CHAPTER – II

REVIEW OF LITERATURE

2 Review of Literature

2.1 Hot Melt Coating

Patel N, et al., (2021) developed lipid based oral controlled release formulation system for anti-epileptic drug Oxcarbazepine using HMC. The active ingredient in core pellets was prepared using extrusion Spheronization and coated with hot-melt coating technology. The formulation and process parameters were optimized to achieve a targeted drug release profile and product profile, with a focus on HMCP. Quality by design (QbD) with DOE approach was used for formulation development, involving risk assessment, screening, and optimization studies. The study found that the drug release rate in a formulation is influenced by the level of low melting coating component and hydrophilic component, and can be optimized by adjusting these components. Other factors like coating temperature, atomization air, pressure, spray rate, coating efficiency, and particle size also impact the release rate. The dissolution data model fitting to the Higuchi model suggests drug release is predominantly by diffusion.[1]

Bannow J, et al., (2020) performed hot melt coating of amorphous carvedilol. Amorphous drug delivery systems can improve bioavailability of low molecular weight drugs with poor aqueous solubility. However, these drugs often suffer from recrystallization during storage and lumping upon dissolution. This study used hot melt coating (HMC) to coat amorphous carvedilol particles with tripalmitin containing 10% and 20% of polysorbate 65 (PS65) in a fluid bed coater. The lipid coated particles were evaluated for their stability during storage and drug release during dynamic in vitro lipolysis. The release of CRV during lipolysis is primarily dependent on the concentration of PS65 in the coating layer. A 20% concentration results in an immediate release profile. However, the lipid coating negatively affects the physical stability of the amorphous CRV core, leading to recrystallization at the interface between the crystalline lipid layer and the drug core. The study suggests lipid spray coating as a viable strategy for modifying drug release from amorphous systems.[2]

Diogo G L, et al., (2017) reviewed hot-melt coating as a solvent-free technology grants faster and more economic coating processes with reduced risk of dissolving the drug during the process. The HMC process, which can be modified to enable

traditional coating equipment, has advantages and is still limited in the pharmaceutical industry due to the need for alternative materials. The review focuses on HMC formulations and their properties, particularly their crystallization and solid-state behavior, which impact the performance of coated drug products, particularly on the stable drug release profile. The need for alternative materials is a major obstacle to widespread application. The development of stable formulations for pharmaceutical products requires extensive work, requiring a mechanistic understanding of macroscopic properties and stable solid-state behavior. This is crucial for the successful implementation of HMC as an advanced coating technology.[3]

Jannin V, et al., (2013) reviewed on hot melt coating with lipid excipients highlights their use in drug protection, taste masking, coloration, and modified drug release. These coatings require dilution or dispersion in solvents and gliding agents to prevent particle sticking. Lipid excipients offer an attractive alternative to standard polymer coatings as they only require melting before application directly onto the substrate.[4]

Tiwari R, et al., (2013) developed and optimized oral controlled-release formulations for highly water-soluble model drug Venlafaxine hydrochloride using a combination of hot melt sub-coatings-based coating polymer and aqueous polymer coating. The hot melt sub-coating was achieved using a centrifugal granulator, while Acrylate-based polymer coatings (Eudragit RS 30D and Eudragit NE 30D) were used. The study found that using hot melt sub-coating reduced the polymer coating level of pellets by half, resulting in a sustained release profile. The study found that the optimal release profile for pellets was achieved at a 4% level of hot melt sub coating and 15% level of Eudragit® NE30D polymer coating combination. This technique successfully prepared sustained-release pellets containing venlafaxine hydrochloride, satisfying the first order plot with a R2 = 0.9434, indicating the release of water-soluble drug from porous matrices.[5]

Patil A, et al., (2012) demonstrated utility of hot melt coating technique for enteric coating. Pellets made from extrusion-spheronization were chosen as the core for diclofenac sodium due to their advantages over single-unit formulations. Stearic acid and palmitic acid were evaluated as enteric hot melt coating materials. The coating

was carried out in a modified pan, achieving a 5-15% w/w coating level. The results showed excellent enteric coating ability of both SA and PA.[6]

Homar M, et al., (2011) prepared immediate release clarithromycin microparticles using a hot melt fluid bed technique. Key process parameters were identified and optimized during course of study. Their influence on process yields and microparticles characteristics was determined. % yield was around 70% and 60% in the case of PEG and poloxamer 188 respectively. The dissolution rate and equilibrium concentration of clarithromycin released from prepared microparticles was improved compared to similar particles prepared by wet granulation.[7]

Guan T, et al., (2011) The study compared the stability of venlafaxine hydrochloride sustained-release pellets, which were prepared using double-polymer coatings, hot melt sub-coating, and Eudragit® NE30D outer coating, ensuring drug dissolution met standard requirements and acceptable storage stability.[8]

Chandrikapure PL, et al., (2011) utilized cetyl alcohol and beeswax as hot melt coating agents in preparation of multi-particulate sustained release formulations for water soluble drug like diclofenac sodium. Targeted release profile cannot achieve by the use of either cetyl alcohol or beeswax. Therefore, ethyl cellulose was used as rate controlling polymer in combination with cetyl alcohol or beeswax. [9]

Patil A, et al., (2011) demonstrates the use of hot melt coating to mask bitter or unpleasant tastes in bromhexine hydrochloride and salbutamol sulphate pellets. Beeswax and cetyl alcohol were evaluated as hot melt coating materials. The panel method determined the threshold bitterness concentrations and taste evaluation of the coated pellets. Beeswax and cetyl alcohol were found to be better taste masking agents at 5% coating level.[10]

Chen H, et al., (2010) used extrusion-spheronization and hot melt coating technologies to enhance moisture-proofing of Guizhi Fuling (GF) compound herbal extracts. The pellets were coated with a 96:4 mixture of stearic acid and polyethylene glycol 6000, resulting in better moisture-proofing than Opadry AMB due to different moisture sorption mechanisms. The Higuchi model was the best fit for the hot melt coating, while Opadry AMB fitted the Nuttanan model.[11]

Patel JU, et al., (2010) prepared Ranolazine sustained release tablets using hot melt coating technique. The pH-dependent binders Eudragit L100® 55 inhibit rapid release of drugs from a tablet during residence time in stomach. Ranolazine tablets were coated with hydroxypropyl methyl cellulose phthalate, hydrogenated castor oil using hot melt coating technique. In vitro drug dissolution study proved that amount of drug release was depends upon concentration of rate controlling polymer Eudragit L100® 55 present in the formulation. The drug release in stomach was negligible in 2 hrs. The drug release from sustained release occurred by diffusion of drug from tablet, reflects Higuchi model.[12]

Sakarkar DM, et al., (2009) studied has developed sustained release pellets of diclofenac using cow ghee as a hot melt coating agent. The study found that the release from the pellets depends on the drug's physicochemical properties, specifically its aqueous solubility. The study successfully prepared these pellets by using cow ghee and ethyl cellulose as a coating agent.[13]

Knezevic Z, et al., (2009) utilized hot melt coating process for designing a lipid based controlled release drug delivery system of paracetamol. The study analyzed the effects of varying lipid levels on the release pattern of paracetamol granules, which were then compressed into tablets. The results showed that the granule composition can affect the drug release rate, and the lactose-based formulation with 9% lipid coating was found to be suitable for controlled delivery over 12 hours, making it suitable for highly water-soluble drug candidates like paracetamol with a twice daily dose regimen. Moreover, the dissolution data adequately fitted into Higuchi model suggesting that the drug release occurred predominantly by diffusion.[14]

Pham LT, et al., (2009) prepared controlled release of acetaminophen (APAP) beads using hot melt coating by direct blending method. The single and dual coated beads were coated by hot melt coating using oleaginous waxes to achieve near zero-order release pattern. The beads were prepared by coating sugar spheres (420-500 μm) with thirteen different waxes containing APAP by direct blending. The efficiency of drug loading was 75-85% depending on the wax used. The drug release rate profiles from the beads followed pattern that was consistent with the hardness of the waxes. The drug release was observed to be faster in case of softer waxes and slower in case of

harder waxes. Initial burst of drug release was observed in single coated beads while a lag time in drug release was observed in dual coated beads. The convolution predicted therapeutic plasma APAP concentrations lasting 16 hr for dual coated beads. The hot melt dual coating by direct blending released APAP in a consistent near zero-order release pattern for 16-24 hr.[15]

Yang ZY, et al., (2008) Pseudoephedrine hydrochloride sustained release pellets were prepared using a combination of hot melt sub-coating and polymer coating. The pellets met USP-29 dissolution requirements for extended-release capsules. The polymer coating level was reduced by half due to the hot melt sub-coating. This technology successfully prepared sustained release pellets containing pseudoephedrine hydrochloride, meeting the dissolution requirement.[16]

Padsalgi A, et al., (2008) prepared sustained release tablets of theophylline by using hot melt wax coating technology. The effect of different coating technique i.e., pan spray method and pan pour method and the effect of different pore former like sodium lauryl sulfate (SLS) and hydroxypropyl methyl cellulose (HPMC) on release pattern of theophylline for SR tablets were studied. The pan spray technique was reported as the best technique than pan pour method, and faster release was seen when SLS was used as a pore former in lower concentration than HPMC.[17]

