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REVIEW

Recent Advances in Propranolol Hydrochloride Formulations for the Treatment of Infantile Hemangiomas

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Abstract: Infantile hemangiomas (IHs) are a kind of skin soft tissue benign tumors in infants, with a high incidence rate and significant harm. Rapid early proliferation can cause severe cosmetic deformities and organ development disorders. Propranolol Hydrochloride (PRH), a non-selective adrenergic β-receptor blocker, has become the first-line treatment for IHs due to its good efficacy and safety compared to other drugs. To further improve the bioavailability of PRH, deliver it more safely and effectively to the lesion site, and enhance patient compliance, researchers are continually developing new PRH formulations for the treatment of IHs. This article briefly introduced the pathogenesis of IHs and the therapeutic mechanism of PRH. It also provided a detailed overview of various new PRH formulations developed over the past 12 years for the treatment of IHs, including improved oral formulations, topical creams, gels, liposomes/nanoparticles, transdermal patches, microneedles, and targeted injectable formulations. This article summarized the development prospects and technical challenges of these new formulations. It aims to provide a comprehensive review of recent advances in new propranolol formulations and technologies for treating IHs, offering a reference for further research and application. At the same time, it is hoped that various new formulations of PRH can be safely and efficiently used in clinical practice in the future.

Keywords: infantile hemangiomas, propranolol, propranolol hydrochloride, formulation

Introduction

Infantile Hemangiomas (IHs) are the most common soft tissue tumors in infants, characterized by the rapid proliferation of vascular endothelial cells, developing into disorganized clusters of blood vessels.[1] The incidence rate is as high as 4%-10%, with even higher rates in premature or low birth weight infants, about 23% of whom weighing less than 1000 g will develop IHs, and this trend is increasing annually.[1–3] IHs have a recognized natural progression, which includes the proliferative phase, involution phase, and involution-completion phase.[4] Although the probability of natural regression of hemangiomas is high, large and rapidly growing hemangiomas may leave behind pigmentation, vascular dilation, fibrofatty tissue accumulation, and scarring after regression. About 10% of IHs may ulcerate, bleed, become infected, and cause pain, affecting the quality of life. IHs located in special areas may cause organ dysfunction such as impaired vision, restricted joint movement, breathing difficulties, and other more serious complications, which can even be life-threatening. Additionally, when the disease occurs on the face and limbs, it not only causes physical harm to the child but also imposes significant psychosocial stress on the child during their developmental period.[5,6] Therefore, most IHs require active treatment.

At present, the treatment of IHs mainly focuses on inhibiting the proliferation of vascular endothelial cells. The therapeutic drugs include β-blockers, corticosteroids, urea, interferon, anti-tumor drugs, and radionuclide.[7] However, different drugs have different side effects. With the continuous development of medical technology, some non-drug treatment methods such as

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laser therapy, surgical resection, and cryotherapy have also been introduced into the treatment of IHs.[8] However, non-pharmacological treatment methods have significant limitations and are subject to stringent conditions, so pharmacological treatment remains predominant. Drug treatment can be administered locally or systemically. Local administration is generally used for smaller, more superficial IHs or IHs with contraindications to systemic treatment; systemic administration is typically used for larger areas, dysfunction, high risk of disfigurement, or other initially treatment-resistant cases.[9] Therefore, finding a drug that is effective, safe, and suitable for systemic or local administration is urgently needed.

Propranolol Hydrochloride (PRH) is a non-selective β-receptor blocker, which is commonly used in clinical practice to treat arrhythmia, hypertension and angina pectoris. In 2014, it was the only drug approved by the US Food and Drug Administration (FDA) for the treatment of IHs.[10] Domestic and foreign scholars have also widely carried out clinical trials of propranolol in the treatment of IHs, and the results showed that its efficacy was proven and side effects were low. Compared with other drugs, PRH is a promising and relatively safe drug for the treatment of IHs.[11,12] However, PRH is prone to cause adverse reactions such as sleep disorders, hypoglycemia, hypotension, bradycardia, bronchospasm, peripheral vasoconstriction, and diarrhea. In addition, individual tolerance to PRH varies greatly, so individualized medication is needed.[13,14] To reduce its adverse reactions and make it safer and more effective for children, researchers continue to develop new dosage forms and find new drug carriers to deliver PRH to lesions safely and efficiently. This article reviewed the reports of various formulations of PRH for the treatment of IHs and discussed the research progress of its clinical application, so as to provide a reference and basis for the development and use of new formulations of PRH (Figure 1).

