REVIEW ARTICLE

Drug delivery approaches of an antiviral drug: A comprehensive review

Ramya Devi Durai

Department of Pharmaceutical Technology, School of Chemical and Biotechnology, SASTRA University, Thanjavur, Tamil Nadu, India

The guanine derivative antiviral drug acyclovir (ACV) is one of the oldest molecules laying successful market until date, being commercially available in various dosage forms for oral, topical and parenteral administrations. Clinical application of this drug is superior to new antiviral agents due to its potential values such as suppression of recurrence, safety profile, minimal drug interactions, and being inexpensive. ACV is slightly water-soluble, less permeable and poorly bioavailable, yet more potential antiviral molecule, the physicochemical modifications and novel dosage form approaches resulted with more than 100 research works within a decade. The survey of literature showed enormous reports on ACV formulation development, which includes modified tablets, particulate drug delivery, vesicular drug delivery, polymeric nanoparticles, bioadhesive systems, floating dosage forms, *in situ* gelling systems, transdermal delivery, implantable systems, emulsified dosage forms, polymeric films/patches, etc. As the drug could be administered via multiple routes for effective site targeted action at various doses, and attracted the attention of many researches, the review of the current approaches for the delivery of ACV could be more beneficial for the new scientists. This paper is a review of recent researches highlighting the development of newer techniques and novel dosage forms of ACV for better therapeutic efficacy, which were aimed at enhancing its solubility, permeability and bioavailability.

Key words: *Acyclovir, bioadhesive, complexation, floating, hydrogel, implant, particulate, vesicular*

INTRODUCTION

The synthetic purine nucleoside analogue acyclovir (ACV) approved by Food and Drug Administration (FDA) in 1982, was the first effective antiviral molecule, which is very extensively used to cure the wide range of infections caused by herpes simplex virus (HSV) 1 and 2, varicella-zoster virus (VZV), Epstein–Barr virus and cytomegalovirus in major parts of the body. Since the time of synthesis and discovery in 1974, none of the latest antiviral medicine has been shown to be more successful than ACV for the management of HSV infections. It is commercially available in the form of tablets, capsules, oral suspensions, topical creams, eye drops, nasal ointment, rectal gels, intravenous injections, intravenous infusions, powder for infusion solution, etc., marketed in brand names such as Zovirax, Avirax, Virax, Civar, Lovir, GenRX worldwide, with the dose ranging from 200 mg to 800 mg, 5 times/day; the dose and dosing frequency depending on the severity of infections and the intra and inter-subject variability in their responses.

Even though there are new antiviral medicine invented in the field, including its prodrug molecule, it has shown significant positive effects such as very effective suppression of recurrent genital herpes and HSV shedding, excellent clinical safety profile specially for the pregnant women (till date, the unpleasant effects reported in fetus or newborn are nil), negligible hazards of drug interactions, reasonably priced, administration in all the routes, that make the molecule successfully continued for antiviral therapy till date. The mechanisms of its antiviral activity are competitive inhibition of viral DNA polymerase, incorporation into and termination of the growing viral DNA chain and inactivation of

Address for correspondence:
Prof. Ramya Devi Durai,
Department of Pharmaceutical Technology,
School of Chemical and Biotechnology, SASTRA University,
Thanjavur - 613 401, Tamil Nadu, India.
E-mail: ramya@scbt.sastra.edu

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the viral DNA polymerase. ACV has also proved minimal toxicity since it does not interfere with DNA synthesis in the uninfected cells.

Acyclovir was classified under BCS class III according to World Health Organization guidelines, whereas some scientists propose that this molecule can be classified under class IV, considering its highest dose strength of 800 mg. The drawbacks observed in the physicochemical and pharmacokinetic properties of this guanine derivative such as slight water solubility (1.3 mg/mL at 25°C), poor permeability (0.12×10^{-6}–2.0×10^{-6} cm/s), short half-life (2.5-3.3 h) and poor oral bioavailability (10-20%) have attracted the attention of many researchers to make efforts in designing modified novel dosage forms, ultimately aiming to achieve 100% success in its therapy. Since the physicochemical characteristics of an active pharmaceutical ingredient (API) are the exclusive criteria responsible for its stability, solubility and permeability, certain scientists have worked on these properties of ACV such as ionization,[1] structural and electronic properties,[2] polymorphism and pseudopolymorphism,[3-5] compatibility study with excipient,[6] which ultimately helped in the suitable modifications for the dosage form designing.

This paper is a review that focuses on different research works, especially aimed on the modification and development of ACV drug therapy by applying modern techniques as shown in Figure 1, to enhance the bioavailability and therapeutic efficacy of the drug.

FORMULATION DESIGNS

Modified release tablets

The release modification aspect is effectively achieved in single dose systems like tablets. Since tablets are the conventional type of dosage form for most of the drugs including ACV, modifications in such systems are easily acceptable by the patients. The variety of tablets have been described by various researchers such as buccal, sublingual, dental, floating, bioadhesive, vaginal, rectal, etc., based on matrix or reservoir type of drug composition in the system.

