasts and epithelial cells, that is, cells from solid tissues, whereas IFN-αs are more efficiently induced in blood leukocytes. IFN-β produced by human fibroblasts in response to viruses or double stranded (ds) RNA inducers is a protein antigenically distinct from the other group of type I Interferons, the IFN-α subtypes.[12]They are involved in the innate immune response as IFN alpha. The sub types namely IFNB1, IFNB2, IFNB3 are present. IFNB1 is used in the treatment of multiple sclerosis as it reduces the relapse rate. But it is not the appropriate treatment for patients with progressive, non-relapsing forms of multiple sclerosis. It is momeric and a globular protein with 5 alpha helices with a molecular weight of 20kDa.[9]

**TYPE 3 IFNS:**

TypeI I IFNs (IFN-λ1, 2 & 3) were discovered as interleukin (IL)-29, 28a & 28b and have many immune activities in common with type I IFNs .[13,14] A new member, termed IFN-λ4, was later discovered and can be expressed only by individuals who carry the gene symbol (IFNL4-ΔG allele [rs368234815]) It is involved in the regulation of immune and inflammatory responses. It also has anti- tumor effect. It is a dimer of two sub units each of molecules designated IFNGR1 and IFNGR2. Mature IFN Gamma is an antiparallel homodimer. There is only one type of IFN Gamma.[9]

**Based on their cellular source**

Interferons are classified into three main types based on their cellular source and inducing agents:

**Table 2: Classification of interferons**

| Characteristics | Interferon-alpha | Interferon-beta | Interferon-gamma | Interferon-lambda |
|---|---|---|---|---|
| Other designation | Intron-A, pegasys. consensus | IFN-b2. At one time mistakenly called IL-6 | Macrophage activating factor: Immune interferon | IL28A, IL28 B IL29, IFNA14 |
| Number of genes | 24 (+)? | 1 | 1 | 3 (+) |
| Chromosomal location | 9p22 | 9p21 | 12q14 | 19q13.13 |
| Introns in gene | None | None | Yes | Possibly yes |
| Cell of origin | Leukocytes | Fibroblasts | Lymphocytes, macrophages, NK cells, dendritic cells | Epithelial cells |
| Inducers | Virus, dsRNA | Virus, dsRNA | Antigens, mitogens, other interferons, cytokines, IL2, NK receptors | Virus |

**MECHANISM OF ACTION:**

The interferons (IFN) are one of the body's natural defensive responses to such foreign components as microbes, tumors, and antigens. The IFN response begins with the production of the IFN proteins (α, β, and γ), which then induce the antiviral, antimicrobial, antitumor, and immunomodulatory actions of IFN.[15]

**INTERFERON RECEPTORS:**

IFNs exert their actions through cognate cell surface receptors that are largely species specific.[16]The alpha, beta, and omega IFNs appear to have a common receptor consisting of two subunits, IFNAR-1 and IFNAR-2.[17]IFN-γ binds to a receptor distinct from that used by IFN-α/β. Two kinds of subunits also constitute the IFN-γ receptor complex.[16] IFN signaling involves an IFN-mediated heterodimerization of the cell surface receptor subunits, IFNAR-1 and IFNAR-2 with IFN-α/β and IFNGR-1 and IFNGR-2 with IFN-γ.[17]





· **Measurement of Zone of Inhibition for Antifungal activity**

Antifungal studies were determined by employing the agar well diffusion method using different Petri dishes having a cork bore size of 6mm. The fungal strain *C. albicans*, were inoculated as per the standard protocols for cultivating microbial cultures. 0.5mL of culture (*C. albicans*) was placed in the centre of a sterile Petri plate using a sterile graduated pipette and placed in a laminar flow chamber. The agar media was allowed to solidify. After the media was solidified, 4 wells of cork borer 6mm in size were placed in the center. The first well consists of 100mg Carbopol gel containing drug-free nanosponges, which acts as a negative control (labeled as A). The second well contains the marketed cream of Voriconazole (labeled as B). The third well contains Carbopol gel containing drug encapsulated (1:1), equivalent to 100mg voriconazole nanosponges (labeled as C). All the petri plates were incubated at 37ºC for 48 hours [18, 19]. After 48 hours, the zone of inhibition was measured, and results were reported, depicted in Figure 5.

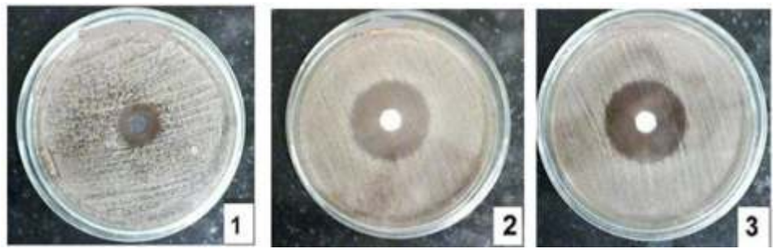



**Figure 5: Comparative ZOI (Antifungal activity), 1: Carbopol gel free nanosponges (ZOI: 2.8±1mm), 2: Voriconazole marketed cream (ZOI: 19±3mm), 3: Voriconazole nanosponges loaded Carbopol gel (ZOI: 21.2±2mm**

**Results**

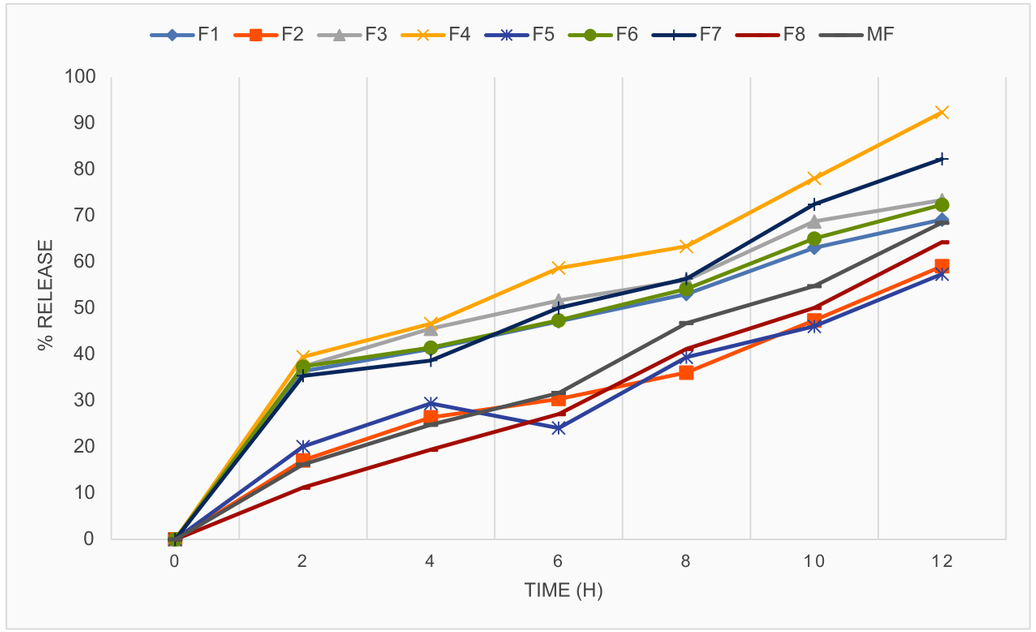
The mean particle size, P.D.I., and zeta potential of the prepared nanosponges suggested the particles are good enough to maintain physical stability. The zeta potential indicated that the physical stability of nanosponges was excellent (Table 2, Figure 1). The *in-vitro* release kinetics data were constructed for zero order, first order, Higuchi, and Korsmeyer-peppas (Figure 2). The results suggested that $R^2$ value 0.9914 for zero order shows linearity and provided controlled release up to 12h. Korsmeyer-Peppas release showed an $R^2$ value of 0.9863, n=0.6693, more than 0.5 (non-fickian diffusion) following the super case-II transport mechanism. The S.E.M. and TEM photographs suggested a spherical, spongy, and good structural composition of prepared nanosponges with a definite boundary (Figure 3). The antifungal results suggested that the optimized formulation (F4) of voriconazole loaded Carbopol gel showed better potency than the marketed formulation, showing promising antifungal effects against *C. albicans*.

**Discussion**

Optimized formulation (F4) showed narrow and uniform particle size distribution. Zeta potential ranges from (19.62) - (32.3 mV), suggesting the physical stability. Further, particle size ranges from 129.7-178.3 nm, indicating that particle size increases as the ratio of polymer increases; further, at lower drug concentrations and high polymer ratios, less polymer is available to encapsulate the drug, and the thickness of the polymer membrane decreases. The increased stirring speed suggested reduced particle size and improved % yield. The study further revealed that the polymer adheres to the stirrer surface at high speed and decreases % E.E. (entrapment efficiency). F8 formulation showed a decreased % E.E. for voriconazole compared to F4 by varying the speed. Another critical factor determined during the formulation of nanosponges was with increased D.C.M. volume, the viscosity of formulated dispersion was reduced, ranging from

**Table 5: *Ex-vivo* permeation Data**

| *Ex-vivo* permeation Voriconazole | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Time (h) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | MF |
| 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 36.4 | 17.1 | 37.4 | 39.5 | 20.1 | 37.4 | 35.4 | 11.2 | 16.2 |
| 4 | 41.2 | 26.4 | 45.6 | 46.7 | 29.4 | 41.5 | 38.7 | 19.4 | 24.8 |
| 6 | 47.2 | 30.4 | 51.7 | 58.7 | 24.1 | 47.4 | 50.1 | 27.1 | 31.7 |
| 8 | 53.1 | 36.1 | 56.1 | 63.4 | 39.4 | 54.2 | 56.4 | 41.2 | 46.8 |
| 10 | 63.1 | 47.4 | 68.8 | 78.1 | 46.1 | 65.1 | 72.5 | 50.1 | 54.8 |
| 12 | 69.2 | 59.1 | 73.4 | 92.4 | 57.4 | 72.4 | 82.3 | 64.3 | 68.5 |