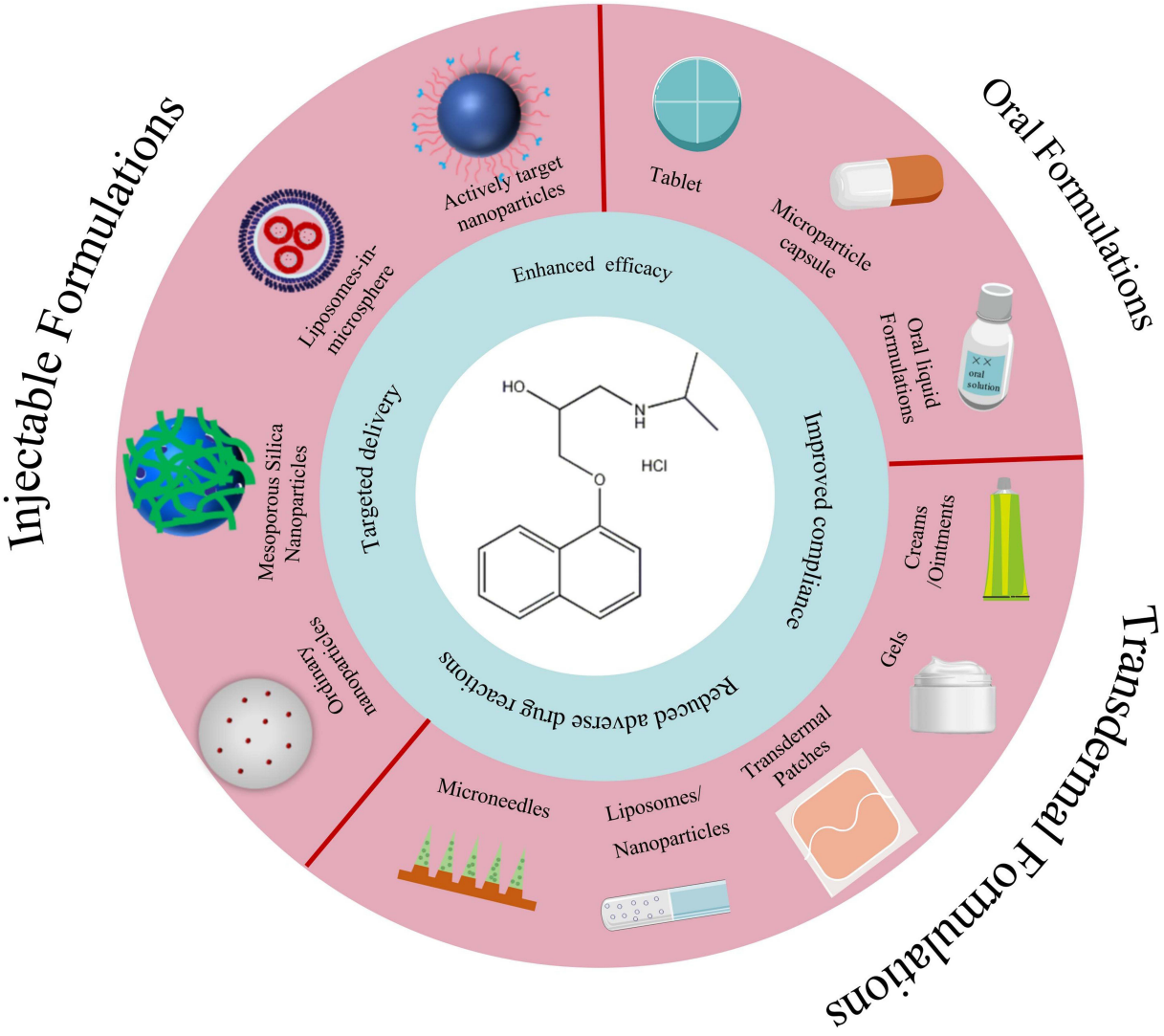

Figure 1 Various formulations of PRH for the treatment of IHs.

The Pathogenesis of IHs

The pathogenesis of IHs is quite complex. Currently, there are multiple reports on the pathogenesis of IHs.

Pattern of Inheritance

Although most IHs occur sporadically, familial aggregation has been reported, and variable gene expression was observed in IHs during proliferation and regression.[15,16] A positive family history (first-degree relatives) increased the risk of IHs formation.[16,17] It has been reported that more than one-third of pediatric patients had a family history, and the inheritance mode was autosomal dominant and maternal inheritance, and the linkage site was chromosome 5q31-33.[18,19] Meanwhile, in a study of familial IHs, three candidate genes: Fibroblast Growth Factor Receptor-4 (FGFR4), Platelet-Derived Growth Factor Receptor-Beta (PDGFRB), and Fms-like Tyrosine Kinase-4 (FLT4), were identified, and their encoded products were associated with the pathogenesis of familial IHs.[20] However, existing studies still cannot fully explain the occurrence of IHs by genetic model, and further studies are needed to better describe the genetics and epigenetics of IHs.

Placental Origin Theory

As early as 2000, North PE et al first detected surface markers specifically expressed in placental villus endothelial cells in hemangioma tissues, such as glucose transporter 1 (GLUT-1), FCR γ II (CD32), Lewisy antigen, stratification protein, etc.[21] Subsequently, the researchers found that GLUT-1 could accurately distinguish hemangioma and vascular malformation by immunohistochemistry.[22,23] Meanwhile, GLUT-1 is highly expressed in hemangioma cases, suggesting that IHs may originate from placental cells. Barnes et al also confirmed the high similarity between IHs and placental tissue by detecting the gene chip of expression profile.[24] Mihm et al proposed the metastasis niche theory to clarify the development of IHs: IHs precursor cells originated from the placenta and were regarded as "benign metastasis", which occurred on the embryonic fusion substrate.[25] At the same time, the placental theory can explain the programmed life cycle of IHs: proliferation phase, regression phase, and regression completion phase.

Hypoxia Stress Theory

Hypoxia is widespread in the process of tumor formation. Studies have shown that hypoxia exists throughout the entire growth process of IHs and has been recognized as a common driving factor in the pathogenesis of vascular proliferation.[26] Researchers detected hypoxia-inducible factor-1α (HIF-1α) in proliferating hemangiomas. Local hypoxia increases HIF-1α, which, through the upregulation of vascular endothelial growth factor (VEGF), leads to abnormal proliferation of endothelial cells and an imbalance in the number of blood vessels, resulting in abnormal vascular proliferation and differentiation, thereby forming hemangiomas.[27,28] GLUT-1 on hemangioma tissue is also an important sensor of hypoxia and promotes glucose transport.[29] Retinopathy of prematurity (ROP) is a proliferative vascular disease that occurs in premature infants due to ischemic damage to the microvascular system, leading to hypoxia-induced neovascularization. Therefore, there is a pathophysiological link between ROP and IHs.[30,31] Similarly, risk factors for IHs (such as preeclampsia, placenta previa, extremely low birth weight, and placental insufficiency) also indicate that the occurrence of IHs is under hypoxic conditions.[26]