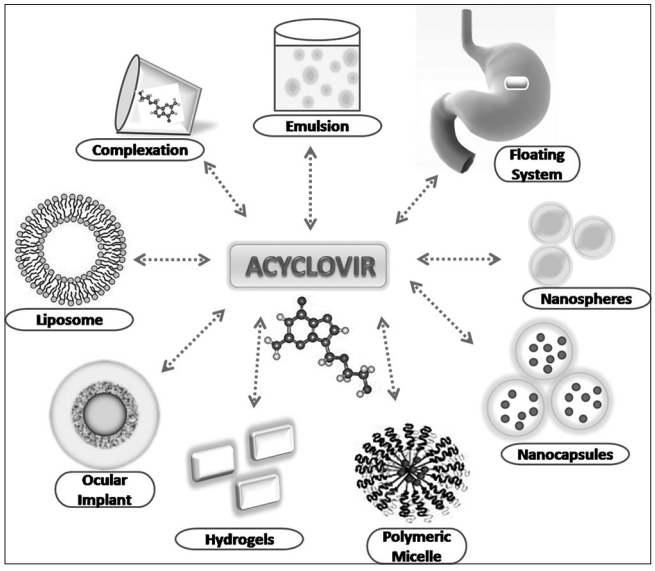

Figure 1: Novel formulation approaches of acyclovir for antiviral therapy

Oral disintegration tablets of ACV were developed by direct compression and wet granulation methods with the addition of super disintegrants like croscarmellose sodium and sodium starch glycolate. Tablet containing sodium starch glycolate showed excellent *in vitro* dispersion time, with maximum drug release in 10 min.[7]

In another study, a matrix type of ACV tablets was prepared using hydrophilic polymer hydroxy propyl methyl cellulose (HPMC) K4M and was estimated for percolation threshold by kinetic parameters with respect to excipient volumetric fraction at time zero plus initial porosity, and water uptake measurements using modified Enslin apparatus. According to percolation theory, the critical points observed in dissolution and water uptake studies can be attributed to the excipient percolation threshold. This threshold was situated between 20.76% and 26.41% v/v of excipient plus initial porosity.[8]

As a model of responsive drug delivery system, magnetic depot tablet was designed for the peroral administration to prolong the gastrointestinal transit. *In vivo* bioavailability study was carried out in healthy male volunteers to investigate the influence of extracorporal magnets. When the magnet was positioned in stomach region, the amount of ACV in plasma was significantly higher at 7, 8, 10, and 12 h and the estimated area under the concentration-time curve $(AUC)_{0-24}$ was 2802.7 ng/h/mL.[9]

Floating delivery systems

Floating systems effectively targets the stomach and upper part of the small intestine through its buoyancy and are specifically valuable for the drugs, which exhibit absorption window in such sites. They can be designed as both single unit and multiple unit dosage forms.

The single unit dosage form of floating capsules of ACV was designed using low density polymers, in which HPMC K4M provided a zero order sustained release of the drug.[10] The same group tried to develop floating matrix tablets using the similar excipients with the addition of Comprito 888 ATO (Gattefosse, France) to enable direct compression of the mass, which showed zero order drug release mechanism.[11] Other matrix type floating tablets of ACV was also formulated using HPMC K100M, HPMC K15M and natural gums such as locust bean gum, sodium alginate and xanthan gum, the former two being done by direct compression and the later three done by effervescent technique.[12,13] Similar type of controlled release floating matrix tablets of ACV was designed

using combination of HPMC K15M CR and polyethylene oxide (Polyox WSR 303). The 3^2 factorial study showed best results with respect to drug release and stability for the optimized formulation containing 50 mg of Polyox WSR 303 and 15 mg of HPMC K15M.[14]

Multiple unit floating microspheres was designed using ethyl cellulose by double emulsion solvent evaporation method which showed sustained release for 10 h and buoyancy up to 12 h.[15] With the similar concept, ACV-chitosan floating system was also prepared using novel lyophilization technique.[16] An oil entrapped floating beads were prepared by the emulsion-gelation method, in which the percentage of oil played an important role in controlling the floating behavior. The beads containing 20% oil and 2:1 drug: polymer ratio showed an optimum entrapment efficiency of 89.54% and sustained release for 8 h, with Higuchi model kinetics $n < 0.5$ under fed state conditions.[17]

***In situ* gelling systems**

The *in situ* gelling system have been identified as one of the successful techniques for the delivery of drugs by various routes, including oral, parenteral, nasal, ophthalmic, rectal, vaginal administration, through suitable mechanisms like temperature sensitive, pH sensitive and ion-sensitive triggers.