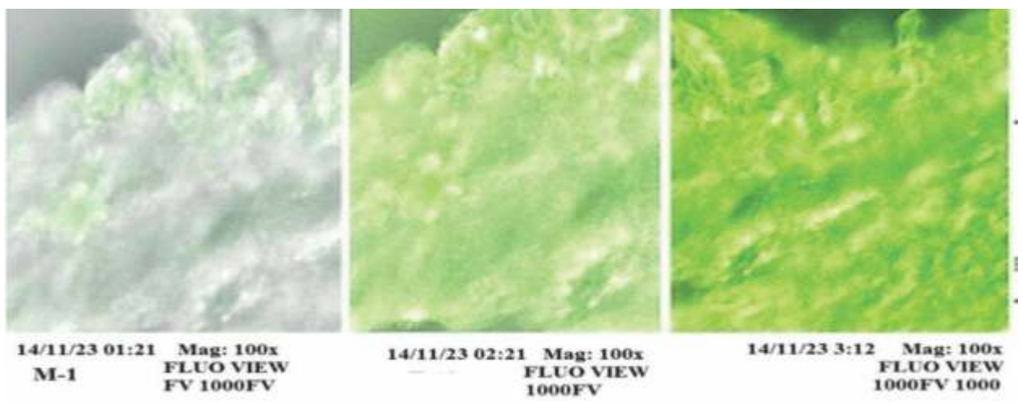




**Figure 4: *Ex vivo* permeation graph of different formulation and CLSM photographs**

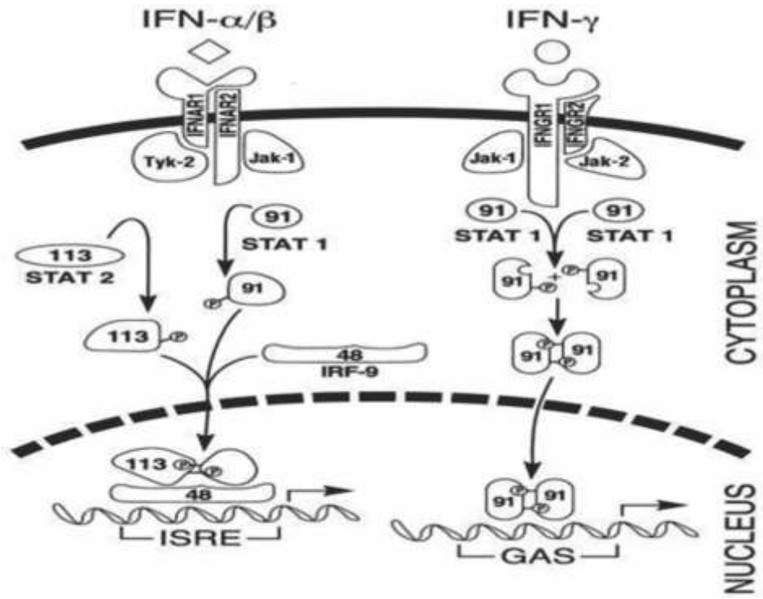




**JAKS AND STATS PATHWAY:**

IFN-mediated signaling and transcriptional activation of cellular gene expression are best understood in the context of JAK-STAT pathway proteins.[19] The signal transducer and activator of transcription (STAT) family of proteins are latent cytoplasmic transcription factors that become tyrosine phosphorylated by the *Janus* family of tyrosine kinase (JAK) enzymes in response to cytokine stimulation. There are seven known members of the STAT protein family, Stat-1, Stat-2, Stat-3, Stat-4, Stat-5a, Stat-5b, and Stat-6, and four members of the JAK family, Jak-1, Jak-2, Jak-3, and Tyk-2. Different members of the JAK and STAT families have distinct functions in cytokine signaling. Receptor-associated JAKs are activated following binding of IFNs to their cognate multi-subunit transmembrane receptor. Of the known JAKs and STATs, the Jak-1, Jak-2, and Tyk-2 kinases and the Stat-1 and Stat-2 transcription factors play central roles in mediating IFN-dependent biological responses, including induction of the antiviral state.[20,21,22]Overlapping subsets of JAKs are involved in signaling by the two types of IFNs. Jak-1 and Tyk-2 kinases function in IFN-α/β signaling, and the Jak-1 and Jak-2 kinases function in IFN-γ signaling .[17,23]

Figure -1 Mechanism of action of interferon alpha,beta and gamma.[24]




**CLINICAL APPLICATION OF INTERFERON:**

The first interferon to be investigated was a natural leukocyte IFN Alpha. A mixture of acid stable IFNs produced by white blood cells exposed to Sendai cells were investigated in vitro. The clinical application of IFN are as follows:

1. Hairy cell leukemia
2. AIDS related Kaposi's sarcoma
3. Chronic myelogenous leukemia
4. Malignant melanoma
5. Condylomata acuminate
6. Chronic hepatitis C
7. Chronic hepatitis B
8. Multiple sclerosis
9. Chronic granulomatous disease

**1. Hairy cell leukemia:**

Alpha interferons effectively reduce leukemic infiltrates in the bone marrow and other organs with attendant resolution of cytopenias. Alpha interferons have shown efficacy in the treatment of patients in all clinical stages of the disease including those previously untreatedand may become the treatment choice for hairy cell leukemia.[25]The first substantial therapeutic intervention in this previously "untreatable" chronic leukemia was made with the introduction of interferon-α (IFN-α) in 1984 with response rates of 80–90 % (≤90 % partial remissions, PR; ≤40 % complete remissions, CR) and extension in survival.[26,27,28] In the absence of long-term safety data for these novel agents, however, induction and maintenance therapy with IFN-α may still represent a viable therapeutic option when the profound immunosuppressive side effects of purine analogues are to be avoided, e. g., in the presence of significant comorbid conditions and ongoing infectious complications.[29]Alpha interferon has been shown to induce significant responses in HCL patients. With interferon treatment the platelet count normalizes first, followed by the haemoglobin and neutrophil counts. The number of hairy cells in the bone marrow decreases and granulocytic, erythroid and megakaryocytic cells increase.[30]Treatment of patients suffering from hairy cell leukemia (HCL) with human recombinant alpha IFN results in significant tumor regression, with clinical improvement in a high percentage of cases. Binding of human alpha 2 IFN to circulating hairy cells was analyzed before and during IFN therapy in ten patients selected on the basis of high numbers of peripheral hairy cells.[31]alpha-interferon receptor analysis, oncogene expression, study of the sensitivity of hairy cells to natural killer cells, and the effects of interferon on T-cell receptor gene rearrangement and on the function of T-cell clones.[32]

**2. AIDS related Kaposi's Sarcoma.**

Interferon alfa (IFNA) was one of the first agents to be used therapeutically in AIDS-associated Kaposi's sarcoma (KS) more than 25 years ago, and induces tumor regression in a subset of patients. Although much has been learned about the clinical role of IFNα in KS treatment, little is currently known about the mechanism(s) by which IFNA causes KS regression. This is despite a growing understanding of both KS pathogenesis and relevant IFNA activities. To a large extent other agents have supplanted IFNA as treatments for KS, but there may still remain a therapeutic role for IFNA, possibly in combination with other agents targeting angiogenesis and/or HHV-8-encoded human gene homologs that encode proteins involved in cell cycle regulation and signaling.[33] Interferon alfa is most effective when the CD4 count is greater than 150-200/μL or when administered in conjunction with antiretroviral therapy. Combination interferon and chemotherapy has been no more effective than chemotherapy or interferon alone.[34]

**3. Chronic Myelogenous leukemia:**

Interferon alfa (IFNa) has been extensively studied as treatment for patients with chronic myeloid leukemia (CML) since 1981, initially using partially purified IFNa , followed by recombinant IFNa-2a .35Biological agents have long been used in the treatment of cancer, and interferon-alpha was the first human cytokine to be widely studied in this setting. Chronic myeloid leukemia (CML) is a hematopoietic stem cell disorder for which interferon-alpha has demonstrated substantial activity. In the 1980s interferon-alpha became first- line therapy for patients with chronic-phase CML, not eligible for allogeneic stem cell transplantation.36The following studies using natural as well as recombinant IFN-alpha preparations confirmed the high remission rates with this therapy (70% CR and more than 30% cytogenetic responses) in patients with CML. Flu-like symptoms are recorded in more than 90% of the patients in the initial therapy phase. IFN-alpha seems to have no activity in patients in accelerated phase or blast crisis. High doses of IFN, i.e. more than 4,000,000 per day, achieve high response rates.[37]

Several randomized clinical trials in chronic myeloid leukaemia have reported better patient survival with interferon alfa than with standard chemotherapeutic agents, such as busulfan or hydroxyurea. [38]

**4. Malignant Melanoma:**

According to the national cancer institute, melanoma is defined as a form of cancer that begins in melanocytes. Melanocytes are cells that make the pigment melanin. Melanoma may begin in a mole (skin melanoma) but can also begin in other pigmented tissues, such as in the eye or in the intestines.[39] The use of high dose of IFN2b for the adjuvant therapy of stage IIB and III melanoma patients was approved by FDA in 1995. A study by Kirkwood et al.[40] in 287 patients





· **Viscosity, Extrudability and Spreadability Measurement**

The viscosity measurement of the gel was determined using a Brookfield Viscometer (LVDV- E) with spindle TS6 at 25°C with 50rpm. The prepared nano gels were filled in a capillary tube and sealed. The tube was gently pressed to extrude the gel. Spreadability was measured by placing gel between two slides; one end was tied with thread, and the other side weight was placed. The time taken by the two slides to slip from the prepared gel determines the spreadability, calculated using the formula:

Spreadability (S)= WXL/ T, W: Weight (g) on slide (upper), L: Length (cm) on slide (upper), T: Time (min) taken to separate slides (upper and lower) (Table 4).

**Table 4: Evaluation parameters of prepared gel**

| S. No | Gel Codes | Extrudibility (g. sec) | Appearance | Homogeneity | Viscosity | pH | Skin Toxicity | % Drug content (VOR) |
|---|---|---|---|---|---|---|---|---|
| 1 | A | 0.94 | Smooth, transparent, White | Excellent | 1314.4±0.47 | 6.4± 0.47 | No | 90.05 |
| 2 | B | 0.81 | Smooth, transparent, White | Excellent | 1011.5± 0.11 | 6.1± 0.11 | No | 91.11 |
| 3 | D | 0.85 | Smooth, transparent, White | Excellent | 1106.4± 0.02 | 7.1± 0.15 | No | 93.14 |

A: Carbopol gel-934 (mg) free nanosponges, B: Marketed cream, C: Voriconazole loaded Carbopol gel (All 100 mg)

· ***Ex vivo* permeation studies**

Goat animal abdominal skin was collected from the slaughter house and hydrated with phosphate buffer 7.4 pH for an hour. Hairs were removed using a razor, subcutaneous fat tissues were exposed, and around 2.5cm$^2$ area was cut. Then, the skin was mounted on a Franz diffusion cell, and around 2mL nanodispersion was applied to the stratum corneum of abdominal skin facing the donor compartment. 30 mL buffer was filled in the receptor compartment, and the temperature was kept at 32±0.5ºC, agitated at 100rpm on a magnetic stirrer. The drug content was evaluated at regular intervals. An aliquot sample of 2mL was withdrawn and replaced with a fresh buffer. Using a UV-visible spectrophotometer at 283nm the drug content of samples was estimated (Table 5). Furthermore, Confocal Laser Scanning Microscopy (CLSM) An *ex vivo* CLSM study was performed to check the permeation for the optimized formulation [14-17], presented in Figure 4.