Homar M, et al., (2008) fabricated immediate release and prolonged release microparticles using hot melt fluid bed technique. Hot melt methods use molten or softened materials like polymers, waxes, and lipids as binders in solid dosage forms like tablets, microparticles, pellets, and granules. Fluid bed technology is used to prepare agglomerates using meltable binders like polyethylene glycol, poloxamer 188, Gelucire 50/13, or glyceryl monostearate. The study examines the mechanism of agglomerate growth, binder droplet size, viscosity, starting material size, and binder type. Microparticles are characterized by their dissolution rate of clarithromycin.[18]

Chansanroj K, et al., (2007) designed multi-unit floating drug delivery system using hot melt coating technique. A study on metoprolol tartrate and hydrogenated soybean oil (HSO) was conducted to develop multi-unit floating drug delivery systems. The drug was coated on inert nonpareils in a fluid bed chamber, and the drug release varied due to brittle fractures. The coated pellets showed good floating properties in

vitro, suggesting the use of a drug-lipid dispersion coating for drug delivery systems. The study also highlighted the influence of process parameters and the potential optimizations or limitations of the binders used.[19]

Le H et al., (2007) A hot melt coating method was used to create a sustained release nifedipine dosage form. Sugar beads were coated with various waxes, including Gelucire 50/13, stearic acid, Syncrowax HGLC, natural beeswax, polawax regular, and carnauba wax. Single and dual layer coated beads were fabricated, and a 24-hour drug release study was conducted. The convolution process in Kinetica 2000 software was used to predict plasma concentrations for commercial products Adalat® CC and Procardia® XL 30 mg. In vitro dissolution test results showed dual coating was more effective.

Two-process hot melt coating technique can be used to prepare dual coated beads with high and low melting point waxes. The method yielded capsules with similar dissolution profiles and plasma concentrations to Procardia XL, demonstrating the feasibility of producing zero-order kinetics for drug dissolution. Multiple coating can improve the coating and ensure acceptable sustained release of nifedipine.[20]

Sinchaipanid N, et al., (2006) examined the impact of catalyst amount, hydrogen pressure, and temperature on hydrogen consumption, hydrogenation time, reaction rate, and final product quality. The study found that increasing catalyst and temperature significantly improved reaction rate and acid values. The product showed thermal tolerance to high temperatures, with unchanged exothermic peaks. Hydrogenated soybean oil can be used for modified release formulations through hot melt coating.[21]

Wen-Ting K, et al., (2006) analyzed the physicochemical characterizations of ambroxol SR matrix tablets, which contained hot melt coated granules of ambroxol with Compritol® 888. The dissolution study was conducted over 24 hours, and the pharmacokinetic study on 16 healthy male human subjects showed that Amsolvon tablets provided a slow and less variable release of ambroxol. The study concluded that Amsolvon SR tablets offer optimal therapeutic efficacy and improve patient compliance.[22]

Nguyen C (2005) developed sustained release capsules by tamper-resistant coatings using hot melt coating. The capsules were filled with verapamil, chlorpheniramine, or diltiazem and coated with Gelucire 50/13, cetyl alcohol, and polyethylene glycol 300. The weight gain led to slower drug release, lasting up to 12 hours. The capsules also had a pulse release pattern with a lag time of 4 to 6 hours between the two releases.[23]

Jannin V, et al., (2005) ibuprofen capsules were fabricated using hot melt coating with mixtures of Compritol™ 888 ATO and non-ionic surfactants. Non-ionic surfactants in Compritol™ modify the release of ibuprofen after hot melt coating. Surfactants should be miscible with Compritol™, water-soluble and liquid. Labrasol™ was the promising surfactant as it allows obtaining the greatest dissolution efficiency after compaction and release profiles equivalent whatever the dosage form.[24]

Freitas Luis AP., et al., (2004) prepared paracetamol tablets in spouted bed using hot melt coating. The paracetamol tablets and beeswax beads were loaded in the column and a cycle of heating/cooling while spouting caused the beeswax melting, substrate coating and wax solidification. The data revealed that only the effects of tablets load and the squared air temperature were significant at 5% and 10% level, respectively. The results revealed that it was a promising method for particles coating in spouted bed.[25]

Sinchaipanid N, et al., (2004) demonstrated the application of hot melt coating in design of controlled release of propranolol hydrochloride pellets. The study investigated the use of Gelucire 50/02 and Precirol ATO5 as drug release regulators. Results showed that the dissolution of coated pellet decreased with increased Precirol ATO5 proportion and coating thickness. The linear relationship between log% drug release and reciprocal of time was found, suggesting that drug release can be adjusted by adjusting these factors.[26]

Mittal B, et al., (2003) demonstrated taste masking of aspirin using hot melt coating. The coated aspirin were analyzed for changes in particle size distribution and specific surface area. The coated aspirin was compressed into fast orally dissolving tablets. Taste testing of coated API was conducted amongst 4 volunteers. Reduced dissolution in the mouth during the first minute leads to better taste masking. The present

research was a follow up study that will continue to examine the effect of these variables on the coating process using Precirol ATO®5.[10]

Jannin V, et al., (2003) conducted a study comparing the lubricant performance of Compritol 888 ATO using blending and hot melt coating found that hot melt coating induces homogenous repartition on the lactose surface, making it an efficient method for large surface area particulate systems producing high friction, unlike classical blending procedures.[28]

Achanta AS, et al., (2001) studied the water sorption behavior of excipient films encapsulated by hot melt coating was studied. The study investigates the interaction of water with moisture-protective coatings using lipidic and polymeric coating excipients. It found that temperature and film thickness significantly influence the nature of moisture interaction and distribution in the excipient films, allowing for the encapsulation of water-labile, drug-loaded substrates. [29]

Faham A, et al., (2000) prepared hot melt coated granules of chloroquine by using Compritol 888 ATO as coating agent using fluidized bed coater. The study suggests that controlling granule size can adjust chloroquine release rate, with dissolution profiles characterized by a rapid release phase followed by a slow-release phase. The study indicated that the active substance diffused across the Compritol matrix generated during compression. Determination of the dissolution kinetics using the Higuchi model demonstrated the diffusion release mechanism.[7]

Faham A, et al., (2000) studied the effect of Compritol® 888 ATO and granule size on theophylline release using hot melt coating performed in a fluidized bed apparatus. The dissolution profiles of prepared granules differed from those coated with classical agents and varied among sieve fractions. Drug release was characterized by rapid and slow phases. Results indicate that Higuchi model was the best model to describe the release kinetics of the drug from tablets.[30]

Barthelemy P, et al., (1999) coated drug-loaded sugar beads and lactose granules with Compritol® 888 using hot melt coating. Theophylline was layered on the granules of lactose and beads of sugar. Several competing mechanisms were involved in the drug release, including a diffusion-controlled process and a dissolution mechanism. Dissolution profiles appear to be consistent from one batch to another.[31]

Griffin EN, et al., (1999) designed hot melt coated multi-particulate controlled release dosage forms using lipophilic materials. The release kinetics were determined using a dual equation that combined first-order and square-root-of-time kinetics. The study found the dual equation to be a superior model for the chosen controlled release system and applicable to other literature.[32]

Kennady JP, et al., (1998) demonstrated extended-release applications for solid dispersion hot melt fluid bed coatings using hydrophobic coating agents. Chlorpheniramine maleate (CPM) was chosen as a model drug. The CPM-loaded nonpareils and hydrophobic coating agents was charged in the solid state in fluid bed chamber. Dual coatings demonstrated a cumulative extension of release superior to than a single coat. The method was proved as a viable alternative to the hot melt spray coating method. Multiple coatings that have a cumulative effect on release retardation are feasible.33

Kennady JP, et al., (1996) optimized solid dispersion using Hot Melt fluid bed coating using polyethylene glycol as a model coating agent. They have charged substrate and polyethylene glycol into the fluid bed chamber in the solid state for the set objectives. The technique was proved to be a viable alternative to hot melt spray-coating processes. Organic solvents, spraying equipment, steam jackets, and/or heating tape are eliminated from the process.[34]

Bodimeier R, et al., (1992) have studied the effect of process variables and formulation variables in the preparation of wax microparticles by melt dispersion. Ibuprofen-wax (bees wax, Caurnauba wax, paraffin wax, and glyceryl esters like Gelucire 64/02 and Precirol ATO5) microparticles were prepared using solvent free coating. The study proposed that the drug release was controlled by the hydrophobicity of the wax. The wax microparticles could be formulated into an aqueous sustained-release oral suspension.[35]

Jozwiakowski MJ, et al., (1990) characterized the fine granules of a hydrophobic drug and sucrose coated by hot melt fluid bed coating using partially hydrogenated cottonseed oil. The physical properties of wax-coated granules fabricated using combinations of process variables were examined. The response surface analysis was used to determine the optimum process settings in terms of dissolution, particle size

and density of the coated product. The study revealed that uniformly coated granules were obtained at the optimized conditions.[36]

2.2 Tenofovir

Ulu A, et al., (2024) prepared a controlled drug release of Tenofovir Alafenamide-loaded chitosan nanoparticles and evaluated cell viability study. The researcher developed chitosan nanoparticles (CHS NPs) loaded with TAF, which showed a spherical and homogeneous shape. The NPs had a hydrodynamic diameter, zeta potential, and PDI of around 340 nm, 48.9 mV, and 0.65, respectively. The encapsulation efficiency was around 50%, and TAF was released around 93% after 80 hours at pH 7.4. TAF-loaded CHS NPs had 1.24 times less viable cells than the control, suggesting they could be an effective formulation for treating chronic HBV infection.[37]