Various polymers identified for this purpose includes Pluronic F127, Gelrite, Carbopol 934P, HPMC K100M, sodium carboxymethyl cellulose, methyl cellulose, xyloglucan, tamarind seed polysaccharide (TSP), sodium alginate, carrageenan, and certain hydrogels. Using the former 4 polymers, a novel emulgel for ACV was designed, which was identified to follow non-Fickian anomalous transport of release kinetics.[18] The ocular *in situ* gel developed using xyloglucan and TSP (0.2-0.8%) with alginate (0.8%) base provided around 75% drug release at 8 h, with enhanced precorneal residence time proved by gamma scintigraphic technique.[19]

Another pH sensitive *in situ* gel system for ophthalmic delivery was developed, which exhibited pseudoplastic type of flow, for which the corneal permeation test was also done using rabbit cornea in Franz diffusion model. The ocular residence time (22.4 ± 1.4 min) of the *in situ* gel was found to be 5.6 times higher than eye-drops (4.0 ± 0.5 min).[20] ACV niosomes was developed by reverse phase evaporation method and incorporated in carbopol 934 with methyl cellulose combination gels to develop a novel *in situ* hydrogel system for ocular delivery. The drug present in the hydrogel released its content within 4-5 h, followed by the niosomes showing its sustained release for still longer time.[21]

The effect of carrageenan on poloxamer 407 based composite thermo sensitive *in situ* gel for vaginal route of administration was studied through an *in vivo* experiment, which indicated that the presence of carrageenan have prolonged the local residence of ACV significantly and enhanced the bioadhesive effect of acrylic acid polymers like carbopol synergistically.[22] Similarly, the effect of pluronic on ACV skin permeation and accumulation was investigated for its sol system using rabbit ear frozen skin in Franz diffusion cell.[23]

Implantable delivery systems

Implantable system (matrix or reservoir type) which can provide controlled release of drug in the target site was well suited for the delivery of ACV. This was found to be more successful in the treatment of viral infections caused by HSV, especially in the ocular region being used as ocular inserts, in vaginal region as vaginal inserts or rings, and also for subcutaneous delivery using implants.

Matrix type ocuserts of ACV were fabricated using water-soluble polymers like polyvinyl alcohol and methyl cellulose by film casting method, in which the rate and drug release profile was easily modified by varying the additives.[24] In another matrix type implant, ACV-cyclodextrin complex was dispersed in HPMC medium and then sandwiched between cellulose acetate phthalate (CAP) for controlling the rate of drug release. This product remained stable with shelf life of 1.8 years. The *in vitro* release was found to be most favorable with 5% CAP in the membrane and the *in vivo* evaluation carried out in rabbits showed a significant *in vitro/in vivo* correlation (IVIVC) with the release studies.[25]

Reservoir type ocular inserts were also developed with HPMC K4M, Polyvinylalcohol, sodium alginate, Eudragit RL 100 and Eudragit RS 100 (Paras Pharmachem., Pune, India), which showed zero order release and was found to be stable, sterile and nonirritant.[26] An implant containing 2.5% sodium alginate with 3.5:1.5 ratio of Eudragit RL 100 and RS 100 *in vivo* showed the presence of 1.7 μg/ml of ACV in the aqueous humor after 8 h, which remained up to 5 days and also supported with high IVIVC.[27] ACV incorporated as a binary system with β-cyclodextrin and dispersed into HPMC, was made as the reservoir for the implant, and the release was controlled up to 20 h with non-Fickian diffusion behavior and high IVIVC in release rate studies.[28]

Controlled drug release was achieved by soluble ocular insert containing the combination of natural hydrophilic and hydrophobic polymers.[29] A novel bioengineered corneal implants with ACV loaded silica nanoparticle carriers was fabricated for the controlled release of the drug during the corneal transplantation surgery. The drug release from the biosynthetic implants was sustained over 10 days, in comparison with free ACV incorporated directly into the hydrogel constructs. This enabled effective prevention of virally-induced cell death, which could not be observed with the free drug.[30] ACV was incorporated into microporous polycaprolactone matrices for designing as controlled release intravaginal ring insert for the female genital tract viral infections. A zero-order controlled release of the drug

was observed for 30 days and the improvement in antiviral activity was proved using vero cell lines.[31]

As the long-term administration of ACV can reduce the frequency and severity of reactivation of HSV and VZV infections, a subcutaneous delivery system was designed using an implantable silicone (MED-4050 and MED-4750) device. The *in vitro* observations showed protection against both viruses, and the device provided quantified drug release with an initial burst effect for 5 days, followed by a long period of sustained release, with an average daily release of 1.4 μg over 20-60 days.[32]

Vesicular delivery systems

Vesicular systems are suitable for encapsulating both hydrophilic and hydrophobic drugs, and also provide controlled release with improved efficacy and bioavailability. They include liposomes, niosomes, ethosomes, etc., which were reported as better choice for designing ACV drug delivery [Table 1] since it is slightly soluble in aqueous media and also have poor permeability across biological membranes.

Various bioavailability studies of the niosomes and liposomes have been reported with remarkable improvement in drug delivery. Niosomal delivery on *in vivo* oral availability demonstrated using rabbit models proved 2 fold improvement in bioavailability in relation to the free solution with an evidence of increase in the mean residence time (MRT).[45] Bioavailability of liposomal mucoadhesive gel through intranasal route was 60.72% that was comparable with the intravenous route.[46] Ocular pharmacokinetics of ACV encapsulated in liposomes compared to an ointment showed that the aqueous humor concentration and AUC was significantly higher in the liposomes.[47]

Microparticulate delivery systems

Particulate type of delivery systems include microspheres, microcapsules, nanospheres, nanocapsules, microbeads, co-crystalline particles, etc., each have specific objectives and scope in drug delivery to the target sites. ACV microparticulate systems have been reported by different researchers, as summarized in Table 2. They are biodegradable or nondegradable depending upon the polymers employed in its design (natural/synthetic) and the mechanism and site of drug release.