Hemangioma Stem Cell Theory

Stem cells are undifferentiated cells in the human body, capable of self-replication and possessing multipotent capabilities. Under certain conditions, they can differentiate into various functional cells. The discovery of hemangioma stem cells has had a significant impact on the theories regarding the origin of IHs. Khan et al first isolated CD133+ hemangioma endothelial cells (HemSCs) with primitive mesenchymal cell characteristics from proliferating IHs. These cells possess the ability for self-renewal and multilineage differentiation. Transplanting HemSCs into immunodeficient mice produced tumors with characteristics of hemangiomas, thus establishing the first animal model of IHs.[32] Therefore, CD133+ hemangioma endothelial cells are recognized as hemangioma stem cells and play a significant role in the pathogenesis of IHs. Other reports suggested that HemSCs may originate from normal bone marrow mesenchymal stem cells. Their strong proliferative and angiogenic capabilities could act as pathogenic factors for IHs.[33] The above evidence suggests that hemangioma stem cells might be the source of IHs, providing new insights for the clinical treatment of IHs.

Angiogenesis Theory

Angiogenesis is the process by which endothelial cells proliferate to form lumens, and subsequently, perivascular cells adhere to the endothelial layer, resulting in the formation of a complete vessel wall.[34] IHs are characterized by early rapid growth and development into disorganized clusters of blood vessels. Mutations and defects in cytokine regulatory pathways are among the reasons for abnormal angiogenesis in hemangiomas.[35] The Notch signaling pathway is crucial for angiogenesis. When Notch ligands bind to their respective receptors, they trigger a series of biological reactions that induce angiogenesis. In the Notch pathway, mutations in DLL4 can lead to severe vascular rupture, resulting in related vascular diseases. VEGF is currently known as the strongest angiogenic factor. When VEGF binds to VEGFR on endothelial cells, it induces endothelial cell division, proliferation, and migration, promoting the formation of new blood vessels. There are two types of receptors: vascular endothelial growth factor receptor 1 (VEGFR1) and VEGFR2. VEGFR1 activation is closely linked to endothelial proliferation inhibition, while VEGFR2 activation promotes angiogenesis. DLL4 can inhibit angiogenesis by upregulating VEGFR1 and downregulating VEGFR2.[36,37] Therefore, when the Notch pathway is abnormally expressed, blood vessels may proliferate excessively, which may be related to the occurrence of hemangiomas. At the same time, during the process of angiogenesis, other pro-angiogenic factors such as basic fibroblast growth factor (bFGF) and related proteinases, including matrix metalloproteinases (MMP-2 and MMP-9), are increased in various cell types of IHs, including endothelial cells, pericytes, and fibroblasts.[38]

Mechanism of Propranolol in the Treatment of IHs

Because of the unique growth pattern of IHs, characterized by a rapid proliferation phase and a spontaneous involution phase, the choice of treatment strategies for IHs has been controversial until PRH began to be used for treating IHs in 2008.[39] The exact mechanism of PRH in the treatment of hemangioma is complex. Previous studies have reported that the therapeutic effect of PRH is mainly through β-AR inhibition of HemSCs and hemangioma endothelial cells (HemECs).[40] With further research, it has been found that propranolol mainly affects lesions in three aspects (Figure 2).[38] The early effect is to alleviate the symptoms of IHs, primarily by blocking β2 receptors and inhibiting the cyclic adenosine monophosphate (cAMP)-protein kinase A (PKA)-nitric oxide signaling pathway, leading to a reduction in nitric oxide release. This causes capillary constriction, reduces blood flow within the hemangioma, and slows IHs growth. The intermediate effect is to inhibit IHs growth, mainly by blocking β2 receptors, which suppresses the expression of HIF-1α, pro-angiogenic factors [VEGF and bFGF], and matrix metalloproteinases (MMP-2 and MMP-

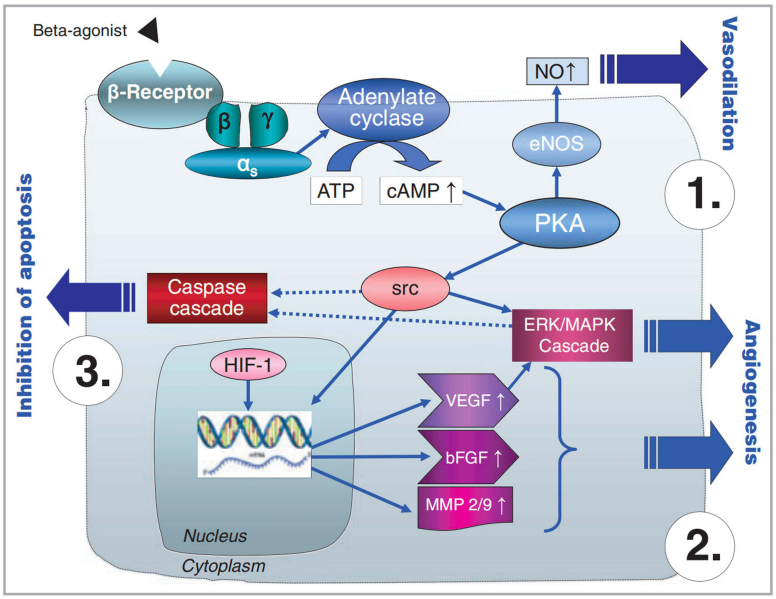

Figure 2 Molecular processes in IHs that may be affected by propranolol. Reproduced from Storch CH, Hoeger PH. Propranolol for infantile haemangiomas: insights into the molecular mechanisms of action. *Br J Dermatol*, 2010. 163(2): 269–274. © 2010 British Association of Dermatologists.[38]