Mahajan N, et al., (2024) developed a self-emulsifying drug delivery system to enhance oral delivery of tenofovir. Tenofovir (TNF) is known for its poor membrane permeability and low oral bioavailability. To improve oral availability and membrane permeation, a self-emulsifying drug delivery system (SEDDS) was developed. The system was formulated using eucalyptus oil as an oil phase, Kolliphor EL and Kollisolv MCT 70 as surfactants and cosurfactants, and glycerol as a cosolvent. The optimized SEDDS formulation, F6, produced oil droplets with a size of 98.82 nm and a zeta potential of -13.03 mV, indicating good stability. F6 is a fast-release drug with higher drug permeability than basic TNF and TNF-marketed tablets. Its pharmacokinetic research in rats showed greater Cmax and AUC0-t than commercial tablets and pure drug suspension. SEDDS formulation showed significantly increased bioavailability by 21.53-fold compared to marketed tablets and 66.27-fold compared to pure medicines. This suggests that SEDDS containing eucalyptus oil, glycerol, Kolliphor EL, and Kollisolv MCT 70 could improve TNF absorption and oral bioavailability of weakly water-soluble medicines.[38]

Rao H, et al., (2022) studied tenofovir disoproxil fumarate in patients anguish from chronic hepatitis B and advanced fibrosis or compensated cirrhosis. A study assessing the efficacy and safety of TDF in patients with chronic hepatitis B and advanced fibrosis in China found that it was effective in preventing newly diagnosed

hepatocellular carcinoma (HCC) and disease progression. The study enrolled 197 patients and found that the prevalence of HCC was 2.1%, and disease progression was observed in 3.6%. The mean change in liver stiffness was 5.1 kPa. 67.7% of patients experienced one adverse event, 13.8% experienced TDF-related adverse events, and 16.4% experienced serious adverse events. The study found that at week 144 of TDF treatment, low frequency of HCC and disease development were reported, with virological suppression in 94.1% patients, related to fibrosis regression, and no new safety events were identified.[39]

Del Amo J, et al., (2022) studied effectiveness of TDF /emtricitabine (FTC) and severity of coronavirus disease 2019 in people with HIV infection. Coronavirus disease 2019 (COVID-19) requires antivirals that are effective, safe, and inexpensive. Tenofovir may be effective against COVID-19, but no large-scale human studies have been conducted. A 2020 study in Spain investigated HIV-positive individuals on antiretroviral medication (ART) at 69 clinics. The study collected data on sociodemographics, ART, CD4+ cell count, HIV-RNA viral load, comorbidities, and outcomes. It compared 48-week hazards for different regimens, adjusted for clinical and sociodemographic factors using inverse probability weighting. A study of 51,558 eligible persons found that 39.6% were on TAF/FTC, 11.9% on TDF/FTC, 26.6% on ABC/3TC, and 21.8% on other regimes. There were 2402 confirmed SARSCoV-2 infections, with 425 hospitalizations, 45 ICU admissions, and 37 fatalities. TDF/FTC had higher risk ratios of hospitalization, ICU admission, and death compared to ABC/3TC. TDF/FTC had comparable RRs of hospitalization in individuals over 50 years old and younger people.[40]

Paredes AJ, et al., (2022) developed tenofovir alafenamide dissolved implanted microneedle patches to deliver drug systemically. About 37.7 million people already infected and 1.5 million new cases reported each year. The current oral administration of antiretroviral medications leads to pill tiredness and poor treatment adherence. To address this, innovative formulations for administering ARV medications via alternate routes are being developed. Microneedle array patches (MAPs) offer a user-centric platform for painlessly applying medications to the skin. This study focuses on creating dissolving and implantable MAPs loaded with tenofovir alafenamide (TAF) for systemic drug delivery. The study found that both MAPs were effective in

penetrating newborn pig skin and creating drug stores. In-vitro release studies showed quick drug delivery in all conditions. Franz cells experiment showed dissolving and implantable MAPs deposited 47.87 ± 16.33 μg and 1208.04 ± 417.9 μg of TAF in skin after 24 hours. In rats, TAF metabolized quickly into tenofovir, and was quickly eliminated from plasma. [41]

Garcia CR, et al., (2022) studied the effect of drug-to-lipid ratio on nanodisc-based tenofovir drug delivery to the brain for HIV-1 infection. The study explores the use of nanotechnology-based drug carriers, such as nanodiscoidal bicelles, to treat HIV-1 in the brain. The researchers used tenofovir-loaded nanodiscs for both in vitro and in vivo treatment, capturing the medicine in their hydrophobic core and releasing it in a regulated manner. The study also compared nanodisc formulations in both models, identifying potential applications for nanodiscs in HIV-1 treatment development. This approach could help address the persistence of HIV-1 in the brain.[42]

Stalter RM, et al., (2021) Tenofovir levels in urine were evaluated using a new immunoassay to predict human immunodeficiency virus protection. Novel tools are needed to improve pre-exposure prophylaxis (PrEP) obedience for HIV anticipation, especially those that provide real-time response. In a large, recently finished PrEP experiment, appropriate urine tenofovir levels evaluated with a new immunoassay predicted HIV protection and demonstrated good sensitivity and specificity for detectable plasma tenofovir.[43]

Plum PE, et al., (2021) studied impact of switch from tenofovir disoproxil fumarate-based regimens to tenofovir alafenamide-based regimens on lipid profile, weight gain and cardiovascular risk score in people living with HIV. The study analyzed the impact of switching from tenofovir disoproxil fumarate (TDF)-based regimens to tenofovir alafenamide (TAF) regimens on the lipid profile, weight gain, and cardiovascular risk change in HIV-infected patients with suppressed viral load. The patients were divided into two groups: those who had been treated continuously with TDF-based regimens, and those who had been treated with TDF regimens for at least 6 months before switching to TAF regimens.

The study examined various factors such as age, gender, ethnicity, and lipid profile in patients with ARV. It found that switching from TDF to TAF-based therapy led to a

significant increase in triglyceride levels, total cholesterol, and HDL cholesterol. However, LDL cholesterol and total cholesterol/HDL ratios did not significantly change. The calculated cardiovascular risk increased after switching from TDF to TAF-based therapy. The study suggests that considering the unfavourable influence of TAF on lipid profile is crucial when proposing personalized ARV treatment.[44]

Bagus SB, et al., (2021) described a Tenofovir disoproxil fumarate prenatal as a complementary treatment to prevent vertical transmission of hepatitis B virus. Vertical transmission is the most common mode of hepatitis B transmission in endemic countries, with 1% to 4% of newborns at risk of immunoprophylactic failure. Tenofovir disoproxil fumarate (TDF) is preferred over lamivudine and telbivudine due to its potency and reduced resistance. A systematic review of 3,765 participants found that six studies reduced viral load HBV DNA levels in the treated group, and five investigations showed a higher vertical transmission rate than in the control group. The systematic review of studies found that prenatal TDF administration and prophylactic procedure can lower vertical transmission rates and the risk of immunoprophylactic failure in infants aged 6-12 months old. No significant safety differences were found between the intervention and control groups. The public health sector and clinicians should explore TDF prenatal as a supplemental treatment for preventing vertical transmission.[45]

Safari JB, et al., (2021) developed pH-sensitive chitosan-g-poly (acrylamide-co-acrylic acid) hydrogel for controlled drug delivery of tenofovir disoproxil fumarate. Free radical polymerization was used to create thermally stable chitosan-g-poly hydrogels with well-defined holes on a fibrous surface. These hydrogels were pH and ionic strength sensitive, with swelling reduced under acidic and strong ionic strength conditions but increased in neutral and basic solutions. Cytotoxicity experiments on HeLa cell lines demonstrated the material's cytocompatibility and preparedness for physiological applications. TDF encapsulation in hydrogels was optimized, resulting in 96% efficiency and 10% drug loading percentage. More intriguingly, in vitro release tests revealed a pH-dependent release of TDF from hydrogels. The drug release at pH 7.4 was five times greater than at pH 1.2 within 96 h. The novel formulated hydrogel-loaded TDF proposed as a smart delivery system for oral administration of anti-hepatitis B drugs.[46]

Sarma A, et al., (2020) designed nanostructured lipid carriers (NLCs)-based intranasal drug delivery system of tenofovir disoproxil fumarate (TDF) for brain targeting. Brain is one of the main reservoirs of HIV. The Blood Brain Barrier (BBB) presents a substantial hurdle in the distribution of TDF to the CNS following systemic injection, rendering it therapeutically ineffective. The intranasal route provides direct access to the brain, bypassing the BBB. As a result, these novel TDF-loaded biodegradable NLCs administered intranasally have the potential to deliver TDF to the brain at a therapeutic level. TDF is modestly soluble in water (13.4 mg/ml) and is pumped out by the BBB's endothelial layers. The current study focused on developing TDF-loaded NLCs made from Compritol 888 ATO and oleic acid. The drug content and entrapment efficiency were determined by UV analysis. The stability investigation demonstrates that NLCs are highly stable in refrigerated conditions and are safe. Three cell line and a histopathology analysis on pig nasal mucosa. TDF NCLs was showing sustained release profile from in CSF. In-vivo pharmacokinetics studies on rat plasma and brain indicated that NLCs are rapidly available in the brain, resulting in increased MRT, Cmax, and AUC. CLSM images of brain cryosections labelled with caumarin-6 NLCs reveal that NLCs localize and accumulate in the brain, delivering TDF over time. The findings indicate that the produced NLCs have the ability to administer TDF in the brain for an extended period of time in the treatment of NeuroAIDS.[47]