Nanoparticulate delivery systems

Under particulate type of delivery systems, nanoparticles (NP) have been identified to show effective targeting at cellular level and also in permeation into the site of action. These systems have multi-route function depending on the different type of polymers and design of the dosage form. Furthermore different methods are employed for research on its physiochemical results. Several authors have also optimized the formulations through factorial design and proved the effectiveness of the NP through *in vivo* animal study models. The data collection of optimized formulations through factorial designs is shown in Table 3.

A nonpolymeric nanoassemble type of drug delivery was designed and its *in vivo* pharmacokinetic performance in rabbits was evaluated. In this work, chemical linking of ACV was done to synthesize a new ampiphilic prodrug which was then formulated as NP through nanoprecipitation method. The pharmacokinetic profile of the nanoassemblies in tear fluid and aqueous humor showed increased absorption of the drug as compared to free drug solution.[87] Recently, five new molecules were synthesized and characterized for their capacity to form NP in water and to encapsulate ACV with high loading and sustained release.[88]

The features of NP used in clinical therapeutics like US FDA-approved nanomedicines were characterized through various analytical methods for physicochemical characterization, sterility, pyrogenicity assessment, biodistribution (absorption, distribution, metabolism and excretion) and toxicity studies.[89]

Modified release systems based on complexation

Complexation of a drug with polymeric excipients results in solubility enhancement, stability modification, sustained release, etc., depending on the principle mechanism of complex formation and the type of polymer involved in the process.

The solubility of ACV was enhanced by solid dispersion and inclusion complexation phenomenon using solvent evaporation method.[90,91] ACV formed a Crick-Watson hydrogen-bonded complex with cytosine in presence of dimethylsulfoxide which demonstrated solubility characteristics with 12-fold increase as compared to the saturated solubility of pure ACV. The solid-state ^{13}C nuclear magnetic resonance (NMR) experiment results showing the spectra and T1 relaxation times evidenced that this complex can be isolated.[92] Similarly, the complexation of tricyclic ACV derivatives in buffered aqueous solutions of hydroxypropyl-β-cyclodextrin at pH 5.5 and 7.0 have showed a noticeable increase in their solubility, at 25°C and 37°C. The formation and presence of this inclusion complex was proved by ^{1}H-NMR and DSC analysis.[93] The complexing capacity of β-cyclodextrin/poly (amidoamine) copolymer with ACV was determined and the antiviral activity of complexed ACV was evaluated against virus cell cultures of HSV type I, for which the complex was found to elicit greater antiviral activity than the pure drug.[94]

A reconstituted High Density Lipoprotein-ACV palmitate complex was formed with the aim of targeting liver and anti-hepatitis B virus (HBV) activity. This complex resulted in encapsulation efficiency up to 97% when the ACV palmitate and phosphatidylcholine ratio was 1:20. The *in vitro* HBV

Table 1: Vesicular systems of ACV for antiviral therapy

Vesicular system	Materials used	Processing methods	Significant results
Liposomes	Anion and cation inducers, cholesterol, phospholipid, phosphotidyl choline, phosphatidyl ethanol amine, soya lecithin	Film hydration method, reverse phase evaporation method, thin layer evaporation method	Positively charged liposomes resulted in effective increase in ACV absorption. Oligolamellar and multilamellar vesicles with 5-10 fold increase in drug entrapment and significant change in flux and drug release[33-36]
Liposome based topical gel	Carbopol, soya lecithin and cholesterol	Reverse phase evaporation method	ACV loaded liposome with mean particle size <112 nm in topical gel showed negligible skin irritancy, better skin tolerance and prolonged drug release than the marketed product[37]
Multivesicular liposomal depot delivery	Amphipathic lipids cholesterol, tributyrine	Reverse phase evaporation method	Bioavailability of liposomes was 1.5-and 3-fold superior than conventional liposomes and free drug solution, respectively[38]
Niosomes	Cholesterol, span 80, span 60, span 40, span 20, tween 80	Hand shaking method, ether injection method, film hydration method, reverse phase evaporation method	Ophthalmic niosomal formulation showed more sustained release and in vitro corneal permeation study for its hydration level was performed using corneal membrane of rabbit eye and ocular irritation study done qualitative *in vivo*[39-41]
Proniosomes	Span 60, cholesterol, maltodextrin	Slow spray coating method, slurry method, coacervation phase separation method	Proniosomes was a stable carrier for oral delivery and its *ex vivo* intestinal permeability studies showed that the drug diffused at a quicker rate from the proniosome compared to the drug solution[42]
Ethosomes	Ethanol and phospholipid	Sonication method	Ethosomes prepared with 30% ethanol showed highest entrapment efficiency and particle size of 1.411 μm[43]
Nanoliposomes and nanoniosomes	-	Comparison study - niosomes better, stable and suitable for intravenous delivery	Liposomes demonstrated 90% drug release in 150 min whereas only 50% of drug was released from niosomes in 200 min, confirming that niosomes were stable and better than liposomes for intravenous delivery[44]

ACV: Acyclovir

inhibition assay showed 20% inhibition level and the biodistribution level evaluated at 30 min after injection proved that the dose could be recovered from the tissues as 71.2%, 10.2% and 18.6% from liver, plasma and rest of the body, respectively.[95]

Bioadhesive drug delivery systems

The adhesive systems can be single unit (tablet/capsule) or multi-unit (particulate type or vesicular type) dosage forms, which adhere to the mucous lining of the biological membranes or surfaces of the specific site of action and provide drug release for prolonged period of time. Since ACV can be administered by many routes, these types of systems can be well suited for different site-specific targeted delivery of the drug.