9) during the proliferative phase of IHs. This inhibition also suppresses the ERK/MAPK cascade reaction, thereby inhibiting angiogenesis. The long-term effect of lesion regression is caused by the apoptosis of proliferating endothelial cells. It has been reported that β-adrenergic antagonists can relieve the inhibition of apoptosis mediated by src, MAPK, and caspase cascades, leading to an increase in the rate of apoptosis.[41]

PRH of New Dosage Forms in the Treatment of IHs Application Potential

In 2008, Léauté-Labrèze et al first discovered that PRH had a therapeutic effect on IHs.[39] In March 2014, the FDA approved oral PRH (Hemangeol) for the treatment of proliferative IHs requiring systemic therapy. Numerous clinical studies have evaluated its efficacy and safety, and it has now replaced corticosteroids, becoming the internationally recognized first-line treatment.[11,12,42] Currently, the commonly used propranolol tablets in clinical practice are difficult to adjust flexibly according to children's weight, while propranolol solution has an intolerable bitter and salty taste, reducing children's compliance. Additionally, propranolol solution has a short half-life (requiring administration 2–3 times daily), is unstable under light, and is only stable at pH = 3. Therefore, researchers are continuously improving the formulation of oral preparations (Table 1) and developing new drug carriers to enhance the efficacy of the drug and improve children's compliance with medication.

Oral Formulations

Oral Liquid Formulations

To improve the palatability of the drug and enhance children's compliance, Sylva Klovrzová used citric acid solution and/or citrate-phosphate buffer solution as carriers and monosaccharide syrup as a sweetener to prepare a temporary pediatric oral solution of PRH at a concentration of 2 mg/mL. This oral solution is easy to prepare, effectively masks the unique odor of propranolol, has good stability, and is suitable for temporary preparation in hospital pharmacies.[43] It can be used for treating IHs and pediatric cardiovascular diseases such as hypertension. However, the American Medical Association recommended limiting the use of such synthetic sweeteners in food and medications for pediatric populations.[46] The European Medicines Agency also advised that "products containing high levels of propylene glycol should not be administered to pediatric patients below the age of 4 years". Alternative methods should be used to mask

Table 1 Summary of Studies on Oral PRH Formulations for the Treatment of IHs

Main Materials	Preparation Methods	Physicochemical Properties	Main Effects	Year[Ref]
Sweetener: simple syrup; F1:Vehicles-CPB; sodium benzoate; F2:Vehicles-citric acid; sodium benzoate; F3:Vehicles-citric acid; preservative-free	Mixing	F1: pH 3.14; taste sweet and sour; F2: pH 2.89; taste sweet, slightly bitter F3: pH 2.87; taste sweet, slightly bitter	F1 is better than F2 for its sweet and sour taste; F3 can be expected for use in the therapy of neonates under the supervision of a caregiver.	2013[43]
HPβCD	Physical mixtures or dry co-grinding	pH: 5.5; drug solution: 0.2% w/v; drug stabilization: 55%	Improves photo stability and storage stability, reduces the degradation rate and bitterness of the drug	2023[44]
EUDRAGIT®EPO; Sodium dodecyl sulphate; Stearic acid	Prilling-congealing technique	F1: PS ~356.8μm; DL: 38.4%; EE 100.0%; F1n: PS ~663.5μm; DL: 38.4%; EE: 100.0%	High EE% and DL%, reduce drug bitterness, and stability of physicochemical properties for six months; Low release and dissolution in artificial saliva, and a prompt dissolution in simulated gastric media	2020[45]

Abbreviations: CPB, citrate-phosphate buffer solution of pH 3; HPβCD, hydroxypropyl-β-cyclodextrin; PS, particle size; DL, drug loading; EE, encapsulation efficiency.

the unpleasant taste of formulations instead of adding sweeteners or flavoring agents.[45,47,48] An ideal pediatric oral formulation should allow for flexible dosing, be easy to administer and palatable, possess appropriate physical and microbial stability, and contain only excipients that are safe for children.[49] Cyclodextrins can enhance the water solubility of poorly soluble drugs, mask the unpleasant taste of drugs and improve their chemical stability.[50] Marzia Cirri prepared a liquid formulation with a concentration of 0.2% w/v by co-grinding PRH with hydroxypropyl-β-cyclodextrin (HPβCD) as a complexing agent.[44] HPβCD is an inert material approved by the FDA, which can be used for oral and intravenous drug delivery. It has good biocompatibility and is a safe and ideal drug carrier material.[51] The experimental results showed that after 1 hour of UV irradiation, the drug degradation rate decreased by 75% and the bitterness decreased by 30%, confirming the photostability and taste-masking properties of the formulation. This study effectively avoids the use of organic co-solvents, acidifiers, sweeteners, and flavoring agents, and meets the requirement of using minimal excipients to reduce potential safety and incompatibility issues.[44] This contributes to the development of oral liquid formulations of PRH.