Tao X, et al., (2020) studied efficacy and safety of the regimens containing Tenofovir alafenamide versus tenofovir disoproxil fumarate in fixed-dose single-tablet regimens for initial treatment of HIV-1 infection using a meta-analysis of randomized controlled trials. A study comparing the non-inferiority of a TAF-containing combination regimen to a TDF-containing fixed-dose single-tablet regimen in HIV-1-infected individuals compared data from seven eligible randomised controlled trials (RCTs). The study found that TDF can cause renal and bone damage when combined with high plasma tenofovir concentrations in HIV-1 patients receiving antiretroviral therapy. The study used a meta-analysis model built with Stata/SE, combining data from seven RCTs, totalling 6269 individuals. The meta-analysis found that TAF-containing regimens were effective, safe, and tolerable for HIV-1 treatment,

outperforming fixed-dose single-tablet regimens in terms of renal function, bone metrics, and lipid profile in naive patients. [48]

Wassner C, et al., (2020) reviewed about the clinical understanding of TDF against Tenofovir alafenamide. HIV is a chronic medical condition with no cure, and lifetime therapy with a mix of medicines is essential to limit viral replication and prevent consequences. Tenofovir, a newer, more tolerable nucleotide reverse transcriptase inhibitor, is a mainstay in many antiretroviral therapy combinations and is available in two formulations: Tenofovir disoproxil fumarate (TDF) and Tenofovir Alafenamide (TAF). However, their pharmacokinetics significantly influence their efficacy and safety, as they have vastly different pharmacokinetics. Manuscript discusses the history of TDF and TAF development, their distinct pharmacokinetics and pharmacology, clinically significant adverse effects, monitoring, interactions, resistance, a review of clinical studies, guideline recommendations, and clinical applications for tenofovir's various indications.[49]

Puri A, et al., (2019) developed a transdermal delivery system for Tenofovir Alafenamide, a prodrug of tenofovir with potent antiviral activity against HIV and HBV. This study aimed to create a transdermal patch containing TAF for HIV prevention, as oral TAF regimens require daily ingestion, reducing adherence and increasing viral resistance risk. Two types of TAF patches were produced: transparent with acrylate adhesive and suspended with silicone and polyisobutylene adhesives. Vertical Franz diffusion cells were used for seven days to conduct in vitro permeation investigations. An optimized silicone-based patch was evaluated for adhesive qualities and skin discomfort.

The study shows that silicone-based transdermal patches can deliver a therapeutically meaningful dosage of TAF for HIV and HBV control, with acrylate-based patches achieving a maximum flow of 0.60 ± 0.09 μg/cm^2/h and silicone-based patches achieving maximum penetration of 7.24 ± 0.47 μg/cm^2/h. [50]

Venter WD, et al., (2018) describe tenofovir therapy in renal disease for HIV. Antiretroviral therapy (ART) is often linked to TDF-induced nephrotoxicity, with patients on ART at higher risk of developing renal illness due to ART and comorbidities. Clinicians need to control renal illness in TDF patients. TDF is not

commonly associated with acute kidney injury (AKI) or chronic kidney disease (CKD), so doctors should rule out other possibilities. In cases of TDF-associated AKI, TDF should be stopped or ART discontinued entirely. TDF poisoning can manifest as acute kidney injury or chronic kidney disease. TDF significantly impacts kidney function, causing a 10% drop-in glomerular filtration rate (GFR) due to altered tubular function in individuals exposed to TDF for treatment or pre-exposure prophylaxis. Renal function should be evaluated using creatinine-based estimated GFR at the beginning of TDF, after 1-3 months if ART is modified, and every 6-12 months if stable. Specific tubular function tests are not recommended, but spot protein or albumin: creatinine ratios are preferred. Patients with established CKD or risk factors may require more regular monitoring.

Common risk factors for kidney disease include comorbid hypertension, diabetes, HIV-associated kidney disease, co-infection with hepatitis B or C, and TDF combined with ritonavir. Prioritizing these conditions is crucial. If eGFR is below 50 mL/min/1.73 m2, abacavir and dose-adjusted TDF are preferred. If kidney function declines or proteinuria worsens, clinicians should review ART, potentially nephrotoxic medications, comorbidities, and conduct additional testing. If kidney function doesn't improve after treating reversible causes of renal failure, a nephrologist is recommended. In severe CKD cases, prompt referral for renal replacement therapy is advised. Tenofovir alafenamide, a less harmful prodrug, may eventually replace TDF.[51]

Spinks CB, et al., (2017) characterized novel tenofovir liposomal formulations for enhanced oral drug delivery: in vitro pharmaceutics and Caco-2 permeability investigations. Tenofovir disoproxil fumarate, a drug used against HIV/AIDS, has low oral bioavailability. This study aimed to increase its bioavailability by developing and characterizing model liposomal formulations. The entrapment procedure was carried out using the film hydration method, and formulations were evaluated for efficiency and Caco-2 permeability. An effective reverse-phase high-performance liquid chromatography method for tenofovir quantification was devised and confirmed in both in vitro liposomal formulations and Caco-2 permeability samples. Separation was performed isocratically on a Waters Symmetry C8 column.

A method was validated using a flow rate of 1 mL/min and a 12 minutes elution period. The injection volume was 10 µL, and UV detection was done at 270 nm. The positive charge-imparting agent determined the amount of tenofovir encapsulated in the liposomes. The calibration curves were linear, with r2 > 0.9995, and the accuracy and precision varied from 95% to 101% and 0.3% to 2.6%, respectively. The vectors potentiated tenofovir permeability by ten times compared to oral solution. In conclusion, novel and validated method was successfully applied to characterize both in vitro encapsulation efficiency and Caco-2 permeability transport for the pharmaceutical assessment of novel tenofovir formulations.[52]

Ray AS, et al., (2016) published a clinical review of Tenofovir Alafenamide used to treat HIV. Antiretroviral regimens to suppress HIV infection and improve long-term, chronic therapy safety are needed. TAF has superior qualities compared to TDF, which is powerful and well-tolerated but has been linked to renal function changes, decreased bone mineral density, and rare renal adverse effects. TAF is more effective in improving HIV therapy and addressing lifetime therapy in an older, comorbid HIV population, and is more effective in addressing the needs of an increasingly comorbid HIV population. TAF enhances the production of TFV diphosphate, the active metabolite, in HIV-target cells with lower oral dosages. This enhances stability in biological matrices and quick cell activation. All TFV produced in the body is eventually removed renally, reducing off-target kidney exposure. Effective therapy achieves 90% reduced systemic TFV exposure, leading to significant improvements in safety metrics like bone mineral density and kidney function markers.[39]

Agarwal K, et al., (2015) conducted twenty-eight-day safety, antiviral activity, and pharmacokinetics of tenofovir alafenamide for treatment of chronic hepatitis B infection. Tenofovir alafenamide, a phosphonate prodrug of tenofovir, efficiently delivers active drug to hepatocytes while reducing systemic exposure. A study randomized 51 non-cirrhotic, treatment-naïve subjects with chronic hepatitis B to receive either alafenamide or disoproxil fumarate for 28 days. Safety, antiviral response, and pharmacokinetics were assessed, followed by a 4-week off-treatment period. All patients completed the research treatment, with no major or severe adverse events reported.

Tenofovir alafenamide showed similar mean changes in serum HBV DNA at week 4 compared to the control group. The pharmacokinetics of viral decrease were linear and proportional to dose. Doses ⩽25 mg resulted in a 92% reduction in mean tenofovir area under the curve compared to tenofovir disoproxil fumarate 300 mg. Tenofovir alafenamide was safe and well tolerated, with HBV DNA decreases comparable to tenofovir disoproxil fumarate at all dosages tested. [54]

Duwal S, et al., (2012) pharmacokinetics and pharmacodynamics of the reverse transcriptase inhibitor tenofovir and prophylactic efficacy against HIV-1 infection. This study aims to estimate the efficacy of preventive regimens using Tenofovir-disoproxil-fumarate (TDF) and analyze its sensitivity to time, manner of administration, adherence, and the number of transmitted viruses. A pharmacokinetic model for TDF and its active anabolite, tenofovir-diphosphate (TFV-DP), was created and validated using data from four trials with different dosage regimens. The model was applied to an HIV model, and viral decay during TDF monotherapy was predicted based on current data.