For the nasal administration, ACV liposome formed by thin film hydration method using L-α-Dipalmitoylphosphocholine and cholesterol were incorporated into bioadhesive system of polyvinyl pyrrolidone (2-6%)/chitosan 2%/carbopol 2%. The *in vivo* study in rabbits proved 60.72% of bioavailability through intranasal administration, which was 3 fold increase compared to oral route (15-20%).[96] A similar type of liposome incorporated bioadhesive hydrogel was sketched by polyol dilution method for the vaginal delivery liposomes of ACV into bioadhesive hydrogel of carbopol 974P resin. The stability of the gel was perfect that after 24 h incubation of hydrogel, 35% of drug retained in the hydrogel.[97] An *in situ* forming mucoadhesive hydrogel of ACV was fabricated using novel combination of poloxamers and hyaluronic acid. The rheological analysis (Newtonian/pseudoplastic behavior), photon correlation spectroscopy (micellar diameter) and mucoadhesion studies (mucin adhesion) were observed for the formed hydrogel.[98]

Mucoadhesive multiparticles (microspheres) were developed with ethylcellulose and carbopol 974P NF being used as microsphere matrix and mucoadhesive polymer, respectively. In this study, the eggshell membrane was identified to show a potential use for *in vitro* mucoadhesion measurement in place of stomach mucosa. Prolonged residence time was observed in rats' gastrointestinal tract, with improvement in the bioavailability measured as AUC_{0-t} and MRT of 6055.9 ng/h/mL and 7.2 h respectively, which were higher than that of ACV suspension (2335.6 ng/h/mL and 3.7 h).[99] Another mucoadhesive multiparticles (microcapsules) were prepared by ionotrophic gelation technique with coating using alginate,

Table 2: Microparticulate drug delivery approaches of ACV

Microparticulate systems	Polymers employed	Method adapted	Significant results
Biodegradable microspheres	Polylactides and PLGA biopolymers	Spray drying method	Efficient for intravitreal administration[48]
Microspheres	Carbopol	Spray drying technique	Optimized formulation from 3^2 full factorial experimental design showed higher percentage yield (33%) and encapsulation efficiency (91.23%)[49]
Microparticles	PLGA	Solvent evaporation technique	The drug distribution study of microparticles in porcine skin layers showed higher drug concentration in the basal epidermis, as compared with plain drug suspension, hence more effective for topical administration[50]
Microspheres	Sodium alginate, HPMC, sodium CMC	Ionic gelation method	Particles in size range of 100-200 μm and controlled drug release reaching 98.8% after 12 h[51]
Microcapsules	Egg albumin, guar gum and ethyl cellulose	Solvent diffusion method and heat coagulation method	Particle size was similar and narrow range (700-1000 μm), but the morphology was varying as, wavy surface with guar gum, porous in ethyl cellulose and smooth in egg albumin formulations[52]
Microcapsules	Bakers yeast	Mechanical stirring	Mean particle size was 8 μm and showed Fickian model of diffusion mechanism during the *in vitro* release studies[53]
Microencapsulated particles	Ethyl cellulose	Solvent evaporation method	Multiparticulate delivery system statistically optimized by simplex lattice mixture design showed drug entrapment efficiency of 88-96% and the controlled release of 11-81% after 8 h[54]
Microencapsulated particles	Ethyl cellulose	Novel solvent evaporation matrix erosion and spray drying technique	In both methods, the size of the particles was in the range of 7-25 μm with spherical geometry due to high cross-linking density, encapsulation efficiency was as high as 91% and also provided more sustained release by spray drying method compared to the solvent evaporation method[55]
Microspheres	Acrylamide grafted dextran and chitosan	Emulsion-crosslinking method	A semi-interpenetrating polymer network of microspheres was obtained using gluteraldehyde as cross-linking agent with the grafting efficiency of 94% showing average particle size of 265-388 μm and encapsulation up to 79.6%[56]
Microspheres	Malonyl chitosan	Coacervation phase separation process	Cross-linked microspheres were synthesized by treating malonic acid with gelled chitosan microparticles which exhibited median release time of 5.5 h showing non-Fickian and super case II kinetics at pH 1.2 and 6.8, respectively[57]
Microparticles, micro and NP	Chitosan	Spray drying process	The drug was transformed into amorphous form in the microparticles as proved by the DSC and XRPD analysis. The amounts of ACV effectively diffused in 24 h were 30, 430 and 80 μg for the ACV solution, microparticles and NP respectively. SMI assay proved that chitosan-based particles induced moderate irritation and mild tissue damage[58,59]
Co-crystals	Tartaric acid, citric acid	Solution-crystallization method and liquid-assisted cogrinding	Co-crystallization and amorphization of ACV with tartaric acid and citric acid improved the physical characters and dissolution properties[60]
Co-crystals	Chitosan	Simple solvent change method	Fabricated ACV-chitosan co-crystals was identified as one of the simple approach with effective stability, compatibility, drug content and sustained release of drug[61]
Complex and co-crystals	Maleic acid, fumaric acid and glutaric acid	Reaction crystallization	Three different ACV complexes such as one salt with maleic acid and two cocrystals with fumaric acid and glutaric acid, have been reported with enhanced solubility and permeability of the drug, through the dissolution study and *in vitro* skin permeation experiment, respectively[62]