Oral Solid Formulations

In addition to liquid formulations, microparticles have recently been used as new oral dosage forms. They can improve drug stability, achieve sustained release, and even encapsulate biologics. Microparticles can overcome or circumvent physiological barriers that limit the efficacy of oral administration, or enable oral targeted drug delivery.[52,53] Antonio Lopalco et al used a granulation-coagulation technique to produce EUDRAGIT® EPO (a synthetic pharmaceutical excipient) microspheres for encapsulating PRH. EUDRAGIT® EPO is a cationic, gastro-resistant derivative of poly-methacrylate that dissolves only at pH below 5 and swells at pH above 5. It has a relatively pleasant taste and can form a barrier between the drug and taste buds, with a small amount typically sufficient to effectively mask the taste.[45] EUDRAGIT® EPO has been previously packaged with paracetamol to mask the bitter taste of paracetamol.[54] EUDRAGIT® EPO has also been used to prepare microcapsules and nanoparticles to improve the solubility of poorly water-soluble drugs.[55] The advantage of this preparation is that the dose can be flexibly adjusted to mask the bitter taste of the drug. It has good stability during storage and transportation. However, further studies are needed to assess the toxicological risk of substrates used for chronic or acute diseases.

Transdermal Formulations

Most oral drugs are absorbed slowly and can lead to unpredictable absorption due to degradation by stomach acid and enzymes. After absorption, they are extensively distributed throughout the body, including in important organs, leading to unwanted side effects.[56] Studies have shown that oral doses of PRH ≥2mg/kg/day can achieve better therapeutic effects, but the incidence of systemic adverse events is significantly increased, suggesting that the cumulative dose of PRH is a potential reason for side effects risks.[57] Therefore, developing new formulations of PRH is urgent and meaningful. IHs most commonly located in the head and neck area (60%), followed by the trunk (25%) and limbs (15%).[58] The lesions involve the epidermis, dermis, and subcutaneous fat of the skin.[59] Thus, researchers have developed various topical formulations of PRH for transdermal delivery (Table 2), which offer unique advantages over oral formulations, such as overcoming limitations of small dosage, slow onset of action, and multiple adverse reactions. Topical formulations can effectively control sustained drug release, bypass first-pass metabolism, reduce the incidence of systemic ADRs, and increase drug concentration at the lesion site. Additionally, topical formulations are convenient for patients, promote compliance, and allow for the immediate discontinuation of the medication if problems arise. Since it is administered topically to the site of lesions, the indication for topical formulations is IHs.

Creams/Ointments

Topical application of PRH can maintain high drug concentrations at lesion sites. Animal studies indicate that topical application of PRH on guinea pig skin does not cause sensitization, phototoxicity, or photosensitization. However, it may cause skin irritation, which increases with increasing dosage and application times.[60,85] In topical formulations, creams and ointments are easy to prepare, convenient to use, and extensively studied in clinical settings. Lipophilic creams and ointments have a high skin retention rate but low permeability.[86] Therefore, PRH creams and ointments typically use

Table 2 Summary of Studies on Transdermal Formulations of PRH for the Treatment of IHs

Formulations	Main Materials	Preparation Methods	Physicochemical Properties	Experimental Model	Main Effects	Year[Ref]
Creams/ Ointments	Petroleum jelly; PEG400; et al	Mixing	Concentration: 1% to 5%	–	Well tolerated in topical application; no serious adverse effects; safe and effective treatment for superficial IHs;	2012[60,61] 2013[62] 2014[63] 2018[64] 2022[65]
Gels	Sodium hyaluronate	Mixing	Concentration: 1%	148 patients	Strong signs of resolution under treatment; Relevant serum levels of propranolol were not found.	2014[66]
	HM-HPMC	Mixing	Concentration: 0%, 1% and 5%	15 patients with superficial IHs	No serious adverse events occurred; twice-daily external applications were well-tolerated and resulted in good compliance.	2022[67]
	Chitosan; glycerol; azone	Mixing	Concentration: 3%	51 patients with superficial IHs	86.27% were considered medium or better in terms of efficacy; Superficial IHs respond better than deep or mixed IHs	2012[68]
	HPMC;farnesol; isopropanol	Direct swelling method	pH: ~6.87; Viscosity: ~63.2 Pa S; Consistencies: ~192.7; DC: 100.1 ± 0.4%	Piglets; rabbits; SD rats; 36 superficial IHs children	Increased cumulative penetration; no skin irritation; high concentrations in dermis with a low concentration in plasma; positive results in clinical studies	2015[69]
	Gellan gum	Mixing	Cumulative penetration over 24 hours: 21.1μg	-	PRH accumulation was 21.2 times higher than gels and 2.6 times higher than HPMC gels.	2022[65]
Nanoparticle Gels	Glycerol; PEG400; sodium benzoate; nanoparticles of colloidal silicon dioxide; PVA	Adsorption and dispersion	Concentration: 0.5%; PS: 5 to 10 nm	50 outpatients with superficial IHs	Overall efficacy of 86%, a clinical complete clearance rate of 6%, excellent rate of 74%, and moderate rate of 6%; devoid of local or systemic side effects	2015[70]
	Lipoid S45 (lecithin); GMS; poloxamer 188; chitosan; cellulose membrane	Double emulsion solvent evaporation	EE: 53.62%; PS: ~443.04nm; pH ~5.68	Wistar rats	Full factorial design to optimize the formula; enhance the deposition of the drug in the skin; reduce the drug dose along; minimize systemic side effects	2021[71]
	GMO; phytantriol; Pluronic F127; 1% xanthan gum	pH-gradient process	EE: ~90.15%; PS: ~90nm; PDI<0.1	EOMA cells; SD rats	Improved EE%; improved drug permeation through the skin; improved the cytotoxicity towards the EOMA cells	2020[72]

(*Continued*)

Table 2 (Continued).