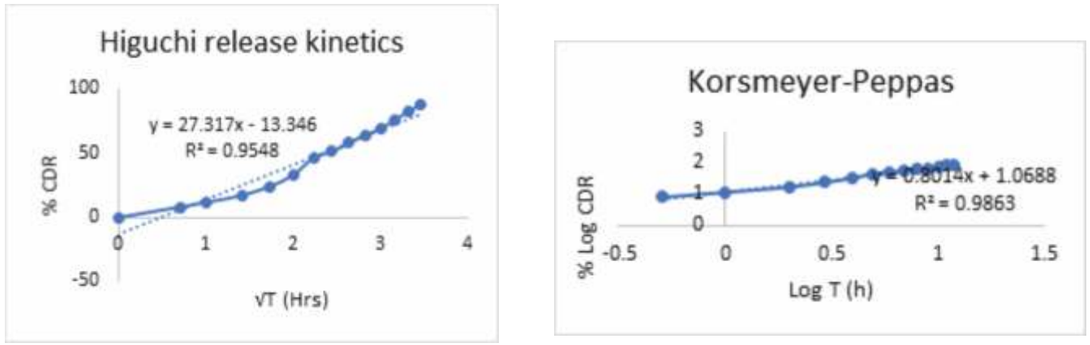



**Figure 2: Release kinetics Graphs of Optimized formulation (F4)**

**Surface morphology of Optimized formulation (F4)**

· **SEM and TEM Studies**

Scanning electron microscopy (S.E.M.) and Transmission electron microscopy (TEM). analysis of an optimized formulation was performed to study the surface morphology (JSM 6100 JEOL, Tokyo, Japan) [13] and shape of particles (Figure 3).

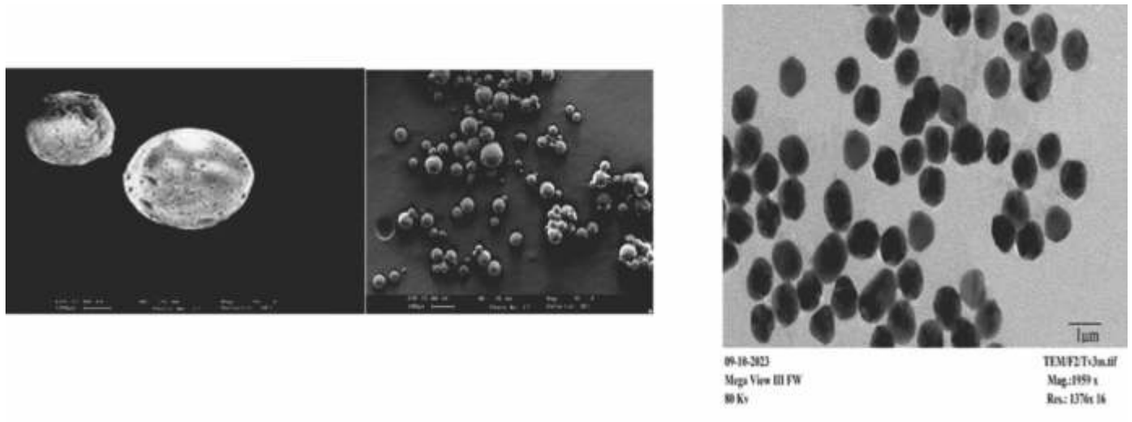



**Figure 3: SEM and TEM images of Optimized formulation (F4)**

**Formulation of Gel base**

Carbopol-934 was dissolved by slowly adding it to 70mL of distilled water, allowing it to swell for 3 hours. The polymeric solution of Carbopol-934 was then stirred on a magnetic stirrer for 3 hours to form a viscous, transparent, gel-based film. Sodium benzoate (S.B.) 0.3mL was added to the formulated herbal gel base as a preservative, and the pH was adjusted to 7.4 with triethanolamine (T.E., 0.6mL). The resultant polymeric solution was again stirred for another 10 minutes after adding T.E. and S.B. Permeation enhancer propylene glycol (2 mL) was then added to the resultant solution, characterized for further parameters [13, 14].

**Evaluation parameters of Gel** [13, 14]

· **Physical inspection, homogeneity and pH measurement**

All the prepared gels were visually inspected for physical appearance and homogeneity for their appearance. A digital pH meter determined the pH of the prepared gels (Table 4).





compared intravenous administration of hIFN- 2b at 20 MU/m$^2$ for 1 month and subcutaneous administration at 10 MU/m$^2$ for 48 weeks with observation alone. It was reported that prolongation of disease-free survival and prolongation of overall survival occurred in comparison to observation. In 1989, the Scottish melanoma group applied a randomized trial to compare observation alone with 6 months' therapy with subcutaneously low dose interferon at 3 MU/day (three times weekly). The result showed that there was a statistically significant improved disease-free survival for up to 24 months.[41] A Systematic Review of Randomized Controlled Trials by Lens and Dawes stated that there was no clear benefit of hIFN-2b on overall survival in melanoma patients. A large randomized controlled trial is needed to study the effectiveness and beneficiary of hIFN-2b treatment.[42]

**5. Condylomata Acuminate:**

Genital warts, which are also called condylomata acuminata or venereal warts, are the most common sexually transmitted disease (STD) in the general population. The incidence of it is increasing rapidly and closely related human papillomaviruses(HPV) have been associated intimately with cervical neoplasia and other genital tract neoplasms.[43] Interferon has been shown to be active against HPV both in vitro and in vivo, to protect murine cells against infection with bovine papillomaviruses and to eliminate extrachromosomal viral DNA from infected cells. The chief mechanism of its potential efficacy probably consists of following three fronts: (1) It acts as an antiviral agent; (2) it has an antiproliferative effect; and

(3) it elicits an immune response from the host. Based on these properties, interferon may lead to encouraging effects in the treatment of genital warts. It is reported that interferons exert their activities mainly by binding to specific membrane receptors on the cell surface. Once bound to the cell membrane, interferons initiate a complex sequence of intracellular events. In vitro studies demonstrated that these include the induction of certain enzymes, suppression of cell proliferation, immunomodulating activities such as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells, and inhibition of virus replication in virus-infected cells.[44,45]

**6. Chronic Hepatitis C:**

Hepatitis C virus (HCV) infection remains a threat to global public health. Treatment with pegylated interferon (IFN) plus ribavirin leads to a sustained virologic response in about 50% of patients. New therapies using direct antiviral agents have the potential to cure patients unresponsive to IFN-based therapies. The current standard therapy for hepatitis C consists of pegylated interferon-α (IFN-α), administered once weekly, plus daily oral ribavirin (RBV) for 24 to 48 weeks. This combination therapy is quite successful in patients with HCV genotype 2 or 3 infection, leading to sustained virologic response (SVR, defined as the absence of detectable HCV RNA in a patient's blood 6 months after the completion of antiviral treatment) in about 80%-90% of patients treated. Interferons are natural cellular proteins that can have different actions in humans, e.g., direct antiviral effect, inhibition of cell growth and control of apoptosis, and promoting immune responses. The effectiveness of IFN in HCV treatment can be significantly enhanced by the addition of RBV.[46,47,48] Studies have shown that response to IFN based treatment for HCV may be affected by differences in IFN signaling and induction. It is likely that HCV has mechanisms to avoid recognition by the innate immune response, and as such inhibits the ability of HCV- infected cells to generate IFN.[49]

**7. Chronic Hepatitis B:**

Interferon is an approved anti-HBV drug that not only exerts direct antiviral activity, but also augments immunity against HBV infection.[50] Interferon-α (IFN-α) therapy can convert CHB into inactive hepatitis B virus (HBV) infection in 20-30% of the treated patients. In spite of the low response rate, Interferon therapy may be associated with an improvement in quality of life for CHB patients.[51] Chronic HBV infection can be successfully treated with IFN monotherapy. Loss of viral DNA and antibody formation are successful outcomes associated with IFN treatment. The mechanism of IFN antiviral activity varies depending on HBeAg-positive or HBeAg-negative disease. In HBeAg-positive patients, an immune response is stimulated by IFN whereas in HBeAg-negative disease, IFN acts directly as an antiviral. HBeAg-negative disease tends to be more difficult to treat and is associated with a longer duration of disease and a higher

likelihood of complications such as cirrhosis.[52]

**8. Multiple Sclerosis.**

Multiple sclerosis (MS) is an immune-mediated demyelinating disease, with an increasing prevalence in India, as is seen in the recent studies. Beta-Interferon is the most widely used treatment option. There is a paucity of studies on beta-interferon in relapsing remitting multiple sclerosis (RRMS) in India.[53] Multiple sclerosis is a demyelinating entity with autoimmune etiology, which affectsmyelin of the central nervous system. It also represents a neurological disease of unknowncause that intermittently affects the white matter (myelin) of thespinalcord and brain. As aresult, nerve communication is delayed or interrupted, with myelin being replaced byhardened tissue plaques (sclerosis).[54] IFNB-1b, administered subcutaneously every other day to ambulatory patients with relapsing-remitting MS, significantly reduces annual exacerbation rate and percentage change from baseline MRI T2-weighted total lesion area. There is also evidence that IFNB-1b reduces the number of new gadolinium-enhancing lesions in patients with relapsing- remitting MS. IFNB-1a (Avonex), administered intramuscularly every week to patients with relapsing MS, significantly reduces annual exacerbation rate, the number and volume of new focal gadolinium-enhanced T1-weighted lesions, and slows the accumulation of physical disability over time.[55]

**9. Chronic Granulomatous Disease:**

Chronic granulomatous disease (CGD) is a rare X-linked or autosomal inherited disease characterized by recurrent life-threatening infections. The basic defect is an inability of phagocytic cells to produce superoxide anions and hydrogen peroxide, as a result of a defect in one of the subcomponents of the NADPH oxidase in these cells.[56] Pharmacologic alteration of phagocyte oxidative metabolism is now possible through the use of recombinant interferon-γ. *In vitro* studies have shown that neutrophils and monocytes derived from patients with autosomal recessive cytochrome *b*-positive CGD respond to interferon-γ with an enhanced respiratory burst (superoxide production) and increased bactericidal activity. Furthermore, subcutaneous interferon-γ administration improves bactericidal activity in neutrophils and monocytes derived from patients with X-linked, cytochrome *b*-negative CGD, despite the lack of effect on superoxide production. This suggests that interferon-γ also stimulates nonoxidative bactericidal pathways. Data from a multicenter clinical trial indicate sustained administration of interferon-γ is effective in the management of CGD. In addition, related studies indicate that modern molecular and genetic technologies offer the possibility of improved management or cure for CGD.[57]

**10. Coronavirus Response**

The impacts of interferon (IFN) signaling on COVID-19 pathology are multiple, with both protective and harmful effects.[58] Type I and III interferons (IFNs) are innate cytokines that are important in the first-line defense against SARS-CoV-2 has evolved mechanisms for evading the antiviral effects.[59]

**TOXICITY OF INTERFERON:**

The most side effects include flu like symptoms such as headache, muscle aches, joint aches, fever/chills, feeling sick vomiting, loss of appetite, feeling tired, depression, mood swings, poor concentration, vagueness. Administration of Ibuprofen, acetaminophen and naproxen and intake of fluids help to alleviate these symptoms. Less common effects include metallic taste, dry skin, dry mouth, skin rashes, loss or thinning of hair(temporary), pins and needles in the hands and toes, difficulty in sleeping, gastrointestinal upset, elevated liver function test, chronic fatigue, neurological complaints, cytopaenia. While ongoing of the treatment, temporary reduction of the WBC and platelets and thyroid problems may occur. This leads to more vulnerable infections, bleeding or bruising.[60] IFN-α therapy is associated with substantial toxicity in relation to the neurologic, cutaneous, musculoskeletal, gastrointestinal, cardiovascular, renal, hepatic, and hematologic systems.61

**PRECAUTIONS:**

1. Caution should be exercised for patients with preexisting seizure disorder.
2. Any allergies or allergic reactions that cause due to the drugs should be reported.
3. Alcoholics should be limited.