ACV: Acyclovir, PLGA: Polylactide-co-glycolide, HPMC: Hydroxy propyl methyl cellulose, CMC: Carboxymethyl cellulose, NP: Nanoparticle, DSC: Differential scanning calorimetry, XRPD: X-ray powder diffraction, SMI: Slug mucosal irritation

Table 3: Nanoparticulate drug delivery systems of ACV

Polymers employed	Method used	Significant results
Polybutyl cyanoacrylate	Emulsion polymerization technique, single factor optimization	Size of 108.5 ± 94.8 nm, embedding ratio of 71.8% and drug loading as 18.5%[63]
β-cyclodextrin-poly (4-acryloylmorpholine)	Solvent injection method	Superior antiviral activity in two clinical isolates of HSV-1[64]
PLGA	Solvent deposition method, using 3^2 factorial design	First order drug release with Fickian diffusion mechanism[65]
PLA	Nanoprecipitation	Nanospheres provided high ocular tolerability and bioavailability in aqueous humor[66]
PLA and PLGA	Double emulsion method	Polymeric NP with size 90 nm, showed sudden release within 1 h followed by a sustained release of 60% drug in 48 h identified as suitable for parenteral use[67]
Eudragit RS 100	Quassi-emulsion solvent evaporation method	Polymeric nanosuspension designed for ocular application exhibited non-Fickian diffusion mechanism in *in vitro* and its *in vivo* studies proved that ACV distribution in aqueous humor was more sustained and prolonged[68]
Eudragit RL 100	Nanoprecipitation	Higher ocular stability and physiochemical compatibility[69]
Pluronic F68	Nanosuspension *in situ* gel	Good mucoadhesion, 85% entrapment of drug and 40% of drug release in 3 h and also proved to be safe for administration into rabbit eye through the histopathological reports[70]
Chitosan (150, 400, 600 KDa, molecular weight)	Ionic gelation method	Size, surface charge and entrapment was high, drug delivery dependent on molecular weight of polymer and identified to be suitable for oral and ocular application[71-75]
Eudragit RS 100 and RL 100	Nanoprecipitation method	Relative bioavailability study in volunteers showed AUC (0-12) of Eudragit RS and RL (1:3 ratio) NP as 136.2% and 159.9% respectively, compared to commercial ACV tablets[76]
Eudragit RLPO	Nanoprecipitation method, 32 Factorial design	Non-Fickian type of drug release by diffusion mechanism with first order kinetics[77]
Bovine serum albumin, chitosan, gelatin	Nanoprecipitation	Formulation containing chitosan in 1:1 ratio have showed satisfactory results with average particle size 312.04 nm, zeta potential+33.2 mV, entrapment efficiency 73.4% and suitable for gastro retention of the drug.[78] Around 1.5 fold increase in ACV permeation from the chitosan NP was demonstrated by *in vitro* permeation model using porcine abdominal skin[79]
Polycaprolactone, PEG, chitosan	Ring open polymerization	ACV-polycaprolactone conjugated molecule synthesized through the ring opening polymerization of ε-caprolactone with ACV, could be conjugated with biocompatible hydrophilic polymers to make amphiphilic copolymers or polymeric micelles which are used as nanocarriers for drug delivery[80]
PLGA as 85/15, 75/25 and 50/50	Novel spontaneous emulsification solvent diffusion method	The pharmacokinetics studies performed for stealth NP, in male albino rats showed 60% drug release after 48 h, 29 times increase in MRT and a marked decrease in thrombophlebitis, when injected into rabbit's ear vein[81]
PAN	Elevated temperature electrospinning process	ACV loaded PAN ultrafine nanofibres with diameter of 400-700 nm showed good chemical integrity of the drug that was characterized by 1H NMR analysis[82]
PLGA with PVA	Simple nanoprecipitation and single emulsification solvent evaporation	The trans-corneal studies of the ACV loaded PLGA NP coated with polymers such as chitosan, sodium alginate and poloxamer was performed using the excised goat cornea which showed improved permeation and prolonged action than the commercially available eye ointment[83]

Contd...