Formulations	Main Materials	Preparation Methods	Physicochemical Properties	Experimental Model	Main Effects	Year[Ref]
Liposome Gels	Phosphatidyl ethanolamine; CHOL; carbomer; Triethanolamine	Film dispersion method	PS: ~260nm; pseudoplastic flow; Viscosity: 255.2 Pas (shear rate 0.1 s^{-1})	Rabbits; Kunming strain mice	Non-irritating to skin; weakens the barrier function of SC; promotes drug permeation; higher drug deposition; reduces dosing frequency and side effects on the heart	2015[73]
	Pluronic lecithin organogel; phosphatidylcholine	Insert into liposome	Concentration: 4%	63 patients	82.6% had good or partial response to treatment; Age is a predictive factor for treatment responsiveness	2017[74]
	Phosphatidyl cholines; CHOL; sodium cholate	Reverse-phase evaporation method	EE: 81.84%; PS: ~186.8nm; ZP: −28.6mV; drug penetration: ~111.05lg/cm^2 within 48 h;	Guinea pigs; rats	Higher penetration and retention capacity; reduced side effects; higher subcutaneous tissue distribution	2023[75]
Transdermal Patches	Eudragit NE 40D; N-methyl pyrrolidone	Laboratory coating unit Mathis LTE-S (M)	Optimal prescription: crystal appearance: >9 months; DC: ~765μg/cm^2; Thickness: 50μm; Jmax~12.7μg/h/cm^2	New Zealand male albino rabbits	A 2^4 full factorial design; demonstrated the feasibility of administering (S)-PR by transdermal patches; a patch that is non-irritating to the skin;	2014[76]
	PVA; Eudragit E 100; lauric acid; adipic acid; glycerol	Lamination technique	DC: ~525μg/cm^2; thickness: 40μm; weight: 8.0 mg/cm^2	Pig skin	Short lag time; high proportions of drug retained in the skin; reduces the risks of systemic side effects	2019[77]
	HPMC; CMC; Polysorbate 80; oleic acid	Casting and drying	Optimal prescription: Thickness: ~0.15mm; DC: ~1.98mg/cm^2; water $uptake_{(max)}$: ~190.6%; Flux: 53.42mg/cm^2 h	Pig ear skin	CMC films showed lower drug permeation accumulation than HPMC; the films provided greater permeability; drug permeation can be easily modulated by varying the cellulose and enhancer type.	2015[78]
	Sodium dioctyl sulfosuccinate	-	PRH melt in octanol is 100 times lower than in water; liquid at room temperature	-	Reduction in skin irritation; significant increase in drug transdermal permeability; Amorphous drug melts can be incorporated into different transdermal delivery systems	2019[79]

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Liposomes/ Nanoparticles	Inderal® 40 mg film coated tablets; Lipoid Liposome® 0041	Mixing	PS: ~100nm; PDI: ~0.4; loading ~7%; EE: ~30%	Porcine ears	Sustained drug release; enhanced transdermal permeability; excellent stability; potentially useful for extemporaneous preparations in compounding pharmacies	2024[80]
	Stearic acid; essential oil; soy lecithin S100; sodium taurodeoxycholate;	Microemulsion method	PS: ~569nm, ~824nm; PDI: 0.5; pH 5.5; EE: 99%;	Porcine ear skin; HBMEC	Controlled drug release; avoided drug skin permeation to the deeper skin layers; exhibited toxic, anti-proliferative, and anti-migratory effects over cells;	2023[81]
	Pluronic F127; Peppermint essential oil; methylisothiazolinone solution	Ultrasonic emulsification	PS: 26nm; PDI<0.4; ZP −20mV; pH: 6.7; pseudoplastic fluids;	Human dermal fibroblasts;HaCaT; RAW 264.7; pig ear skin; Wistar rats;	Excellent stability; satisfactory retention in the dermis; promoted cutaneous permeation of the PPN; safe for cutaneous administration	2018[82]
Microneedles	Oleic acid; ethanol; Tween-80; an array containing 5 in-plane stainless steel MNs of 750μm length	Microemulsion method, mixing with solid MNs	PS: 23~93nm; PDI: 0.22~0.35; ZP: −6.95~-22.83mV; Conductivity: 1.92~11.91; pH: 4.91~5.91	Porcine skin	Significantly greater solubility in microemulsions; greater skin-to-receiver ratios; MNs increased skin concentrations and parameters can be flexibly adjusted.	2018[83]
	Hyaluronic acid; PVP-K90; PDMS mold	Micromolding method	Height: 1200μm; side length: 300μm; center-tocenter interval: 600μm; strength: 3N;	Porcine skin; SD rats	Significantly increased permeability and skin retention; excellent mechanical strength; skin acts as a drug reservoir with continuous drug release	2021[84]

Abbreviations: PEG, polyethylene glycol; HM-HPMC, Hydrophobically modified hydroxypropyl-methylcellulose; DC, drug content; PVA, polyvinyl alcohol; PS, particle size; GMS, glyceryl monostearate; EE, encapsulation efficiency; GMO, glycerol monooleate; PDI, polydispersity index; EOMA, mouse hemangioendothelioma endothelial; CHOL, cholesterol; SC, stratum corneum; ZP, zeta potential; CMC, sodium carboxymethyl cellulose; HBMEC, Human brain microvascular endothelial cell; HaCaT, Human keratinocytes; RAW 264.7, murine macrophages; PVP, polyvinyl pyrrolidone; PDMS, Polydimethylsiloxane.

hydrophilic bases, which have higher permeability than hydrophobic and lipophilic creams but may cause systemic side effects and have limited skin retention.[87] Consequently, they are mainly used for treating superficial IHs and are less effective for deeper lesions.