A study used a stochastic technique to estimate the percentage of infections avoided by daily TDF-based PrEP, one-week TDF, and a single dose oral TDF. Analytical solutions were developed to determine the relationship between intracellular TFV-DP levels and preventive efficacy. TDF's expected efficacy was limited by slow accumulation of active compound and variable half-life. Daily TDF-based PrEP provided 80% protection when at least 40% of pills were consumed. Sd-PrEP, with 300 mg or 600 mg TDF, can prevent up to 50% of infections when administered before virus exposure. However, its effectiveness decreases to around 10% when taken 1 hour before exposure. Dosage and administration time cannot boost efficacy. Post-exposure prophylaxis doesn't significantly reduce infection rates. The use of faster-accumulating medicines or local tenofovir gel may eliminate the need for drug administration before viral exposure.[55]

Mesquita PM, et al., (2012) developed intravaginal ring delivery of tenofovir disoproxil fumarate for the prevention of HIV and herpes simplex virus infection. A safe and effective topical preventative strategy will most likely include the continuous supply of powerful antiviral medicines, as well as a delivery technology that exploits

drug distribution while also overcoming adherence-related behavioral difficulties. The epidemiological relationship between HIV and herpes simplex virus (HSV), antiviral activity would be helpful. Authors hypothesize that tenofovir disoproxil fumarate (tenofovir DF), a tenofovir prodrug, is more powerful and more suited for sustained intravaginal ring (IVR) distribution. [56]

Patil AT, et al., (2012) employed hot melt coating technique for enteric coating has demonstrated in the present investigation. Pellets made from extrusion-spheronization were chosen as the core for diclofenac sodium due to their advantages. Stearic acid and palmitic acid were evaluated as enteric HMC materials. HMC was performed on preheated pellets in a modified coating pan, achieving a 5-15% w/w coating level. Both SA and PA showed excellent enteric coating ability.[57]

Yu D, et al., (2011) written an article on Tenofovir in the treatment of chronic hepatitis B. Chronic hepatitis B (CHB) is prevalent worldwide. It can cause major consequences, including cirrhosis, and is the most prevalent risk factor for hepatocellular cancer. Treatment for CHB could last a lifetime, and pharmacological interventions must be both effective and safe. The US FDA authorized TDF in 2008 as a therapy for CHB in adults. The clinical trials of TDF have shown exceptional efficacy with powerful antiviral activities, a high barrier to resistance, and a favorable safety profile. This review will include the outcomes of clinical trials that have investigated TDF's efficacy and safety in the treatment of CHB, as well as a discussion of TDF's comparative effectiveness with other licensed CHB medications.[58]

Le H, et al., (2007) A sustained release dosage form of nifedipine by hot melt coating method was designed. Sugar beads, mesh size 30-35 were coated with different waxes: Gelucire 50/13, stearic acid, Syncrowax HGLC, natural beeswax, polawax regular and carnauba wax. Dual coated beads with high melting point waxes in the inner layer and lower melting point waxes as the outmost layers can be prepared by two process hot melt coating technique. Capsules with dual coated beads, carnauba wax and stearic acid, showed similar dissolution profiles and plasma concentration predictions to Procardia XL. Multiple coating can improve the coating and render acceptable sustained release of nifedipine.[59]

Peterson L, et al., (2007) Tenofovir disoproxil fumarate for prevention of HIV infection in women: a phase 2, double-blind, randomized, placebo-controlled trial. The study aimed to evaluate the safety and efficacy of a daily dose of 300 mg of tenofovir disoproxil fumarate (TDF) versus a placebo in preventing HIV in women. The phase II, double-blind, placebo-controlled experiment was conducted in Tema, Ghana, Douala, Cameroon, and Ibadan, Nigeria, involving 936 HIV-negative women at high risk of HIV infection. The study focused on safety outcomes of a drug for HIV-1 or HIV-2 infection, including serum creatinine elevations, hepatic function elevations, and phosphorus abnormalities. Participants provided 428 person-years of laboratory testing for the principal safety analysis, with no significant differences between treatment groups. The primary efficacy analysis involved 476 person-years of testing, with eight seroconversions occurring during the study.

A study found that two HIV-negative women were diagnosed with TDF and six with a placebo, resulting in a rate ratio of 0.35. However, the study's effectiveness was not conclusive due to the early closure of the Cameroon and Nigeria study sites, and the daily oral use of TDF was not linked to increased clinical or laboratory adverse effects. The small number of HIV infections identified during the trial also hindered further evaluation. [60]

Kuo A, et al., (2004) proposed TDF for the treatment of lamivudine-resistant hepatitis B. Lamivudine resistance in chronic hepatitis B patients is increasing at rates of 16%-32% after 1 year and 49% after 3 years. Adefovir dipivoxil, a nucleotide analogue licensed by the FDA, is effective against HBV but has been linked to kidney damage. TDF, another nucleotide analogue, has shown antiviral effectiveness against both wild-type and lamivudine-resistant HBV. Tenofovir, at the approved dose, has not been linked to renal impairment. A series of 9 patients with lamivudine-resistant hepatitis B was studied.

Tenofovir treatment significantly reduced HBV DNA levels in patients with lamivudine-resistant hepatitis B after 12 months of treatment. It resulted in a median drop of 4.5 log10 copies/mL, HBeAg seroconversion in two patients, and normalization of four of seven individuals with high ALT levels. Tenofovir treatment

was well-tolerated and resulted in significant virological, serological, and biochemical improvements comparable to high-dose adefovir without renal toxicity risk.[61]

2.3 Sitagliptin

Ng II, et al., (2024) identified sitagliptin as an antitumor drug targeting dendritic cells network based screening approach. The priming and activation of tumor-specific T lymphocytes is dependent on dendritic cell (DC)-mediated antigen presentation. However, few medicines that directly target DC activities. The discovery of medicines that target DC has enormous potential for cancer immunotherapy. Researchers discovered that after antigen presentation, type 1 conventional DCs (cDC1s) launched a unique transcriptional programme. Researchers employed a network-based strategy to find cDC1-targeting medicines. The potential drug's anticancer activity and underlying mechanisms were studied both in-vitro and in-vivo. Sitagliptin is used to treat type 2 diabetes, has been discovered as a medication that targets DCs. In animal models, sitagliptin decreased tumour development via improving cDC1-mediated antigen presentation, which led to increased T-cell activation.

Sitagliptin inhibited dipeptidyl peptidase 4 (DPP4), preventing the truncation and degradation of chemokines/cytokines required for DC activation. Sitagliptin improved cancer immunotherapy by allowing DCs to prime antigen-specific T cells more efficiently. In humans, using sitagliptin was associated with a decreased incidence of tumour recurrence in colorectal cancer patients having curative surgery. The results showed that sitagliptin-mediated DPP4 inhibition improves antitumor immunity by improving cDC1 activities. These findings indicate that sitagliptin can be repurposed as an anticancer medication targeting DC, offering a possible method for cancer immunotherapy.[62]

Iswariya VT, et al., (2024) developed gastro-retentive floating tablets containing sitagliptin. The tablets contain Pectin and HPMC K as matrix former and lactose monohydrate serving as a diluent. The effervescent agent, utilizing citric acid was the basis for causing the tablet to float. Magnesium stearate and talc are used in this tablet to increase the flow properties of the powder thus it helps in punching of the tablet. The direct compression method facilitated the production of six distinct formulations.

Evaluation of these formulations focused on pre compression studies and post compression studies of the tablet. Consistency was observed across all formulations, indicated by minimal weight variation and good in-vitro dissolution profiles. Among these formulations, M5 distinguished itself as the most promising. It was composed of 3 mg of Pectin and 7 mg of HPMC K, achieving an extended floating duration of 12 hours coupled with an efficient drug release profile over 8 hrs. The performance of M5 suggests its potential as an effective gastroretentive delivery system for Sitagliptin, offering a controlled release that could enhance patient compliance and therapeutic efficacy.[63]

Kumar SD, et al., (2024) validated bioanalytical method for forced degradation, and pharmacokinetic application of sitagliptin in human plasma spiking tests using the UV-HPLC technique. The Shimadzu LC 20AD liquid chromatographic system, which uses manual injection, developed a simple and accurate approach. The optimised chromatogram was produced using acetonitrile in the isocratic mobile phase technique at a flow rate of 1.0 mL/min. The stationary phase was a thermal C-8 column (4.6 × 250 mm, 5 μm), and the detection wavelength was 265.0 nm, using a UV-Vis detector. The proposed approach was validated using ICH recommendations. The approach was linear from 10 to 50μg/mL, with a correlation value of R2 = 0.9746. Recovery studies predicted percentage RSDs of 19.14, 3, and 9.95, respectively. The injection repeatability values were determined to be % RSD 17 and 10.63 for intraday and interday, respectively. The stress degradation experiments found that sitagliptin degrades faster when exposed to 0.1 NaOH. Human plasma spiking investigations found 3.02 ng/mL at 3.02+/-60 minutes of C and T max, respectively.[64]

Nagao M, (2023) conducted study to determine the effectiveness and safety of sitagliptin therapy in elderly Japanese individuals with T2D. The STREAM study involved 176 T2D outpatients aged 65-80 years with moderately controlled glycaemic levels. They were divided into two groups: those who received sitagliptin as an initial or additional anti-diabetic treatment, and those who did not. The treatment aimed to achieve a HbA1c level of less than 7.4%. The study examined the effectiveness and safety of the treatment over a 12-month period. The mean age of the participants was 70.6 years. A study found that sitagliptin significantly improved the glycaemic profile of elderly T2D patients without major side effects. The sitagliptin group experienced

average changes in fasting plasma glucose, HbA1c, and glycated albumin, while the control group experienced changes of 0.50 mg/dL, -0.29%, and -0.93%. The study concluded that sitagliptin medication significantly improved the glycaemic profile of elderly T2D patients without major side effects. [65]

Ardestani, N. S., et al., (2023) proposed new association experimental model to estimate solubility of sitagliptin phosphate, in supercritical carbon dioxide. The solubility of sitagliptin in supercritical carbon dioxide was determined using analytical and dynamic techniques at various temperatures and pressures. The measured solubilities ranged from 3.02 × 10–5 to 5.17 × 10–5, 2.71 × 10–5 to 5.83 × 10–5, 2.39 × 10–5 to 6.51 × 10–5, and 2.07 × 10–5 to 6.98 × 10−5 in mole fraction. The data was correlated with existing density models and a new association model. [66]

Hossain MS, et al., (2023) developed combination of empagliflozin and sitagliptin dosage form to treat type-2 diabetes might be more economical and patient compliance with an additive improvement in glycemic control due to complementary modes of action. The study aimed to create an instant tablet dosage form of empagliflozin and sitagliptin using a statistically valid research design. The formulation was created using Design Expert Software version v.13, focusing on the effects of crospovidone and croscarmellose sodium amounts on disintegration time and drug release. High-performance liquid chromatography (HPLC) testing techniques were used to analyze the formulations. Mice were used to test the efficacy of the anti-diabetic therapy after a high-fat diet and streptozotocin injections.