Table 3: ***Contd...***

Polymers employed	Method used	Significant results
PLA	Modified nanoprecipitation	Experimental design was optimized for the drug to polymer ratio, antisolvent selection, electrolyte addition, pH alteration and temperature, etc., and finally the drug release was observed with biphasic pattern with Weibull model kinetics[84]
Lipids	Modified hot oil in water microemuslion method	In comparison to free drug solution, nanostructured lipid carriers showed potential enhancement in corneal permeation whereas, the solid lipid NP had reduced the permeation rate significantly[85]
Carboxylated cyclodextrins	Cross-linking	70% of drug loading with no initial burst release, better cell uptake and internalization enhanced antiviral efficacy against a clinical isolate of HSV-1[86]

ACV: Acyclovir, PLGA: Polylactide-co-glycolide, PLA: Poly (lactic acid), PEG: Polyethylene glycol, PAN: Polyacrylonitrile, PVA: Poly (vinyl alcohol), HSV: Herpes simplex virus, ^{1}H NMR: 1H nuclear magnetic resonance, MRT: Mean residence time, NP: Nanoparticle, AUC: Area under the concentration-time curve

carbopol 934P and HPLC E15V. These microcapsules showed controlled release over 8 h with first order kinetics and diffusion controlled release pattern.[100] A polymeric nanodrug delivery system has also been developed using PLGA 50:50 polymer and then incorporated into mucoadhesive polymer of polycarbophil with help of pluronic F68 surfactant. The formulation design was optimized by 2^3 factorial design, which has provided zero-order drug release showing Fickian or non-Fickian diffusion. The mucoadhesion properties of NP studied using *in vitro* intestine model exhibited increased adhesiveness with raising levels of polycarbophil.[101]

For the fabrication of single unit mucoadhesive tablets by direct compression method based on the 3^2 factorial design, the bioadhesive polymer namely carbopol 934P in addition with HPMC K100M was selected. These tablets have shown *n*-value varying between 0.5266 and 0.7110, to exhibit non-Fickian release with coupled diffusion and polymer relaxation, resulting in a controlled and complete drug release for 12 h.[102] Buccal bioadhesive tablets were formulated using spray dried amioca starch/carbopol 940P (5-45%) mixture at varying proportions, showed sustained release for 15 h.[103] Recently, the novel mucoadhesive formulation of ACV buccal tablet is commercialized with US FDA approval, for the treatment of recurring herpes labialis (cold sores). A phase 3 international study of 775 patients showed that in addition to its efficacy, this treatment was unobtrusive and offered simplified dosing with a single application for the entire duration of an episode of herpes labialis.[104]

A unique type of a single unit mucoadhesive *in situ* gelling liquid pessaries was formulated using sodium alginate, poly vinyl pyrrolidone, carbopol, methyl cellulose, poloxamer 188 and polyethylene glycol (PEG) 6000 which exhibited better mucoadhesive force (19500 dynes/cm^2), spreadability (5.5 cm) and gel strength.[105]

Using ACV as model drug, novel thiolated dendrimers were synthesized by conjugating poly amido amine dendrimer with cysteamine at two different molar ratios as 1:30 and 1:60, for mucoadhesive drug delivery. Drug loading was greater in the dendrimer conjugates and showed sustained release, wherein the *in vitro* mucoadhesive activity of 1:60 thiolated dendrimer conjugate showed 1.53 and 2.89 fold higher mucoadhesion compared to 1:30 ratio conjugate and plain dendrimer drug conjugate, respectively.[106]

Emulsified dosage forms

Emulsified systems containing the dispersion of oil and water with the addition of surfactants have shown specific advantages in the delivery of poorly soluble drugs and in masking bitter taste of the APIs. Different types of microemulsion, nanoemulsion and self-emulsified dosage forms were designed by expert persons for the controlled delivery of ACV.

For oral route of administration, a microemulsion developed with Labrasol and Plurol Oleique as surfactant and cosurfactant respectively, showed an increase in bioavailability when compared with the commercially available tablets.[107] In the same way, a novel microemulsion based topical formulation of ACV resulted in total inhibition of herpetic skin lesions.[108] An liquid-in-oil microemulsion system containing 3:2 ratio of tween 80 and span 20 as nonionic surfactants and dimethylimidazolium dimetyhylphosphate as pseudophase was identified to show excellent solubility and skin permeation enhancing effect with Yucatan micropig procine skin. A low cytotoxicity effect was reported for the carriers using reconstructed human epidermal model LabCyteTM EPI-MODEL12.[109]

A different type of nanoemulsion and self-micro-emulsified drug delivery system was designed using mixture of oils, surfactants and co-surfactants, which showed 3.5 fold increase in bioavailability compared with the pure drug solution when administered orally to male albino rats.[110,111]

Polyethylene glycol 400/Miglyol 812 nonaqueous sub-micron emulsions were developed for higher biocompatible topical application, which were stabilized

by poly (2-vinylpyridine)-b-poly (butadiene) copolymer, that limited the Ostwald ripening and so appeared to be more efficient stabilizers than low molecular weight nonionic surfactants. ACV, as a model drug of low water solubility, could be incorporated into the PEG 400 dispersed phase, with no significant modification of the initial emulsion characteristics.[112]

Polymeric films and patches

Films are thin membranes containing the drug as in matrix type or reservoir type, which also can be utilized to amend the extended release of drug at varying sites such as topical, ocular, dental, buccal, nasal, vaginal, rectal, etc. These films can be made as erodible or nonerodable depending on the type of polymers employed for the design with respective to the site and drug release required.