Many researchers have used 1% hydrophilic PRH cream/ointment for treating IHs (applied twice or thrice daily).[60,61,63] Their findings indicate that topical application of 1% PRH ointment is well-tolerated, with no serious adverse reactions (ADRs), making it a safe and effective treatment for superficial IHs. Moreover, using a 2% PRH ointment also showed positive outcomes, with a 75% reduction in lesions after 45 days.[62] Yasuharu Kashiwagura et al increased the concentration of propranolol hydrophilic cream (PHC) from 1% to 3% and noticed that skin permeability increased with higher concentrations. However, there was no significant difference in skin permeability between the 3% and 5% PHC in lab tests.[65] A systematic review analyzing 12 studies on topical PRH (including creams, ointments, and gels) for treating IHs published between 2012 and 2017. The review found that 90% of lesions improved following the initiation of topical PRH, with 59% achieving a good or excellent response, defined as at least a 50% reduction in lesion area. Additionally, earlier treatment initiation (less than 3 months of age) improved outcomes, and the frequency and concentration of PRH usage did not affect the outcomes.[64]

Gels

Gels Formulations

Gel formulations are homogenous or suspended semisolid preparations that are transparent or translucent, made by incorporating the drug into a suitable matrix. Clinically, aqueous gels are commonly used as matrices to facilitate the release of water-soluble drugs. Studies using hyaluronic acid as a matrix have produced a 1% propranolol gel, which halted the growth of IHs in 147 out of 148 patients within a few days of local treatment.[66] Another formulation used hydrophobically modified hydroxy-propyl methylcellulose (HM-HPMC) as a matrix to prepare 1% and 5% gels. Results indicated that as the concentration of PRH increased, there was a slight decrease in the redness at the lesion site, with no severe ADRs reported. However, four patients (21.1%) still complained of itching, indicating that improving the base used for topical application remains a subject for future research.[67] Wang et al treated 28 patients with superficial IHs, 6 deep IHs, and 17 mixed IHs using a 3% PRH gel based on chitosan, applied three times daily. The results showed that 86.27% of patients had moderate or better efficacy, with superficial hemangiomas responding better than deep or mixed types ($P<0.05$).[68]

Superficial IHs are located in the superficial dermis and appear as red, finely lobulated plaques. Deep IHs are located deeper in the dermis and/or subcutaneous tissue, appearing as skin-colored or blue subcutaneous lumps. Mixed IHs involve both layers of the dermis and typically extend into the subcutaneous layer, displaying clinical features of both superficial and deep IHs.[88] To reach the target sites of IHs, PRH must penetrate the stratum corneum and epidermis to reach the dermis.[65] However, the lipophilic part of the stratum corneum of the skin will hinder the percutaneous absorption of PRH. Zhou et al used penetration enhancers to bypass this natural barrier. They used HPMC as a gel matrix and a binary penetration enhancer consisting of 3% farnesol and isopropyl alcohol. The resulting PRH gel exhibited high transdermal permeability and lower plasma drug levels. After applying the gel, the peak concentration of PRH in the skin was 324 times higher than that of the same dose administered orally, but that in plasma was only approximately one-fourth.[69]

Gellan gum can enhance skin hydration and reduce the barrier function of keratin, which is beneficial for increasing the permeability of PRH. Yasuharu et al used gellan gum as the gel base, resulting in an in vitro skin permeability that was 2.6 times higher than that of HPMC gel. However, more in vivo experiments and clinical studies are needed to validate its effectiveness and safety.[65]

Nanoparticle Gels

Propranolol has an oil/water partition coefficient (logP) of 3.48, indicating its lipophilic nature. However, the clinically common formulation of PRH exhibits increased molecular polarity, significantly enhancing its water solubility. Literature reports that the logP is 0.20, making it difficult to passively diffuse through the stratum corneum through transdermal absorption.[75,89] These characteristics limit its ability to diffuse passively through the stratum corneum. Therefore, solely relying on penetration enhancers is insufficient for effective transdermal delivery. Nanoparticles offer unique properties for drug delivery: they can carry a high drug load and have controlled release characteristics, with a small particle size

that enhances permeability. Encapsulating these nanoparticles in hydrogels combines the benefits of both hydrogels and nanoparticles. These gels have significant adhesiveness and fluidity, are minimally irritating, suitable for local application, and exhibit high biocompatibility and biodegradability. These properties make nanoparticle gels a promising transdermal drug delivery vehicle with a wide range of potential applications.[90,91] Chen et al adsorbed propranolol onto colloidal silica nanoparticles and used polyethylene glycol (PEG) as a hydrogel matrix to create a novel nanoparticle-dispersed propranolol hydrogel. These nanoparticles, with a diameter of approximately 5 to 10 nm, significantly increase the contact area with the skin's stratum corneum. The hydrogel serves to protect unstable drugs from degradation and to control the rate of drug release. In a retrospective investigation, 86% of patients had a positive response, while also experiencing reduced side effects and requiring lower doses of propranolol. Interestingly, it was observed that the effects of nano-propranolol were slower compared to oral propranolol, likely due to the controlled-release properties of the nanoparticles, which require more time to diffuse through the polymer matrix to permeate the skin. However, this formulation was specifically considered for superficial IHs, excluding deep or mixed IHs.[70]

Positively charged nanoparticles can adhere to negatively charged skin surfaces.[92] Based on this, Rawia M. Khalil et al fabricated propranolol-loaded nanoparticles (PPL-NPs) by electrostatic interaction between negatively charged phospholipids and positively charged chitosan. These nanoparticles were then incorporated into a hydrogel using Carbopol 940 as the matrix. The lipid/phospholipid mixture enhanced the fluidity of the nanoparticles, while chitosan acted as a permeation enhancer with mucoadhesive properties, prolonging the residence time at the application site. Compared to the drug hydrogel, the PPL-NPs hydrogel showed a 1.56–1.91 fold increase in the area under each skin deposition curve, confirming that the nanoparticles could enhance the accumulation and deposition of PRH in the skin. However, clinical trials in patients with IHs are necessary to confirm the efficacy and safety of its topical use.[71]