F3 was found to have the best in-vitro performance out of nine formulations, with an optimal formulation of 100.99% empagliflozin and 100.19% sitagliptin. The disintegration time was 5.32 minutes, and the percentage release of empagliflozin was 89.05% in 30 minutes, while sitagliptin was 93.76%. F3 administration significantly reduced FBG, total cholesterol, triglycerides, HDL, and LDL levels compared to the diabetic control, similar to metformin treatment. A novel combination tablet with empagliflozin and sitagliptin was created using direct compression technique. [66]

Rao A, et al., (2023) formulated floating microspheres of sitagliptin for the treatment of type 2 diabetes mellitus. Because gastro-retentive dosage forms have a lower bulk density than gastric fluids, they can be used as controlled-release drug delivery

systems. The surface morphology of microspheres was examined using SEM. The microspheres were found to be spherical and porous. The Fourier transform infrared (FTIR) technology was used to conduct compatibility. The manufactured microspheres had a 12-hour medication release and were buoyant for longer than that. In-vitro release kinetics were investigated using various release kinetics models, including zero order, first order, Higuchi, and Korsmeyer- Peppas models, and the best match model was determined to be the Higuchi plot with a release exponent n value smaller than 0.89. It was determined that the produced floating microspheres of Sitagliptin provide a good and feasible technique for long-term drug release, improving oral bioavailability, efficacy, and patient compliance.[67]

Gurjar PN, et al., (2023) studied the impact of selective polymer on optimization of sustained release matrix pellets of sitagliptin. Sitagliptin is used in the treatment of non-insulin-dependent diabetes mellitus. The goal of study was to design a flexible dosage form that controlled release and provided therapeutic effects while minimizing negative effects. Various batches of pellets were created using the extrusion-spheronization technique to determine which batch resulted in a sustained release pattern for Sitagliptin. The pellets demonstrated outstanding flow qualities due to their sphericity, which influenced the dosage production rate, as well as the tiny particle size, which allowed for easy dispersion and helped to reduce dose dumping. The pellets released 89.10% in 12 hours. The study shows that the development of sustained-release pellets using selected excipients results in enhanced medication release while minimizing difficulties.[70]

Shi P, et al., (2022) conducted the pharmacokinetics and bioequivalence of test and reference (JANUMET®) formulations of sitagliptin phosphate/metformin hydrochloride tablets at a single dose of 50 mg/850 mg. The study involved 24 volunteers who received a single oral dose of sitagliptin phosphate/metformin hydrochloride tablets 50 mg/850 mg. Liquid chromatography tandem mass spectrometry was used to measure the amounts of sitagliptin and metformin in their plasma. Pharmacokinetic parameters were generated using WinNonlin 7.0, and bioequivalence was assessed using SAS 9.4.

The study found that sitagliptin and metformin had similar geometric mean ratios under fasting and fed conditions. Under fasting conditions, the Cmax, AUC0-t, and AUC0-∞ values were 101.70-120.62%, 99.81-105.61%, and 100.27-106.12%, respectively. Under fed conditions, the Cmax, AUC0-t, and AUC0-∞ values were 90.39-111.48%, 94.76-109.12%, and 95.76-110.38%, respectively. Both formulations were generally well-accepted and bioequivalent in healthy Chinese participants.[71]

Charoo NA, et al., (2022) assessed methods based on the Biopharmaceutics Classification System (BCS) could be used to assess the bioequivalence of solid immediate-release (IR) oral dosage forms containing sitagliptin phosphate monohydrate, as an alternative to a pharmacokinetic study in human volunteers. The BCS was used to evaluate sitagliptin's solubility, permeability, dissolution, therapeutic index, applications, pharmacokinetics, pharmacodynamics, bioequivalence/ bioavailability problems, and drug-excipient interactions. The findings support sitagliptin's classification as a BCS Class 1 medication. The clinical risks associated with moderately supra-optimal and moderately suboptimal dosages are considered insignificant due to its broad therapeutic index and lack of serious side effects. The BCS-based biowaiver can be used for solid IR oral drug products containing sitagliptin phosphate monohydrate, provided the test product is formulated with excipients commonly found in approved solid IR oral drug products and used in the appropriate amounts, and data supporting the BCS-based biowaiver is obtained using the method.[72]

El-Megharbel SM, et al., (2022) synthesized and characterized sitagliptin with divalent transition metals manganese and cobalt metals and their complexes. Mn (II) and Co (II) complexes were examined and characterized using physical methods such as FTIR, DG/TG, XRD, ESM, and TEM. The study found that STG, a bidentate ligand, functions as a bidentate ligand with a square planner shape. The experiment involved 40 male albino rats divided into four groups: control, STG, STG/Mn, and Co/STG. Biomarkers for hepatic enzymes and antioxidants were found in the blood. STG combined with Mn and Co treatment provided significant protection against hepatic biochemical changes, suppression of oxidative stress, and structural changes. These complexes reduced stress and enhanced hepatic enzymatic levels more than STG alone.

The STG/Mn complex effectively combats Bacillus subtilis and Streptococcus pneumonia, while STG/Co is highly effective against Escherichia coli, Pseudomonas aeruginosa, and Staphylococcus aureus. This synergistic effect on oxidative stress enhances liver tissue structure, and STG metal complexes containing Mn and Co show the most potential for antioxidant and hepatoprotective actions.[73]

Shakir R, et al., (2022) developed a mucoadhesive buccal delivery system for the sustained delivery of metformin (MET) and sitagliptin (SIT) against diabetes mellitus (DM) to improve bioavailability. A polymeric blend of Carbopol® 940, agarose, or polyvinylpyrrolidone K30 was used as mucoadhesive agents in formulations R1-15. The tablets were characterized for solid state, physicochemical, and in-vivo mucoadhesion studies in healthy volunteers. Results showed no unusual peak or interaction between drugs and polymers. The mucoadhesive blend of CP and PVP was superior, with complete drug release for 6 hours and ex-vivo mucoadhesive strength and time of 26.99 g and 8.1 hrs, respectively. The optimized formulation was stable for up to 6 months. The formulation R4 demonstrated Korsmeyer-Peppas model and first-order release for SIT and MET, demonstrating hemocompatibility, biocompatibility, and stability. The CP blend with PVP was found suitable for achieving desired release and optimizing mucoadhesive properties of buccal tablets, ensuring pharmaceutical stability. [74]

Patel YD, et al., (2022) quantitatively computed and stability of phase III composition comprising sitagliptin and dapagliflozin propanediol monohydrate by RP-HPLC. The stability performance of a formulation, such as sitagliptin and dapagliflozin propanediol monohydrate, is crucial before it enters the commercial market or clinical trials. A reverse phase high performance liquid chromatography was used to quantify both components in the presence of degradation products from stress testing. The chromatogram was performed on an Inertsil ODS C18 column using Methyl Nitrile and 0.02 M KH2 PO4 buffer, with a flow rate of 1 ml/minute and monitored at 210 nm. All system suitability criteria indicate good separation.The home formulation showed oxidative instability, indicating predictive results of induced stress. The optimized analytical technique was validated and found highly reproducible with higher specificity, making it suitable for routine quantification of

sitagliptin and dapagliflozin propanediol monohydrate from the proposed formulation, as per ICH Q1 guidelines.[75]

Kazi M, et al., (2021) developed & optimized sitagliptin and dapagliflozin loaded oral self-nanoemulsifying formulation against type 2 diabetes mellitus. This study focuses on developing an oral combination dosage form for two anti-diabetic medicines, sitagliptin and dapagliflozin, using self-nanoemulsifying drug delivery systems (SNEDDS). The SNEDDS were created using bioactive triglyceride oil, mixed glycerides, and non-ionic surfactants. Droplet size and antioxidant activity were tested. In-vitro digestion, bioavailability, and anti-diabetic activities were compared with the marketed medication Dapazin®. The SNEDDS with black seed oil demonstrated good self-emulsification performance.