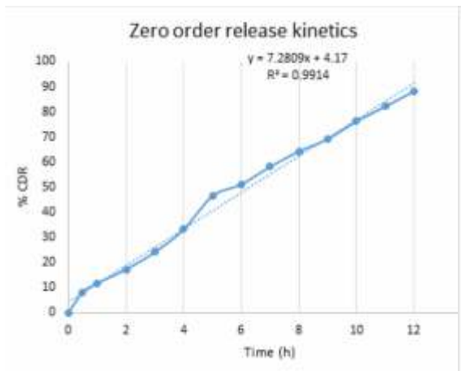


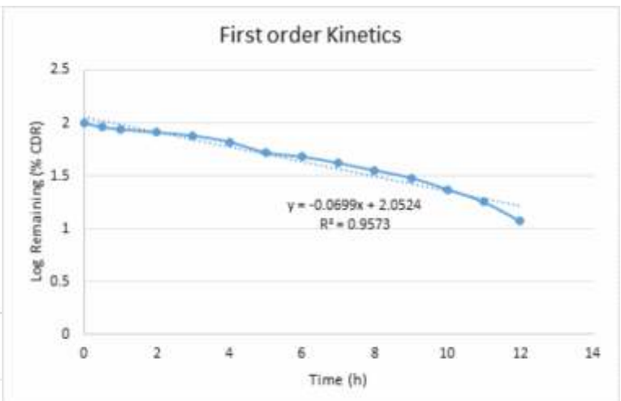
· ***Invitro* drug release**

A modified Franz diffusion cell was used for these studies. Cellophane membrane mounted on Franz diffusion cell. A known quantity of 100 mg of nanosponges was spread uniformly on the cellophane membrane on the donor side. The 7.4 pH phosphate buffer solution was used as the receptor medium. 1mL samples were collected every hour and the same fresh medium was replaced to maintain sink conditions. The study was carried out for 12hours. Samples were analyzed at 283nm against the corresponding blank solution using a UV-visible spectrophotometer [7-13] (Table 3). *In vitro* drug release data for nanosponges was presented in Table 3 and Figure 2 represents the release kinetics graphs.

**Table 3: Invitro release Data (Optimized formulation F4)**

| Time (h) | % CDR | Log % CDR | Log T | | % Remaining | Log Remaining (% CDR) |
|---|---|---|---|---|---|---|
| 0 | 0 | | 0 | 0 | 100 | 2 |
| 0.5 | 8.11 | 0.9 | -0.3 | 0.7 | 91.89 | 1.96 |
| 1 | 11.65 | 1.06 | 0 | 1 | 88.35 | 1.94 |
| 2 | 17.25 | 1.23 | 0.3 | 1.41 | 82.75 | 1.91 |
| 3 | 24.12 | 1.38 | 0.47 | 1.73 | 75.88 | 1.88 |
| 4 | 33.12 | 1.52 | 0.6 | 2 | 66.88 | 1.82 |
| 5 | 46.45 | 1.66 | 0.69 | 2.23 | 53.55 | 1.72 |
| 6 | 51.12 | 1.7 | 0.77 | 2.44 | 48.88 | 1.68 |
| 7 | 58.12 | 1.76 | 0.84 | 2.64 | 41.88 | 1.62 |
| 8 | 64.23 | 1.8 | 0.9 | 2.82 | 35.77 | 1.55 |
| 9 | 69.15 | 1.83 | 0.95 | 3 | 30.85 | 1.48 |
| 10 | 76.24 | 1.88 | 1 | 3.16 | 23.76 | 1.37 |
| 11 | 82.14 | 1.91 | 1.04 | 3.31 | 17.86 | 1.25 |
| 12 | 88.23 | 1.94 | 1.07 | 3.46 | 11.77 | 1.07 |



**Characterization of Nanosponges**

· **Particle size, P.D.I. and Zeta potential Determination**

Particle size, zeta potential, and polydispersity index were determined using Malvern zeta sizer, U.K. P.D.I. measures the variation in particle sizes of nanosponges formulation. The zeta potential measures the surface charge in colloidal dispersion. It determines the physical stability of prepared nanosponges [7-13] (Table 2), Figure 1.


**Figure 1: Particle size, PDI value and Zeta potential of Optimized formulation (F4)**

· **% age Entrapment efficiency (EE)**

100 mg dried voriconazole nanosponges were collected and dissolved in 10 ml ethanol, ultra centrifuged at 15000rpm. The solution was filtered, and the free drug was collected from the supernatant layer and analyzed spectroscopically at 283nm in triplicates to obtain % E.E using the formula [7-13] (Table 2).

%EE= amount (wt.) total drug-free drug (wt.) X dilution factor X100/ amount (wt.) total drug

· **Viscosity**

The viscosity of the prepared nanodispersion was determined using a T-spindle shape and an LV-II Pro Brookfield viscometer [7-13] (Table 2).

**Table 2: Characterization Parameters of Nanosponges**

| Formulation codes | Particle size (nm) | PDI | Z.P (mV) | (%EE) | Viscosity (m. pas) |
|---|---|---|---|---|---|
| F1 | 129.6 | 0.347 | 11.62 | 65.31±0.17 | 34.15±0.01 |
| F2 | 146.8 | 0.714 | 21.73 | 69.53±0.22 | 35.21±0.31 |
| F3 | 164.8 | 0.501 | 18.6 | 76.11±0.19 | 38.12±0.14 |
| F4 | 179.6 | 0.326 | 32.3 | 77.54±0.11 | 39.52±0.44 |
| F5 | 120.7 | 0.264 | 11.4 | 62.32±0.24 | 31.11±0.12 |
| F6 | 131.2 | 0.647 | 14.15 | 66.32±0.71 | 33.48±0.44 |
| F7 | 160.2 | 0.329 | 13.47 | 71.13±0.33 | 34.10±0.25 |
| F8 | 178.3 | 0.204 | 19.62 | 74.65±0.23 | 35.12±0.35 |
| Marketed Formulation | | | | | |





4. Should not undergo any immunization or vaccination without the consult of the physician.
5. Should stay away from patients recently taken oral polio vaccines or flu vaccines inhaled through nose.
6. Combination of IFN with Ribavirin may develop certain blood problems like anaemia and tooth and gum pain.
7. Dry mouth should be prevented with intake of water or saliva substitutes.
8. Caution should be taken for administering to older adults due to the sensitivity of the effect of drug, effect on heart, dizziness or mood changes.
9. Pregnant ladies should not be administered by this as this may end up with problems in the fetus and the mother.
10. Patients with severe neurological defects should not self-administer injections without the assistance.[58]

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**Introduction**

Voriconazole is a potent triazole antifungal medication that causes interruption of ergosterol and binds with enzyme 14α-demethylase. Furthermore, this leads to the accumulation of sterol precursors and the depletion of ergosterol, resulting in cell death and inhibiting fungal growth. Voriconazole treats invasive fungal infections like candidiasis and aspergillosis in immunocompromised patients [1]. Nanosponges are tiny solid nanoparticles having porous voids and are spongy. They are like virus structures with a diameter of less than 1µm. They are capable of entrapping both hydrophilic and lipophilic drugs. They are widely employed for topical, oral, and parenteral delivery. The spongy nature makes these nanoparticles a promising carrier for drug delivery. They can improve solubility, in vitro permeability, bioavailability, skin retention, and patient compliance. They become futuristic nanotechnology-based carriers for the delivery of antifungal agents and topicals, improving the solubility of poorly water-soluble drugs and providing target-based delivery in a controlled manner [2]. Fungal infections have become prominent worldwide and mainly affect immune-compromised patients requiring corticosteroid management. It primarily affects the toes, eyes, nails, and hair. Thus, it becomes challenging to treat with conventional formulations like tablets, creams, ointments, gels, and shampoos due to side effects of penetration, itching, solubility and bioavailability. So, it is essential and challenging for researchers to explore other alternatives where topical nano herbal gels are prepared to overcome drawbacks of poor penetration, solubility, bioavailability, and providing controlled release. One research was carried out using Voriconazole-loaded nanolipid carriers-based hydrogel formulated using the homogenization method for treating *Fungal candidiasis* and reducing skin toxicity, promoting controlled release [3, 4].

**Materials and Methods**

Voriconazole was procured from Chemland India, and other excipients like Carbopol 934, Propylene glycol, sodium benzoate, and triethanolamine were obtained from S.D. Fine Chem Limited. All the reagents were of analytical grade and used throughout the study. *C. albicans* was procured from the Institute of Microbial Technology, Chandigarh, India.

**Formulation of Nanosponges**

In varying ratios, Voriconazole nanosponges was prepared by solvent diffusion evaporation method using ethyl cellulose and other excipients. The organic phase containing 100mg voriconazole, varying ratios of E.C., and 10-20 mL of dichloromethane. The organic phase was probe sonicated for 10 minutes, and slowly dispersed into an aqueous phase containing 500mg polyvinyl alcohol in 100 mL distilled water to form a blueish tinch nanodispersion. Stirred for 2 hours on a magnetic stirrer between 1000-1500 rpm, filtered, followed by vacuum drying to obtain nanosponges. Prepared nanosponges were dried in oven at 40ºC and stored in a desiccator for further analysis [5, 6] [Table 1].

**Table 1: Composition of Nanosponges**

| Formulation codes | EC (mg) | PVA (mg) | Drug (VOR) mg | DCM (ml) | Stirring speed (RPM) | DW (ml) |
|---|---|---|---|---|---|---|
| F1 | 50 | 500 | 100 | 10 | 1000 | 100 |
| F2 | 100 | 500 | 100 | 10 | 1000 | 100 |
| F3 | 150 | 500 | 100 | 10 | 1000 | 100 |
| F4 | 200 | 500 | 100 | 10 | 1000 | 100 |
| F5 | 50 | 500 | 100 | 20 | 1500 | 100 |
| F6 | 100 | 500 | 100 | 20 | 1500 | 100 |
| F7 | 150 | 500 | 100 | 20 | 1500 | 100 |
| F8 | 200 | 500 | 100 | 20 | 1500 | 100 |

EC: Ethyl cellulose; PVA: Poly vinyl alcohol; DCM: Dichloromethane; VOR: Voriconazole;
DW: Distilled water; ml: millilitre; mg: milligram.