By utilizing inclusion phenomenon buccal patch was designed with hydrophilic polymer hydroxylpropyl beta-cyclodextrin which showed a substantial increase from 64.35% to 88.15% drug release, confirming the success of inclusion complexes for the formulation of buccal patch of ACV.[113] In another study, by employing solvent evaporation method, thin films of poly (ethyleneco-vinyl acetate) copolymer matrix was designed for ACV and chlorhexidine combination therapy. The outcome of the drug combination using varying copolymer composition and the effect of coating was studied for its suitability in oral environment. The increase in concentration of vinyl acetate increased the drug release rate whereas coating of films decreased the release rate.[114]

Transdermal iontophoresis delivery systems

Transdermal delivery systems are topically applied forms which allow the permeation of drugs via the stratum corneum, the rate-limiting membrane for absorption through skin. Drugs can be loaded directly or as microreservoir drug core containing the multiparticles dispersed into the matrix or reservoir system.

The potentiality of the application of iontophoresis was investigated for facilitated trandermal delivery and passive diffusion across nude mouse skin for ACV individually and in addition with penetration enhancers like cetrimide and sodium lauryl sulfate, where the former showed 3-fold greater permeation than the later.[115] In the same fashion, the *in vivo* efficacy of controlled transdermal delivery of ACV (topical and systemic antiviral efficacy) was evaluated using hairless mice models for cutaneous HSV-1 infections. This study was demonstrated as a distinctive example of dose/flux-response correlation in local antiviral therapy, since the typical sigmoidal curve of reasonably high reproducibility was obtained for the graph of antiviral efficacy versus rate of drug release.[116]

An innovative method was identified for the significant and rapid delivery of gel by iontophoretic device through intradermal route. A clinical pharmacokinetic study was also carried out for the redesigned version of iontophoretic device (10 min application time) used in conjunction with a novel ACV gel formulation following a single treatment in healthy normal subjects. The results showed mean plasma C_{max} - 990 pg/mL, median T_{max} - 0.21 h and plasma $AUC_{(0–t)}$ as 1410 pg/h/mL.[117] The skin distribution and permeation studies after transdermal iontophoresis resulted after 7 h study had shown homogeneous distribution of the drug in the skin layers.[118] The effect of terpene (nerolidol) on transdermal skin permeation was studied using Franz diffusion cell fitted with rat skin, which resulted in enhancement of ACV flux up to 98.79 fold since nerolidol have the highest lipophilicity.[119] Quantification of ACV into and across the hairless rat skin following topical iontophoretic delivery was also done, where in the iontophoretic delivery from creams and gel was achieved using a cartridge and the quantification of drug accumulation in the skin was performed by *in vitro* microdialysis method.[120]

Research on acyclovir dosage forms - so far

The percentage of the different drug delivery approaches of ACV is shown in Figure 2 wherein, it is obvious that the nanoparticulate, microparticulate and vesicular systems found to contribute high in the novel approaches, as 25%, 13%, and 12% respectively. Yet the other approaches are also found to have better applications due to ease of manufacture, administration route, stability, specificity, dose accuracy, controlled release, etc.

CONCLUSION

This review could provide a comprehensive idea about the various fields of researches, their present studies and future scope of works for the drug. The abundant research works done on pharmaceutical approaches of ACV, have proved it as a potential and versatile molecule for the treatment of HSV infections. Enormous pharmacological studies have also been reported, using various animal models and human volunteers,

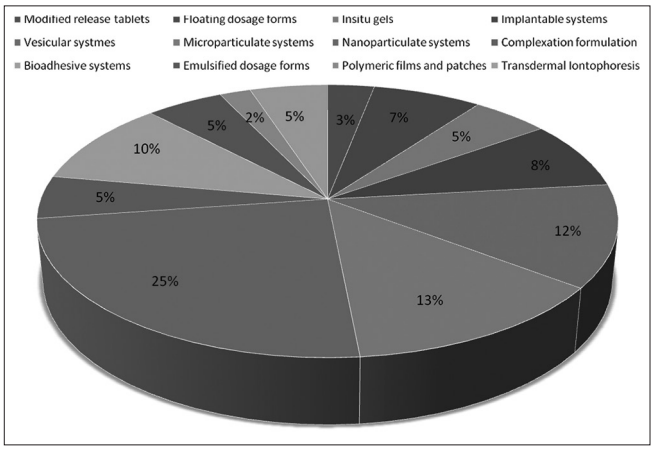

Figure 2: Different levels (%) of research on acyclovir for dosage form development

which add evidence to its successful therapeutic application. Certain clinical trial reports of the drug also confer the proof for its superiority over other medicine existing in the market. A wide range of formulation approaches have been discussed, among them the nano and micro particulate systems and vesicular delivery have gained more importance recently. Consequently, it could be concluded that the novel drug delivery systems play noteworthy key role in the improvement of therapeutic activity of ACV.

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