SNEDDS nanodroplets, sized 50-66.57 nm, have a high drug loading capacity and strong antioxidant activity. They significantly increased the Cmax, AUC, and oral absorption of dapagliflozin compared to the commercial product in a rat model. Anti-diabetic research showed that SNEDDS combination dose significantly inhibited glucose levels in treated diabetic mice compared to solo medication therapy. This suggests SNEDDS could be a potential oral pharmaceutical product for the enhanced treatment of type 2 diabetes mellitus. [76]

Sahu E, et al., (2020) developed bilayer tablet containing Metformin Hydrochloride and Sitagliptin Phosphate as a fixed dosage combination for treating type II diabetes. The study was aimed to lower the dosage, frequency, and adverse effects of Metformin Hydrochloride while also promoting medication synergy. Pre-formulation investigations, including drug excipient compatibility, were done for both medications. Metformin Hydrochloride was examined in several formulations with sustained release employing natural hydrophilic polymers, such as Tamarind seed mucilage. They examined Sitagliptin Phosphate quick release formulations made with synthetic super-disintegrants and microcrystalline cellulose. In-vitro dissolving data identified MF3 and SG8 as the most effective formulations for Metformin Hydrochloride and Sitagliptin Phosphate, respectively. Bilayer tablets were created by compressing Metformin Hydrochloride (MF3) and adding Sitagliptin Phosphate (SG8) to achieve a final hardness of 5.0. They were then tested. The bilayer tablet had

a cumulative medication release of 98.6% Sitagliptin Phosphate in 30 minutes and 97.9% Metformin Hydrochloride in 12 hours. The study demonstrated that tamarind seed mucilage had strong polymeric activity and can maintain release for 12 hrs.[77]

Zhao R, et al., (2020) Diabetes mellitus has been described as a chronic endocrine and metabolic disease, which is characterized by hyperglycemia and the coexistence of multiple complications. Currently, diabetes mellitus is treated with insulin, insulin analogues, non-insulin oral hypoglycemic drugs, and genetic drugs. However, there is no complete therapy strategy due to drug deficiencies and administration routes. Adverse reactions from long-term subcutaneous injections and oral challenges like enzymatic degradation, chemical instability, and poor gastrointestinal absorption are challenges. Therefore, developing appropriate delivery systems and exploring complete therapy strategies based on drug characteristics and diabetes mellitus is crucial.

Delivery systems have shown potential benefits in diabetes treatment, improving drug stability, overcoming biological barriers, and acting as intelligent automatized systems to mimic endogenous insulin delivery. This review provides an overview of research advances, drug therapy trends, and their application in diabetes treatment, offering reference for various drugs in the field. It also highlights the potential of delivery systems in reducing hypoglycemia risk.[78]

Bossi AC, et al., (2020) Long-term clinical data from the single-arm persistent sitagliptin treatment & outcomes project were analyzed, which collected information on 440 patients with TD2 (275 men, 165 women; mean age 64.1 years; illness median duration: 12 years) treated with sitagliptin as 'add-on'. Researchers used the UK Prospective Diabetes Study (UKPDS) Risk Engine (RE) to assess the 10-year cardiovascular (CV) risk for each individual patient. Kaplan-Meier survival curves were used to assess drug survival, while repeated measures mixed effects models were employed to examine the development of glycated hemoglobin (HbA1c) and CV risk following sitagliptin administration. At baseline, the majority of patients were overweight or obese (median BMI (kg/m2) 30.2); median HbA1c was 8.4%; median fasting plasma glucose was 172 mg/dL; and median UKPDS RE score was 24.8%, with males (median 30.2%) scoring higher than women (median 17.0%), as predicted.

The median follow-up period after initiating sitagliptin medication was 5.6 years. The study found that sitagliptin medication significantly improved HbA1c levels, with a quick reduction after 4-6 months. Patients who maintained sitagliptin treatment had a significant difference in HbA1c evolution compared to those who switched to another antihyperglycemic medicine. Sitagliptin therapy also improved UKPDS RE score and BMI at 10 years. Adverse outcomes were infrequent, and patients with T2D treated with sitagliptin had better metabolic control and lower CV risk, with no significant side effects. [79]

SreeHarsha N, et al., (2019) designed novel mucoadhesive prolonged release nanocarrier of Sitagliptin for the treatment of diabetics. Patients typically take sitagliptin 50mg twice daily, but only 38% of the medication is reversibly attached to plasma proteins, while 79% is eliminated in urine. The drug content in formulations is 72.5% ± 5%, with a practical yield of 84.9% ± 3%. Sitagliptin nanoparticles with diameters ranging from 210 to 618 nm contribute to long-term drug release, consistent with the Peppas model. FTIR spectroscopy and DSC studies show no significant interactions between sitagliptin and chitosan.

Mucoadhesive nanoparticles with sitagliptin were found to be effective in the gastrointestinal tract for 12 hours, providing superior oral benefits compared to traditional administration methods. This marks the first time a drug-delivery approach using nanoparticles' mucoadhesive qualities has been shown to prolong sitagliptin's release time.[80]

Shukla KV, et al., (2019) formulated transdermal drug delivery of sitagliptin. Sitagliptin was used for treating diabetes, but its oral administration caused such severe side effects. Transdermal patches containing Sitagliptin phosphate were created using solvent casting evaporation techniques. The physicochemical properties of the patches were assessed, including flexibility, thickness, smoothness, weight variation, moisture content, hardness, folding endurance, and tensile strength. The formulation showed flexibility, homogeneous thickness and weight, smoothness, high drug concentration, and low moisture content. In-vitro diffusion studies showed that the formulation with ethyl cellulose: HPMC polymers had a faster release rate than Eudragit: HPMC. The stability studies showed that all patches maintained their

physicochemical properties and medication content even after storage. The compatibility study found no contact between medication and polymers, enabling sustained release of sitagliptin through transdermal patches.[81]

Nair AB, et al., (2019) designed mucoadhesive nanoparticles to represent a potential drug delivery strategy to enhance the therapeutic efficacy in oral therapy. In this study, HPMC and PLGA-based sitagliptin nanoparticles using a nano spray drier were prepared. They were tested for their efficacy in an animal model. Particle size was optimized using response surface methods by investigating the effect of spray-drying process factors (inlet temperature, feed flow, and polymer concentration) on particle size. Ex-vivo and in-vivo investigations in rats were used to characterize the produced nanoparticles for several physicochemical aspects (practical yield, drug content, shape, particle size, temperature, and crystallographic properties), as well as to assess drug release, stability, and mucoadhesive activity. The experiment design advised that a linear model was used to best suit the given design and values. A study found that mucoadhesive nanoparticles, with a drug content of 90.5 ± 3.5%, could be a useful alternative delivery mechanism for sitagliptin oral treatment. The nanoparticles had a yield of 77.4% and a drug content of 90.5 ± 3.5%. They released drugs in two phases: quickly (24.9 ± 2.7% at 30 min) and gradually (98.9 ± 1.8% over 12 hours). The nanoparticles also increased sitagliptin retention in the gastrointestinal tract (GIT) compared to controls, suggesting their potential as an effective oral medication delivery mechanism. [82]

Begum A, et al., (2019) developed floating tablets of Sitagliptin using hydroxypropyl methyl cellulose (HPMC), Xanthum gum, and Guar gum polymers. Floating pills were created utilizing an effervescent technique using sodium bicarbonate as a gas former. The tablets were prepared using the direct compression method. The polymers were tested based on their swelling characteristics and floating time. The in-vitro drug release profile shows that increasing polymer concentration leads to more sustained release. The formulation with 40% Guar gum was optimized for medication release lasting up to 12 hrs. Optimized formulation with 35 mg of floating agent per tablet achieved the required floating lag time. [83]

Ghumman SA, et al., (2018) formulated a floating controlled release drug delivery system of Sitagliptin phosphate to increase drug bioavailability. Tablets were made by wet granulation with psyllium husk and tragacanth gum as release retarding polymers and sodium bicarbonate as a gas generator. Nine batches of floating tablets were tested for physical properties, with all formulations having a floating lag time of less than 1 minute and floating continuously for 12 hours. In-vitro drug release studies were conducted for 8 hours, and the release mechanism was further analyzed using linear regression analysis. F9, which contained 30% psyllium husk, 10% tragacanth gum, and 18% sodium bicarbonate, maintained drug release for longer duration. All formulations followed first-order Higuchi drug release kinetics, with diffusion being the major mechanism of drug release. The produced floating tablets of STP (F9) may be a viable drug delivery technology with prolonged release action and increased bioavailability.[84]

Revathi S, et al., (2018) studied the effects of different variables on the release profile of sitagliptin microspheres. The study prepared sitagliptin microspheres using emulsion-solvent diffusion and ionotropic gelation methods, using cellulose and sodium alginate as polymers. The formulations were optimized using a 2^3 factorial design, considering drug-polymer ratio, stirring speed, and production mode. FTIR and DSC analysis revealed no incompatibility between the polymers. The microspheres were tested for shape, morphology, particle size, swelling, encapsulation efficiency, and drug release kinetics. The drug release was sustained, and the diffusion path followed the cube root law of Hixson-Crowell kinetics. The batch F3 was found to be desirable and was further characterized by scanning electron microscope for morphology.[85]