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# *Invitro*, *Ex vivo* permeation of Voriconazole loaded nanosponges based gel and evaluation of Antifungal potential

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**Abstract**

The present study aimed to formulate and evaluate nanosponges-based gels of Voriconazole using Ethyl cellulose, P.V.A., D.C.M., and other excipients. Formulated optimized nanosponges of Voriconazole were added to the Carbopol-940 gel base, propylene glycol, and other excipients. The antifungal and antibacterial activity of optimized nanogel was determined against *Candida albicans*. Voriconazole has potent antifungal activity and antibacterial effects. The voriconazole nanosponges loaded with Ethyl cellulose were formulated using different excipients. Optimized formulation (F4) of nanosponges was characterized for particle size, zeta potential, entrapment efficiency, viscosity, *in vitro* drug release, *ex vivo* permeation, drug content, CLSM, S.E.M., and T.E.M. characterization. Nanogel was formulated using polymer Carbopol-934, Triethanolamine, Propylene glycol as a permeation enhancer, and sodium benzoate as a preservative. Formulated nanogels of Voriconazole were studied for antifungal activity against *Candida albicans*. The prepared nanosponges showed uniform particle size and Z.P., indicating the physical stability of nanosponges. S.E.M. and T.E.M. surface morphology showed discrete, spongy particles of prepared optimized nanosponges. The Voriconazole nanogel met all properties and complied with the pharmacopeial standards. The *ex vivo* study of the optimized formulation was subjected to a CLSM (confocal laser scanning microscopy) analysis to confirm the permeation into deeper skin tissues. The gel formulations showed therapeutic efficacy against *C. albicans*, and found effective for topical delivery.

**Keywords:** Voriconazole; nanosponges; nanogel; CLSM; topical delivery; antifungal, SEM; TEM

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# Community Pharmacies' Operational Compliance with PPR 2015: A Pilot Study of Naturalistic Practice Patterns

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**ABSTRACT**

**Introduction:** Community pharmacies in India play a pivotal role in medication management and patient care. Despite regulations set by the Pharmacy Practice Regulations 2015 (2021 amendment), compliance within community pharmacies often falls short.

**Objectives:**

To evaluate the level of compliance with the PPR 2015 among community pharmacies, focusing on adherence to regulatory requirements and standards of practice. **Materials and Methods:** A single blinded cross-sectional observational (pilot) study was conducted over two months (April - May 2024) involving 25 randomly selected registered community pharmacies in Chennai. Data were collected through field visits by trained Pharm. D. students, with compliance to regulations observed and recorded. Data analysis was performed using Microsoft Excel and SPSS software. **Results:** The overall compliance score for the community pharmacies was 67.2%. Prescription was not requested by 88% of the community pharmacies, and 40% of pharmacists failed to consult physicians when faced with prescription misunderstandings. Positively, 80% of pharmacists provided counselling at the time of dispensing, and 92% displayed their registration license. However, a concerning 92% of pharmacists were not wearing formal attire, such as a white coat or apron, reflecting a significant lapse in adherence to dress code standards.

**Conclusion:**

Compliance with Pharmacy Practice Regulations 2015 among community pharmacies is inadequate. The study highlights significant gaps, including failure to enforce prescription requirements and professional attire standards. Recommendations include mandatory Continuing Pharmacy Education (CPE) for pharmacists to improve adherence to regulations and enhance patient care. The pilot study's results underscore the need for broader investigation and intervention.

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**Key words:** Community Pharmacy, Pharmacy Practice, Regulations, Compliance, Blinded





diagnosis and management of conditions like sebopsoriasis is crucial to prevent complications associated with both electrolyte disturbances and hypertrichosis.

This case emphasizes the necessity of vigilant monitoring for adverse drug effects, prompt recognition, and appropriate management strategies to reduce patient discomfort and enhance therapeutic outcomes. Collaborative decision-making involving dermatologists, pediatricians, and other healthcare professionals is essential to provide comprehensive care and address the multifaceted needs of pediatric patients with dermatological conditions and associated drug-related adverse effects.

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DATE: 16-02-2024 SERUM ELECTROLYTES LEVELS AND RENAL FUNCTION TEST

| ELECTROLYTES | RESULT VALVE | REFERENCE RANGE |
|---|---|---|
| CALCIUM | 9.8 | 8.4- 10.2mg/dl |
| SODIUM | 142 | 135-145mEq/l |
| POTASSIUM | **5.7 ( Increased )** | 3.5- 5.1mEq/l |
| CHLORIDE | 109 | 98-107mEq/l |
| PHOSPHATE | 5.5 | 2.5-4.5mEq/l |
| UREA/BUN | **5 ( Decreased )** | 19-43 mg/dl |
| Sr.CREATININE | **0.2 (Decreased)** | 0.6-1.1 mg/dl |
| URIC ACID | 4.3 | 4-7 mg/dl |

DATE: 27-02-2024 STOOL ROUTINE

| TEST NAME | |
|---|---|
| STOOL VEGETATIVE CELLS ,STOOL FAT GLOBULES, STOOL STARCH GRANULES, STOOL MUSCLE FIBRES, STOOL EPITHELIAL CELLS, STOOL CYSTS, STOOL OVA,STOOL RED BLOOD CELLS, STOOL MUCUS | ABSENT |
| STOOL PUS CELLS | PLENTY |
| STOOL PH | 7.5 |
| ST CONSISTENCY | SEMISOLID |
| ST COLOUR | GREENISH |

DATE: 28-02-2024BLOOD GROUP / RH

| | |
|---|---|
| 1-1-BLOOD GROUP / RH | A POSITIVE |

## CONCLUSION

Hypertrichosis is a recognized complication in most therapeutic regimens involving immunosuppressants, whether prescribed alone or in combination with other agents. The development of hypertrichosis, particularly with calcineurin inhibitors like Cyclosporine, is influenced by factors such as dosage, duration of treatment, and the specific type of immunosuppressant used. Therefore, physicians must tailor the dosing regimen based on the patient's pharmacokinetic profile to minimize this side effect.

Cyclosporine is widely employed in various medical conditions due to its therapeutic efficacy. However, despite its benefits, Cyclosporine-induced hypertrichosis remains a prevalent concern that must be factored into treatment planning. Although frequently observed, the impact of hypertrichosis on clinical comorbidity and mortality remains poorly understood. Thus, a deeper understanding of its underlying mechanisms is essential for early detection and effective management.

During Cyclosporine therapy, patients should be closely monitored for electrolyte imbalances, particularly hyperkalemia and hypomagnesemia, as these can complicate treatment. Establishing standardized guidelines for the





## INTRODUCTION

Community pharmacies, also known as retail pharmacies or retail drug outlets, are establishments where medications are stored, dispensed, supplied, or sold. In common parlance, these are often referred to as "medical stores." The professionals working in these settings are known as community pharmacists.

In India, patients expect community pharmacists to ensure that medications are effective, safe, and affordable. Furthermore, they anticipate that pharmacists will dispense medications in accordance with regulations, provide clear instructions on their use, advise on managing adverse drug reactions, and offer guidance on common health concerns. However, it is widely acknowledged that community pharmacists have not always fully met these patient-centered expectations.[1]

A significant number of pharmacy owners, who themselves are not trained pharmacists, employ pharmacists on a nominal basis. Consequently, this often leads to situations where pharmacists are not readily available to dispense medications. Additionally, pharmacists working in retail outlets owned by individuals lacking health-related education or training frequently receive inadequate compensation for their services.[2]

The Pharmacy Practice Regulations 2015, including its 2021 amendment, outline essential standards for both community pharmacies and community pharmacists. Despite these regulations, many community pharmacies continue to neglect these guidelines, failing to enhance their practices for the betterment of society. Notably, the Pharmacy Practice Regulations 2015 strictly prohibit the dispensing of medications without a prescription; however, deviations from this standard persist due to various factors.

Pharmacies are required to adhere to rigorous standards concerning their attire, registration, and document maintenance. They must follow prescribed procedures for dispensing, provide appropriate patient counselling, accurately interpret prescriptions, and seek clarification from the registered medical practitioner (RMP) when faced with unclear prescriptions.[3]

Global studies highlight the crucial role of community pharmacies in medication risk management and enhancing patient medication adherence.[4] It is essential for community pharmacies to comply with established regulations to uphold the required standards of practice. Our study aims to evaluate the extent of compliance with the Pharmacy Practice Regulations 2015, within community pharmacies.

## MATERIALS AND METHODS

A single blinded cross-sectional observational (pilot) study was conducted among community pharmacies in Chennai district for two months (April - May 2024). Samples included 25 random registered community pharmacies in Chennai while excluding Ayurvedic and homeopathic pharmacies, Wholesale pharmacies, hospital pharmacies, government-run free drug distribution centers, and those pharmacies attached to clinics.

### Data collection procedure:

During the initial phase, our study team comprised of trained Pharm. D. students visited the registered community pharmacies as a field visit (not lesser than 4 hours). The visit was also to observe the compliance of the pharmacy with Pharmacy Practice Regulations 2015. The objective of the study was not disclosed with the pharmacists at first, as it was meant to be a blinded study. The motto was explained later to the pharmacists after observing all required fields in the regulations.

### Data analysis:

The collected data was tabulated using Microsoft Excel and the descriptive analysis was performed using SPSS software

## RESULTS

A total of 25 pharmacies in Chennai were evaluated for compliance with the Pharmacy Practice Regulations 2015. The overall compliance score for these community pharmacies was found to be **67.2%.**

Among the 25 pharmacies, 23 (92%) pharmacists demonstrated a professional demeanour by avoiding any visible reactions when reviewing prescriptions. However, 22 pharmacists (88%) did not require a prescription for H and H1 drugs when requested. Additionally, 10 pharmacists (40%) handled prescription misunderstandings independently rather than consulting the prescribing physician for clarification.

Most community pharmacists (n=20) effectively provided patient counselling at the time of dispensing. In terms of record-keeping, the majority (n=23) percentage maintained separate registers to monitor stock clearance.

Approximately 80% of the community pharmacists (n=20) actively checked drug expirations, whereas 20% did not. Table 1 summarizes the assessed parameters and their frequencies.