Haq Asif A, et al., (2018) optimized mucoadhesive nanoparticles of sitagliptin. Due to sitagliptin's short half-life, patients must take 50 mg twice daily, and the protein binding of sitagliptin is about 38%. Roughly about 79% of sitagliptin is excreted intact in urine and eliminated without metabolism. Hence, a better delivery system is required to maximize the benefits of sitagliptin for patients. The optimized sitagliptin nanoparticle sizes ranged from 350 to 950 nm, and their surfaces were smooth and virtually spherical. The drug content and percentage yield were 73 ± 2% and 92 ± 2%, respectively. The optimised sitagliptin nanoparticles showed high bioadhesion time

about 6.1 ± 0.5 h. The swelling of the nanoparticles is 168 ± 15%. The release pattern of sitagliptin from mucoadhesive nanoparticles is consistent with the Korsmeyer-Peppas model. The extended sitagliptin retention time of up to 12 hrs in GIT suggests that the optimised mucoadhesive nanoparticle formulation is more efficient and has a higher potential for oral delivery than traditional sitagliptin administration in the drug solution. The optimized mucoadhesive nanoparticles to improve sitagliptin efficacy.[86]

Jahangir MA, et al., (2018) formulated and statistically optimized sitagliptin-loaded Eudragit nanoparticles (SIT-NPs) and evaluated the in-vitro pharmaceutical quality and in-vivo anti-diabetic assessment. SIT-NPs were created using solvent evaporation and nano-precipitation methods. Factors like eudragit RL100 concentration, tween 80 concentration, and sonication duration impacted particle size, drug loading, and in-vitro drug release. The optimized formulation was tested for surface morphology, CLSM, ex-vivo permeability, and in-vivo anti-diabetic efficacy and stability. The SIT-NPs had a particle size range of 135.86-193.45 nm, 6.36-8.76% drug loading, and extended drug release over 24 hours. The study reveals that SIT-NPopt, a new formulation of SIT, has higher release and permeation rates than SIT-Fs, has been shown to lower blood sugar levels over an extended period, and is stable at both temperatures and has a shelf life of 488 days, indicating its potential for future development in diabetes management. [87]

Mishra RV, et al., (2017) examines pre-clinical and clinical studies on DPP4 inhibitors as prospective treatments for metabolic syndrome. They summaries study findings on DPP4 inhibitors' effectiveness in managing obesity, hyperlipidemia, hypertension, atherosclerosis, and cardiometabolic risk. They discussed formulation techniques for DPP4 inhibitors as a dosage form. Common formulation options for DPP4 inhibitors include instant release, sustained release, and combination treatment.[88]

Griffin JD, et al., (2017) formulated sitagliptin as gel reservoir on a transdermal patch, optimized using mathematical modelling, and verified in-vitro diffusion with Franz diffusion cell. The mathematical model was established the ideal design parameters, which comprised 1% w/w cellulose as a drug reservoir, transdermal patch rate control membranes, 1.25 mM beginning drug concentration, 2 mL initial volume,

and a patch size of 4.52 cm^2. To confirm the modelling, this optimized reservoir composition was produced in the transdermal patch system and tested using Franz Cell. The testing results from the constructed transdermal patch system demonstrated that Sitagliptin may be formulated in a patch to attain the desired effective plasma drug concentration in less than one hour and is capable of maintaining glycaemic control for more than 24 hours.[89]

Hayes J, et al., (2016) published an evidence-based review about Sitagliptin/metformin fixed-dose combination in type 2 diabetes mellitus. Type 2 diabetes is a progressive illness with high morbidity and death. The strict glycaemic management lowers the occurrence and progression of problems. To meet glycaemic objectives, patients frequently require a combination of oral medication and/or insulin, as well as lifestyle changes. Unfortunately, many standard medications for type 2 diabetes are linked with weight gain and hypoglycemia, resulting in low compliance and decreasing glycemic control. The sitagliptin is used in type 2 diabetes treatment offered in a fixed-dose combination with metformin. Phase III clinical studies have shown that this combination improves glucose control while having few side effects. They describe pharmacological action, effectiveness and safety along with role of combinations used in practice currently.[90]

Shakya S. (2016) designed and evaluated 50 mg Sitagliptin Phosphate immediate release (IR) tablet using response surface methodology (RSM) using Minitab 16 for optimization study. Minitab 16 was used to create 13 immediate release formulations using a two-factor, two-level Central Composite Design (CCD). The quantities of Sodium Starch Glycollate (SSG) and Croscarmellose Sodium (CCS) in the IR layer were employed as independent variables, while the percent drug release at 15 min was chosen as the dependent variable for optimization. All formulations were developed and tested with appropriate analytical technology. Based on the in-vitro dissolution data (dependent variable/response), the formulation composition with the best drug release for immediate release was determined and used to create optimized tablets, which were then evaluated. The physicochemical properties of all the tablets were satisfactory. The optimized sitagliptin phosphate IR tablet dissolved in 14 sec and demonstrated an initial Sitagliptin release of 99.072% within 15 min.[91]

Ahmed MG, et al., (2016) formulated gastro retentive floating drug delivery systems (GFDDS) of sitagliptin to increase the therapeutic efficacy & gastric residence time and to reduce frequency of administration. As a result, a controlled release drug was preferred in order to create a longer therapeutic effect while also reducing peak and valley effects in plasma concentrations. They developed gastro-retentive dosage forms that remain in the stomach for an extended period of time, allowing the drug to release near the absorption zone. The tablets were made using the direct compression method with polymers such as HPMCK100, polyvinylpyrrolidone, and polyacrylic acid in varying quantities. The prepared granules were evaluated for angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio, with satisfactory results. The compressed formulations were then evaluated for thickness, friability, hardness, swelling index, and in-vitro dissolution studies. All of the formulations produced satisfactory results that were consistent with pharmacopeial norms. In-vitro dissolution tests were performed in pH 1.2 buffers. In-vitro dissolution experiments revealed that the cumulative % drug release of all formulations ranged between 92.96% and 99.28% after 12 hours. The in-vitro drug release data was fitted to a variety of mathematical models.[92]

Kumari S, et al., (2016) developed gastro retentive matrix sitagliptin tablets are intended to prolonged stomach residence duration, boost drug bioavailability, and sustained drug release. The tablets were made using polymers like HPMC, xanthan gum, and a polymer-sodium bicarbonate combination. They were produced through a wet granulation process and tested for pre-compression parameters, physical properties, in-vitro release, buoyancy time, lag-time, and swelling index. Kinetic release studies revealed drug release was primarily diffusion combined with polymeric relaxation. The F13 formulation, which remained buoyant and released 98% of the drug after 12 hours, remained unchanged in physical appearance, content, and floating lag time after three months of storage.[93]

Sakura H, et al., (2016) studied effect of sitagliptin on blood glucose management in people with type 2 diabetes mellitus who had previously been untreated or who responded poorly to existing antidiabetic medicines. A study added sitagliptin to pre-existing type 2 diabetes treatment and compared changes in glycated hemoglobin (HbA1c) levels after three months. Results showed a significant reduction in HbA1c

levels after one month, with a mean reduction of -0.73%. Patients receiving medium dosages of glimepiride showed the least improvement. However, the percentage of patients with a HbA1c level below 7.0% increased dramatically after one month, reaching 53.1% after three months.

Sitagliptin therapy significantly increased the percentage of patients with a fasting blood glucose level below 130 mg/dL, reaching 50.9% after three months. It improved HbA1c levels and goal control levels in type 2 diabetes patients who were untreated or poorly responsive to conventional medications. However, adding sitagliptin to medium-dose glimepiride only minimally improved blood glucose management when adjusted for baseline HbA1c levels.[94]

Brahmandam KK, et al., (2014) developed a novel gastro-retentive floating tablets of Sitagliptin Phosphate employing a direct compression approach with lactose as a diluent. FTIR measurements were used to determine the drug-excipient interaction. Nine formulations of Sitagliptin Phosphate tablets were created using HPMC K100 and HPMC K4M as release retarding agents. All formulations showed minimal weight fluctuation, quick dispersion time, and rapid in-vitro drug release. The best formulation, with 15% HPMC K100, demonstrated an excellent release profile, with full drug release within 24 hours. This suggests that floating tablets of Sitagliptin Phosphate can be prepared effectively with release retarding polymers.[95]

Surinder K, et al., (2013) disguise the highly unpleasant taste of Sitagliptin Phosphate Monohydrate and develop a rapid disintegrating tablet (RDT) of the taste-masked medication. Sitagliptin Phosphate Monohydrate was complexed with Indion 414 in various ratios to disguise its taste. Drug-Resin complexes were evaluated for drug content, in-vitro taste in simulated salivary fluid (SSF), and molecular properties. Complexes that did not release medication in SSF were taste-masked and selected for formulation RDTs. The complex with drug-Resin ratios of 1:1 and 1:2 was chosen. Tablet attributes like tensile strength, wetting time, water absorption ratio, in-vitro disintegration time, and oral cavity disintegration were studied. The study found that batch F2 tablets containing microcrystalline cellulose for Crospovidone disintegrated faster in 25 seconds, with a strong association between disintegration behavior in-vitro and oral cavity. Sitagliptin Phosphate Monohydrate was scored higher, and batch

F2 tablets demonstrated fast drug release in SGF, indicating that the tablets effectively conceal flavor and disintegrate quickly.[96]

Johnson KM, et al., (2011) described Sitagliptin as a DPP-4 inhibitor for the treatment of type 2 diabetes mellitus. Type 2 diabetes mellitus (T2DM) is an epidemic with global forecasts predicting over 336 million people will have the condition by 2030. T2DM is defined as abnormally high blood glucose levels due to lack of insulin secretion or action. Less than half of patients with T2DM maintain good glycemic control. Sitagliptin, a new diabetes treatment authorized in the US and Europe, reduces the action of DPP-4, a peptidase that degrades GLP-1.[97]

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