**Table 1 Parameters assessed to understand compliance and their frequencies**

| S. No | Questions | Responses | Frequency (n) | Percent (%) |
|---|---|---|---|---|
| 1. | Whether pharmacist asks for a prescription when asked for a schedule H and H1 drug? | Yes | 3 | 12 |
| | | No | 22 | 88 |
| 2. | When a prescription is unclear or any misunderstandings in the prescription are clarified with the physician? | Yes | 15 | 60 |
| | | No | 10 | 40 |
| 3. | Any counselling regarding the drugs is provided by the pharmacist during the time of dispensing the medicine (before the patient asks themselves)? | Yes | 20 | 80 |
| | | No | 5 | 20 |
| 4. | Does the pharmacist show any facial expression upon reading the prescription in front of the patient? | Yes | 2 | 8 |
| | | No | 23 | 92 |
| 5. | Any written information regarding the frequency of drug consumption is provided by pharmacists during dispensing of medicines? | Yes | 15 | 60 |
| | | No | 10 | 40 |
| 6. | Whether expiry is checked by pharmacist while dispensing medicines? | Yes | 20 | 80 |
| | | No | 5 | 20 |
| 7. | (IF) whether the pharmacist maintains a register or a book to record any unavailable drugs to refill the stock in the future? | Yes | 23 | 92 |
| | | No | 2 | 8 |

**Table 2** Depicts the different pharmacy practice regulations that were taken under consideration for the study.

**Table 2 Different pharmacy practice regulations (2015) taken into consideration for the study.**

| Pharmacy Practice Regulations 2015 | |
|---|---|
| Chapter – 2<br>3.3 (b) | Registered pharmacist shall also comply with a dress code of being dressed formally and wearing clean white overall (Coat/apron) with a badge displaying the name and registration number. |
| Chapter – 8<br>13 (g) | Not displaying the registration certificate accorded to him by the State Pharmacy Council in his pharmacy is considered to be misconduct. |
| Chapter – 8<br>13 (b) | Dispensing medicines without the prescription of the Registered Medical Practi tioner which are required to be dispensed on prescription only is considered to be misconduct. |
| Chapter – 8<br>13 (c) | Substitution of the prescription without approval/consent of the Registered Medical Practitioner is misconduct. |
| Chapter – 4<br>9.3 (a) | Upon receipt of a prescription (prescription drug order) and following a review of the patient's record, a Registered Pharmacist shall personally initiate discussion of matters that will enhance or optimize drug therapy with each patient or care given of such patient. |
| Chapter – 3<br>8.1 (a) | Though a registered pharmacist is not bound to attend each and every person asking his services, he shall not only be ever ready to respond to the calls of the sick and the injured, but shall be mindful of the high character of his mission and the responsibility he discharges in the course of his professional duties. |
| Chapter – 4<br>9.1 (d) | Appropriate information shall be provided to the patient or the care giver and, where possible, understanding of this information should be checked. |
| Chapter – 4<br>9.1 g (ii) | Compounding, dispensing and label ling of required drug products should ensure that the drug product is not expired. |
| Appendix III | Responsibilities of Community Pharmacist at community Pharmacy practice site (Drug Store/ Pharmacy) is to keep a register of controlled drugs for legal and stoc k control purposes. |





## DISCUSSION

The case outlines an 8-month-old female diagnosed with sebopsoriasis, undergoing treatment with Cyclosporine (CSA) and corticosteroids for about three months. Among the adverse effects observed, the patient developed generalized hypertrichosis, prompting discussions on its pathogenesis, management, and implications, particularly concerning drug-induced hypertrichosis.

Hypertrichosis is a known side effect of Cyclosporine, though its exact mechanism remains incompletely understood. Typically dose-dependent, this condition primarily manifests in children within the initial six months of treatment. Various theories propose mechanisms such as the induction of the anagen phase of hair follicles, inhibition of the catagenic phase, stimulation of hair growth via matrix cell proliferation, and elevated levels of growth factors such as Vascular Endothelial Growth Factor (VEGF). Moreover, heightened activity of the alpha-reductase enzyme, which converts androgens to dihydrotestosterone, has been implicated.

Concurrent administration of Cyclosporine and corticosteroids necessitates careful consideration due to potential interactions. Their combined use may escalate the risk of toxicity and exacerbate symptoms of steroid excess. Mutual inhibition of metabolism between these drugs can lead to elevated plasma levels, underscoring the importance of vigilant monitoring and dosage adjustments.

Furthermore, the reversible nature of drug-induced hypertrichosis underscores the significance of patient education. Counseling regarding the anticipated timeline for resolution is crucial, as this condition can take several months to years to fully resolve, depending on the area affected. Encouraging patience and adherence to the treatment plan is essential for optimal outcomes.

In summary, the case emphasizes the complexities surrounding drug-induced hypertrichosis in pediatric patients undergoing Cyclosporine and corticosteroid therapy. Understanding its mechanisms, managing potential drug interactions, and educating patients and caregivers about the condition's course are pivotal for effective management and patient satisfaction.

| Test Name | Lab result valve | | | | Reference Range |
|---|---|---|---|---|---|
| | 16/02/2024 | 27/02/2024 | 01/03/2024 | | |
| PCV | 20.4 | 24.0 | 34.2 | Decreased | Male : 40-50<br>Female : 39-46 |
| PLATELET COUNT | 548 | 623 | 802 | Increased | 150-410 |
| LYMPHOCYTES | 37.8 | 36.3 | 29.4 | | 20-40 |
| EOSINOPHILS | 2.6 | 13.6 | 0.7 | | 1-6 |
| Hb | 6.3 | 7.1 | 11.1 | Decreased | Male : 13-17<br>Female : 12-15 |
| MONOCYTES | 6.4 | 4.9 | 2.6 | | 2-10 |
| NEUTROPHILS | 53.1 | 45.1 | 66.6 | | 40-80 |
| TC | 13.66 | 11.59 | 10.18 | | 6-16 |
| MCH | 22.1 | 20.8 | 23.1 | Decreased | 27-32 |
| MCV | 71.6 | 70.4 | 71.1 | Decreased | 83-101 |
| P-LCR | 13.4 | 17.7 | 18.6 | | 15-35 |
| MPV | 8.5 | 9.0 | 9.1 | | 7.5-12 |
| PCT. | 0.46 | 0.56 | 0.73 | Increased | 0.22-0.24 |
| RBC | 2.85 | 3.41 | 4.81 | Decreased to Normal | Male : 4.5 to 5.5<br>Female : 3.8 to 4.8 |
| PDW | 8.4 | 9.0 | 9.2 | Decreased | 10-25 |
| BASOPHILS | 0.1 | 0.1 | 0.7 | | 0-2 |
| MCHC | 30.9 | 29.6 | 32.5 | Decreased to normal | 31.5-34.5 |

An 8 month-old infant was admitted to a female dermatology ward with c/o exacerbation of lesions over trunk, scalp ,b/l ears since three days associated with itching sensation initially developed over trunk and gradually progressed to involve back of neck, ears, scalp, b/l upper and lower limbs. C/o cough, cold since one month on and off associated with sputum, scanty, white, non-purulent, non-blood tinged and non foul smelling, not associated with fever, which relieves on taking medication (oral paracetamol+ phenylephrine+chlorpheniramine and levosalbutamol+ambroxol+guaiphenesin).

The patient was diagnosed with sebopsoriasis + perianal dermatitis with URTI with past medical and medication history: h/o hospital admission 3 months back (BLDE) ivo similar complaints and started. F/u/c/o sebopsoriasis+ perianal dermatitis on oral cyclosporine 5mg/kg/day x 3 months-
>4mg/kg/day x 12 days(on advice)->exacerbation->5mg/kg/day x 2 days(current dose) along with oral hydroxyzine, topical mupirocin(over ears and fingers) and emollient.

H/o application of topical desonide over scalp lesions(on advice, details not known). On examination the patient was conscious and coherent and systemic examinations and cutaneous examinations were performed.

I. Treatment: Syp. Iminoral 100mg/ml : PO 0.35ml once daily 0.35ml-0-0 x 2days (oral cyclosporin-5mg/kg/day)(35mg/day) change to SYP IMINORAL 100mg/ml : PO 0.35ml once daily 0-0-0.35ml x 6 days (oral cyclosporin-5mg/kg/day)(35mg/day)
II. Syp. Omnacortil 5mg/5ml : PO 5ml once daily 5ml-0-0 x 7 days (oral prednisolone-0.7mg/kg/day)(5mg/day)
III. Syp. Atarax 10mg/5ml : PO 3ml once daily 0-0-3ml x 8days
IV. Solvin cold Drops (125mg/ml) : PO 7 drops thrice daily 7-7-7 x 4days
V. Ascoril ls Drops : PO 7 drops twice daily 7-0-7 x 4days
VI. Desowen Lotion : la x once daily 0-0-1 ( do not rub,over scalp lesions) x 8 days
VII. T-bact Ointment : la x twice daily 1-0-1 (over peri anal area,over erosions) x 8 days
VIII. Physiogel Lotion: la x twice daily 1-0-1 (over body) x 8days was prescribed.

On continuous adherence to the treatment plan, patient developed excessive hair growth on cutaneous examination and of increased potassium levels in the laboratory findings was observed which was suspected to be the adverse effect of Cyclosporine induced Hirsutism and Hyperkalemia and there is a possibility of increase in plasma concentration of Cyclosporine due to co- administration of Prednisolone. Paediatrics (DR M M PATIL-UNIT C) Reference taken on 27/2/24: i/v/o recurrent episodes of loose stools and low Hb. Advice: Stool routine and Growth chart-Not suggestive of acute or chronic malnutrition. Concomitant microcephaly present. Review I done on 28/2/24 with lab reports: Advice:- Stool culture, PCV transfusion (10ml/kg), Plan for FFP after PCV transfusion. Review II done on 4/3/24: Advice:- Tonoferon drops (3mg/kg/day) PO 0.5ml twice daily 0.5ml-0-0.5ml x 1month. Vitamin d3 drops PO 1ml once daily 1ml-0-0 x 1month. Syp.Calcimax P PO 2.5ml twice daily 2.5ml-0-2.5mlx 1 month. Complementary feeds advised and Review SOS

Post discussion with the concerned physician soon after identification of this incident, it is advised and practiced the dose adjustment of cyclosporine/predinisolone and it is seen on next day the frequency of cyclosporine was changed to 1-0-0 to 0-0-1, there is a decrease in the loose stools to normal and rest of the medications were continued as per the treatment regimen plan.

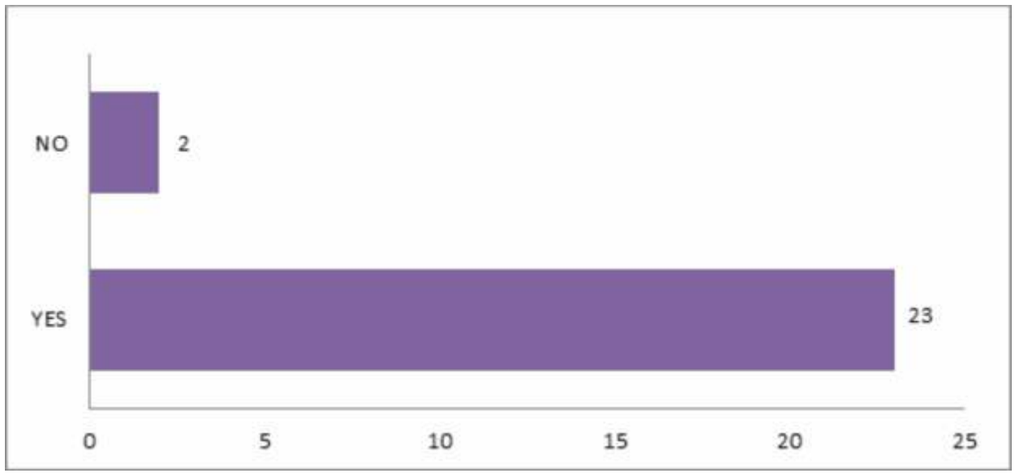




Nearly all community pharmacists (92%) were observed not wearing the white apron or coat while dispensing medications in their pharmacies. Figure 1 illustrates the frequency of community pharmacists wearing a white coat or apron. In contrast, 92% of community pharmacies displayed their registration license for customer viewing. Figure 2 shows the prevalence of community pharmacies displaying their registration license.

**Figure 1 White coat worn by the pharmacist as per PPR**


**Figure 2 Display of Pharmacy license to customer view**




**DISCUSSION**

In developing countries such as India, the healthcare delivery system encounters substantial challenges, notably a severe shortage of qualified doctors, which hampers the provision of quality healthcare services to the wider population. Consequently, many individuals depend on pharmacists and other allied health professionals to meet their primary healthcare needs. Pharmacists, especially those working in community pharmacies, have historically played a crucial role in the healthcare system by delivering essential services and support.[5]

A study conducted in Tamil Nadu highlights this issue further, revealing that 61% of the population engages in non-prescription drug use. This high prevalence of self-medication underscores the reliance on community pharmacists and emphasizes the urgent need for enhanced healthcare infrastructure to ensure that patients receive appropriate and safe medical care.[6]

Pharmacy practice regulations 2015 (Amendment 2021) describes the basic requirements for both the community

pharmacies and pharmacists on the good pharmacy practice.[3] In our study, the overall compliance score was found to be **67.2%**. In comparison, a similar study conducted in Nepal, which assessed Good Pharmacy Practice (GPP) across three districts, reported an overall compliance rate of 55.32%.[7]

A study conducted in Goa found that, on a single day, 63.4% of dispensing encounters occurred without a prescription.[8] Our study similarly reveals a concerning trend, with 88% of community pharmacies neglecting the requirement for a prescription, particularly for antibiotics. This raises serious concerns about the potential for antimicrobial resistance.

Regarding pharmacist attire, our study found that 92% of community pharmacists were not wearing formal attire, such as a white coat or apron, which could enhance patient perception. In contrast, a study from the United States highlighted that pharmacists who wore formal attire were perceived as more approachable by patients compared to those who did not. This underscores the importance of professional appearance in community pharmacies.[9]

An article from Australia demonstrated that facial expressions can significantly improve the doctor-patient relationship by enhancing trust between them.[10] This principle also applies to community pharmacists, as poor facial expressions while reading or interpreting prescriptions may instil apprehension in patients about the prescribed medications. Consistent with this, our study found that most community pharmacists exhibited neutral or positive facial expressions.

Patient medication counselling (PMC) can be defined as the process of providing medication information to patients or their representatives, either orally or in written form. This includes offering proper directions for use(when to take, how to take), advice on potential side effects, guidance on storage, and recommendations for diet and lifestyle modifications.[11] A study from Qatar reported that counselling practices in the region were substandard.[12] In contrast, our study found that the majority of community pharmacists (80%) were actively engaged in counselling patients regarding their prescriptions. However, attending Continuing Pharmacy Education (CPE) programs could further enhance the quality of counselling provided to patients.

## CONCLUSION

Compliance with the Pharmacy Practice Regulations (PPR) 2015 among community pharmacies remains unsatisfactory, which could undermine patient trust in these establishments. To address this, it is recommended that all pharmacies engage in Continuing Pharmacy Education (CPE) to enhance their patient care standards, potentially leading to improved patient outcomes. Given the clear regulations outlined in the Pharmacy Practice guidelines, it is imperative for community pharmacists to stay current with these guidelines and implement them effectively in their practices. Compliance with the declared guidelines not only improves the professional standards but also the reputation of the community pharmacies and further business and trading practice. If a pilot study on compliance yields poor results, the implications for the main study—covering a larger population—would be particularly concerning.

## LIMITATIONS

Since it is a pilot study, it may (or may not) differ from the results from main study.

## ACKNOWLEDGEMENT

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## CONFLICT OF INTEREST

The authors declare no conflicts of interest in the study.





## INTRODUCTION

Cyclosporine, a T cell-specific immunosuppressant and calcineurin inhibitor, selectively inhibits T cell activation by interfering with the production of interleukin-2 (IL-2) through the inhibition of IL-2 gene expression, likely via the inhibition of calcineurin, a Ca2+/calmodulin-dependent phosphatase. This results in the inhibition of IL-2 production and release, a proliferative factor necessary for the induction of cytotoxic T lymphocytes in response to alloantigenic challenge, and plays a major role in both cellular and humoral immune responses. Cyclosporine ,widely used in organ transplantation and autoimmune diseases, revolutionizing therapy approaches and showing efficacy in various dermatological conditions. Despite its therapeutic benefits, Cyclosporine is associated with adverse effects, such as hirsutism and hypertrichosis, gingival hyperplasia, increased incidence of cutaneous neoplasia, and infections. Serious adverse effects include endocrine metabolism issues like hyperkalemia and hypomagnesemia, hepatotoxicity (in 7% or less), renal complications such as hemolytic uremic syndrome and nephrotoxicity (25% to 38%), and infectious diseases. The patient in this study received Cyclosporine at 5 mg/kg/day along with corticosteroids for three months, leading to the development of generalized hypertrichosis and hyperkalemia.

The pathogenesis of Cyclosporine-induced hypertrichosis remains incompletely understood, with theories suggesting dose-dependency and mechanisms such as hair follicle phase modulation and growth factor expression. Concurrent use of Cyclosporine and corticosteroids can pose risks of toxicity and mutual metabolism inhibition, necessitating careful monitoring and dose adjustments. The impact of Cyclosporine on prednisolone elimination is debated, with some studies indicating that Cyclosporine significantly reduces the elimination of prednisolone, resulting in increased serum levels of the steroid [1], while others have shown no significant effect[2,3]. The clinical significance and extent of reduced prednisolone elimination caused by Cyclosporine remain unclear.

Xu et al. have demonstrated that Cyclosporine triggers the anagen phase while suppressing the catagen phase of hair follicles. Their studies in animal models indicate that the drug promotes hair growth by enhancing matrix cell proliferation and increasing the expression of growth factors such as Vascular Endothelial Growth Factor (VEGF)[4]. Conversely, Ponticelli et al. propose that this adverse reaction may be associated with the induction of alpha-reductase enzyme activity, which converts androgens to dihydrotestosterone in tissues. They also note other alterations in the pilosebaceous unit, including sebaceous hyperplasia, keratosis pilaris, and acne, likely resulting from the drug's lipophilic properties that facilitate its elimination via the sebaceous glands[5]. However, in our patient, no cutaneous manifestations other than pronounced hypertrichosis were observed.

Drug-induced hypertrichosis is reversible upon discontinuation of the drug, with complete resolution potentially taking months to years, depending on the hair cycle of the affected area (approximately three months for the face and about one year for the arms)[6]. In this case, the pediatric team adjusted the dosage of the drug to normalize serum potassium levels, achieving this goal and leading to an improvement in the child's loose stools. However, we opted to incorporate temporary chemical epilation until the dermatological changes fully resolved, as the child was experiencing bullying due to her appearance.

This case highlights the occurrence of cyclosporine-induced hypertrichosis, a well-documented adverse effect that is often under recognized by dermatologists.

## CASE REPORT

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JOHP

# Cyclosporine Induced Hypertrichosis and Hyperkalemia in an Infant: A Case Report of an ADR

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## ABSTRACT

This case report presents a scenario of Cyclosporine-induced hypertrichosis and hyperkalemia in an 8-month-old infant patient with a history of sebopsoriasis. Cyclosporine, a potent immunosuppressant widely utilized in organ transplantation and autoimmune diseases, is known for its therapeutic benefits but also carries the risk of adverse effects such as hirsutism. The patient was administered Cyclosporine in combination with corticosteroids, leading to the development of hypertrichosis and hyperkalemia. Vigilant monitoring and dose adjustments are crucial in managing these complications. Understanding the mechanisms and potential drug interactions associated with Cyclosporine therapy is essential for effective treatment and patient care.

Understanding the complexities of drug-induced hypertrichosis, managing potential interactions, and educating patients and caregivers are crucial for effective treatment and patient care. This case underscores the importance of vigilance in monitoring adverse effects of medications, prompt recognition, and appropriate management to optimize treatment outcomes in pediatric patients undergoing Cyclosporine therapy.

**Keywords**: Cyclosporine, Hypertrichosis, Hyperkalemia, Sebopsoriasis.

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## ETHICAL CONSIDERATIONS

Throughout the study period, no ethical conflicts were observed. As a result, it was determined that formal ethical clearance was not deemed necessary.

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# Medication Therapy management

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**ABSTRACT:**

Traditional role of pharmacist includes procurement, storage and dispensing in the healthcare system. This role is constantly evolving and new dimensions are added into it. Medication Therapy Management is also one of them. Medication management is a repeating process that involves patient assessment, creating and implementing a care plan, follow-up and evaluation. Care is provided through collaboration with patients and their healthcare teams, including physicians, nurses, pharmacists, dieticians, social workers, and patient care technicians.1 MTM works on five core elements which are repeated for effective outcome. Various models or interfaces can be used to achieve the improvement in patients' health outcomes through effective Medication Therapy Management. This review paper also discusses one innovative model of MTM and its effectiveness. MTM has many benefits, but still few challenges are also there which need to be recognized and mitigation strategies implemented.

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Graph 1: Effect of MTM on patient adherence

**BENEFITS OF MTM:**

1. Improved patient adherence and use of medications
2. Increased percentage of patients meeting their treatment goals (e.g., blood pressure, blood glucose, cholesterol)
3. Reduced drug duplication, harmful side effects, or interactions between medications, vitamins, and supplements
4. Greater medication cost savings, and medical resource cost savings (e.g., fewer emergency department visits), due to more effective use of drug therapy

**CHALLENGES:**

MTM continues to offer pharmacists the opportunity to use their knowledge; yet, pharmacists have reported challenges with service delivery. Some of the identified challenges are in following areas:

1. Integration of MTM within the pharmacy workflow: This could be due to pharmacist attitudes, lack of time, lack of trained support personnel, excess workload/lack of management support, and physical facilities (e.g. store layout, lack of privacy and lack of space).
2. Integration of MTM within the healthcare team: Lack of pharmacist integration with other members of the health care team was cited as a recurring challenge impacting MTM in all countries and a frustration to pharmacists
3. Use of technology: While access to medical records has been noted as an important driver in the success of MTM, integrating the pharmacist into the health information technology (HIT) infrastructure has been difficult and adoption of shared electronic health record (EHR) systems in community pharmacies has been minimal.
4. Creation of a business model for MTM: Low volume and low reimbursement makes it difficult for many community pharmacies to make a business case for MTM delivery.
5. Encouragement of patient engagement: Literature cited that patients do not understand the expanding role of the community pharmacists in healthcare. Lack of familiarity and limited expectations from the service, not being referred for MTM from physicians, and cost concerns were commonly cited as barriers.

**CONCLUSION:**

MTMs are expected to show improvement in patient health outcomes through improved control of chronic disease and more careful attention to potential drug-drug interaction. Implementation guidance has been developed by various organizations like American Pharmacist Association MTM central. Organizations like NBMTM provide courses for the pharmacists that include training, evaluation and certification. In developed countries like US, MTM is becoming common practice now, but in India it is still in nascent stage. All the healthcare professionals need to understand and implement this concept to achieve maximum patient benefit. In ER2020 PCI has introduced this concept in diploma pharmacy syllabus to train the new pharmacist for implementation of MTM. If all the stakeholders respond to this concept positively, improved patients adherence and ultimately better therapeutic outcome will be achieved.



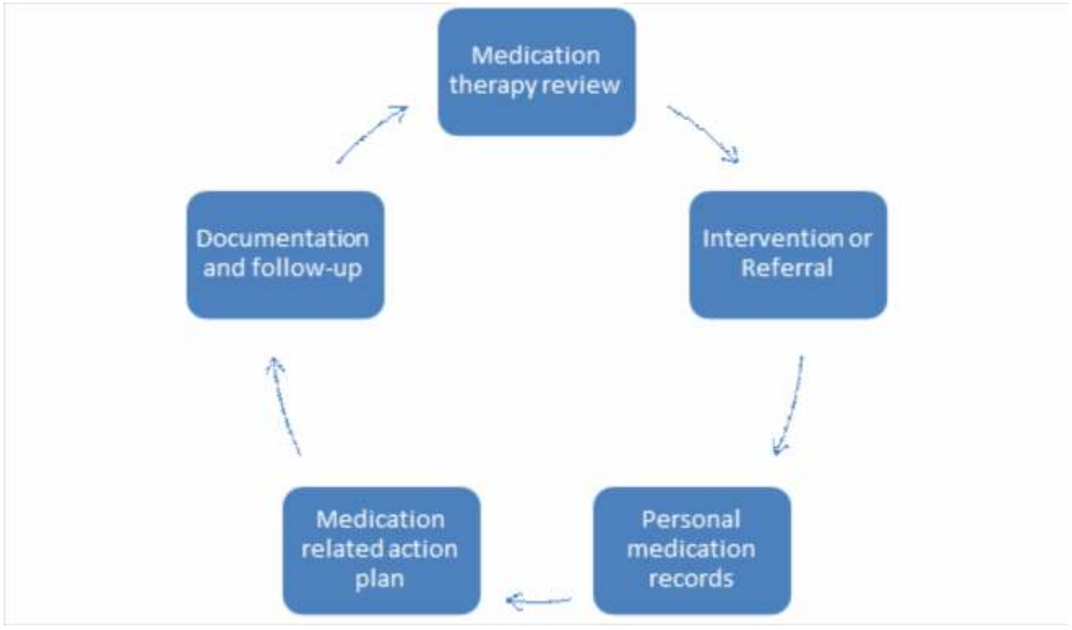


**INTRODUCTION:**

Medication therapy management (MTM) is a patient-centered process to create treatment plans centered on each patient's medication-related goals. During a medication therapy management consultation, a pharmacist trained in comprehensive medication reviews meets with patient to discuss all of his medications, including prescriptions, over-the-counter drugs, vitamins and dietary and herbal supplements. The pharmacist reviews each medication individually to determine possible side effects, negative interactions and unnecessary dosages. If medication issues are detected, the pharmacist will work with the healthcare providers to make beneficial changes to medication regimen.[2] Medication therapy management (MTM) was officially recognized by the federal government in the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA 2003). Even though the term "MTM" was first used in 2003, pharmacists have provided similar services, since the term "pharmaceutical care" was introduced in 1990.[4]

**ELEMENTS OF MTM**:

MTM is a cyclic process which includes five core elements:




**Medication therapy review (MTR):**

MTR is a person-to-person consultation between the pharmacist and the patient. The pharmacist spends dedicated time reviewing the information provided by the patient and provides medication education while addressing other concerns as needed. Sometimes it is also known as a Comprehensive Medication Review (CMR). A Targeted Medication Review (TMR) is initiated when a health plan continuously audits the medication list of their members and sends suggestions for medication changes directly to the prescriber. A TMR does not include a one-on-one consultation with a pharmacist or other healthcare professional. In contrast to a CMR, TMRs may occur with or without the knowledge of the patient.

**Intervention or Referral:**

During an MTM encounter, the pharmacist uncovers and itemizes medication-related problems that may lead to outside referral. A pharmacist may intervene on behalf of the patient to the professional. The recommendations that occur in the course of the MTM must be communicated to other members of the patient's healthcare team to ensure continuity of care and the realization of positive outcomes.

Examples of this type of action may include:

- Referral to another pharmacist who is a Certified Diabetes Educator for targeted education
- Referral to the Primary Care Physician to evaluate and diagnose symptoms newly identified by the pharmacist that cannot be attributed to a current diagnosis or adverse medication events.

**Personal medication records:**

Upon completion of the MTM appointment, the patient should receive a personalized document that lists out their prescriptions, OTC medications, herbal products, and dietary supplements. The PMR contains an up-to-date list of medications that help patients manage their pharmacotherapy. Throughout the MTM process, the pharmacist or patient should generate the document using the information provided. It may be electronic or manually generated. At a minimum, the PMR should contain the following elements for each pharmacotherapeutic:

- Name
- Dose
- Indication
- Schedule (i.e., "When do I take it?")
- Start Date
- Stop Date (If applicable)
- Prescribing provider
- Additional Instructions

Medication-related Action Plan (MAP):

MAP is a solution for medication-related problems that can be addressed in their scope of practice. The MAP does not include problems to be referred out to other members of the patient's healthcare team. Examples of items on a MAP include:

- "I will set an alarm on my phone to help me remember to take my clonidine three times daily."
- "Levothyroxine must be taken on an empty stomach for a consistent benefit; I will begin taking it at the same time each morning before breakfast."

Documentation and Follow-up:

The pharmacist documents the points covered during MTM as part of the patient's permanent medical record. Appropriate documents should protect against professional liability, capture services provided for payment, demonstrate the value of MTM, demonstrate clinical outcomes, and enhance continuity of care. Core elements of documentation are a standardized format (SOAP or SBAR), education, interventions/collaboration, PMR, MAP, follow-up, and time spent. Following an MTM, documentation should be communicated to physicians, payors, and patients/caregivers.

**MODELS OF MTM:**[5]

There are various models which can be used for effective MTM. Few of them are telephonic model, App model, face-to-face model, video based consultation model. Telephonic MTM provides a higher level of access for patients with transportation issues or who do not have an MTM provider in their geographic area. Patients can attend the interview from their homes with comfort.

Aspen RxHealth has launched a phone app that allows pharmacists to leverage their license to establish a professional profile where they can connect with patients and healthplans to perform telephonic MTM consultations. Pharmacists who work for Aspen RxHealth establish a profile in the Aspen RxHealth app. Once verified, the app connects patients with pharmacists in their area that provide a telephonic MTM service. Pharmacists can select a maximum of five specialties to focus on patients with specific disease states within their area of specialization, including:

- Alzheimer's Disease
- Anticoagulation
- Arthritis/Bone Disease
- Cancer





- Cardiovascular
- Diabetes
- End-Stage Renal Disease (ESRD)
- HIV/AIDS
- Mental Health
- Multiple Sclerosis Agents
- Pain Management

Face-to-face models allow the MTM provider and patient to develop a rapport and for the provider to see and interpret much of the information provided by the patient. During a face-to-face visit, the MTM provider can ask the patient to bring in medical records, prescriptions, medicines and other documentation that the provider can review without having to obtain the information verbally from the patient, increasing the fidelity of information. The provider can communicate using multiple teaching methods, including verbal, visual, model (for example injection, inhaler, or glucometer technique), and patient handouts.

Video-based consultation uses video and audio technology to MTM providers to patients over distances using their computer, phone, or other connective technology. example technologies include:

- Video conferencing
- Telephonic communication
- Store-and-forward imaging
- Remote patient monitoring

**Innovative Model for Chronic Patients**[3]**:**

An innovative model of healthcare delivery that can take care of the existing problem in healthcare utilizes India's greatest strength, which is the availability of pharmacies in every part of the country. MTM clinics can be launched at participating pharmacies. The components of MTM with an example are shown in Table1

| Parameter | Location or Action |
|---|---|
| Delivery mode | Face to face (onsite/Zoom/whatsapp) or by telephone |
| Provider | Pharmacist in collaboration with physician |
| Setting | Community pharmacies |
| Condition | Chronic disease |
| Point-of-care service | Blood sugar monitoring |
| Information and teamwork | Patient history at the MTM clinic, in addition to SOAP notes from the physician (collaborative care) |

**Table 1: Components of MTM**

Abreviation: SOAP: subjective, objective, assessment plans.

These MTM clinics can provide care to patients with chronic disease conditions whose acute complications lead to hospitalizations. These diseases include Alzheimer's disease, Chronic heart failure, Diabetes, Dyslipidemia, End-stage renal disease, Hypertension, Asthma, Chronic obstructive pulmonary disease, Osteoporosis, Rheumatoid arthritis, Osteoarthritis, Depression, Schizophrenia, Bipolar disorder. A group of MTM clinics can be linked to one physician who can participate in collaborative care and provide supervision. This model can hence overcome the problem of scarcity of physicians by making use of existing pharmacists.

MTM clinics have shown to improve health outcomes by reducing costs in a number of chronic health conditions in the US. Similar results are shown in Ethiopia. Graph 1 shows how MTM affects patient adherence. Some of the interventions in this study were education on diet and lifestyle modification, regular exercise, comprehensive discussions on the role of medications, and individualized plans created for each patient. One important fact highlighted was that proper MTM guidelines and policy should be set in place to have successful MTM program.