The above PRH hydrogels are unable to reach the deeper dermal and/or subcutaneous tissues to treat deep IHs. In a study, the PRH-loaded cubic nanoparticles (CNPs) were prepared to promote the transdermal effect of PRH.[72] CNPs feature a cubic structure similar to cell membranes, composed of amphiphilic lipids (glycerol monooleate, phytantriol, and stabilizers such as Pluronic F127). Glycerol monooleate can self-assemble into a cubic structure with two nonintersecting water channels, disrupting the structure of the lipid bilayers in the stratum corneum, thus enhancing its fluidity and improving transdermal permeation with excellent transdermal drug delivery performance.[93] CNPs employ a remote drug loading method, resulting in a higher drug encapsulation efficiency (approximately 90%) compared to the traditional passive loading method (about 50%). The skin diffusion rate of PRH-CNPs was 10.55-fold that of PRH solution, and the cumulative permeation of PRH-CNPs at 8 hours was significantly higher than that of PRH solution. To improve drug adhesion on the skin, a hydrogel was prepared with 1% xanthan gum, and it was found that the retention of PRH-CNPs-Gel was much higher than that of PRH-Gel. This nanoparticle gel significantly improves drug permeation and retention in the skin, enhancing the drug concentration in deep IHs, making it a potential candidate for transdermal treatment of deep IHs.[72]

Liposome Gels

Liposomes are spherical vesicles formed by lipid bilayers, which can promote skin penetration and intradermal retention of drugs. The double-layered structure of liposomes is highly compatible with the lipid membrane of the stratum cuticle of the skin, which can increase the accumulation of drugs in the skin and form drug reservoirs in the epidermis and dermis, so that the drugs can sustainably play a therapeutic effect on the lesion site and have good biocompatibility. Studies have shown that liposomes can improve skin permeability, making them excellent carriers for topical drug delivery.[94,95] Incorporating liposomes into hydrogels can enhance their stability, prevent burst release effects, and allow for more precise and convenient transdermal drug administration.[96,97] Guan et al prepared PRH-loaded liposome gel using carbomer as a matrix. Compared to the PRH gel, the PRH liposomal gel significantly reduced the barrier function of the stratum corneum, increasing the drug content in the skin (maximum drug concentrations were 123.34 μg/g and 75.65 μg/g, respectively). Additionally, the area under the curve ($AUC_{0\text{-}8h}$) value after local administration was higher, maintaining effective drug concentrations for a long time. The drug content in systemic circulation was decreased, significantly reducing cardiac side effects, making it a promising carrier for the local delivery of PRH[73] . Pluronic lecithin organogel (PLO) is a very popular gel base used to enhance the skin permeation of drugs. It has been reported that a 4% PRH gel, using a phosphatidylcholine-based liposome of PLO as the carrier, was prepared and used in

treatment.[74] This formulation elicited good or partial responses in 82.6% of patients, with only two patients (2.7%) reporting minor local side effects such as irritation, redness, and scaling of the treated area, with no systemic adverse effects reported. Notably, six cases involved mixed IHs, and their average response to the PRH gel was nearly identical to all other superficial IHs. This suggests that the gel has significant permeability, capable of transdermal penetration into the deeper dermal layers and/or subcutaneous tissues where deep IHs reside. However, given the small number of cases involving deep IHs, more data are required to support this conclusion.

Transferosomes, also known as flexible liposomes, are self-assembling vesicles slightly smaller than liposomes. Their fabrication uses techniques similar to those for liposomes but includes surfactants to enhance deformability. As a novel drug delivery method, transferosomes utilize the skin's natural osmotic pressure gradient to penetrate the stratum corneum. This attribute offers significant advantages in the field of transdermal drug delivery.[98,99] Jiang et al developed a transferosome composed of cholesterol-phosphatidylcholine and an edge activator (sodium cholate) for the delivery of PRH. The transferosome was encapsulated in a hydrogel to maintain skin adherence and prevent burst release. The encapsulation efficiency was 81.84 ± 0.53%, with a particle size of 186.8 ± 3.38 nm. The patch exhibited an in vitro transdermal drug permeation rate through rat skin of 111.05 ± 11.97 μg/cm^2 over 48 hours. The Cmax in the skin was 68.22 μg/cm^2, and the $AUC_{0\text{-}24h}$ was 1007.33 μg/cm^2 × h, significantly surpassing that of commercial tablets and hydrogel patches without transferosomes. This formulation showed enhanced permeation and drug retention, potentially extending dosing intervals, reducing side effects, and improving therapeutic outcomes and patient compliance.[75]

Transdermal Patches

Although semisolid formulations for topical drug delivery are widely used, they also present several drawbacks such as uncertainty in dosage, treatment area, and contact time. Moreover, the evaporation of volatile components, often referred to as vehicle metamorphosis, can alter the characteristics of the formulation and even lead to drug precipitation on the skin surface.[100] To overcome these limitations, employing skin patches or films for drug delivery serves as an alternative approach. Water-soluble films, in particular, exhibit no stickiness in their dry state and only become adhesive when slight moisture is present, enabling them to adhere to the skin. These films are easily removable after washing the skin, offering a distinct advantage in the application of film patches.[77]

A study employing a 24 full factorial design screened the skin penetration enhancers (SPEs), pressure-sensitive adhesive types, matrix thickness, and PRH content in PRH patches. The results indicated that matrix thickness and PRH content were the primary factors affecting PRH diffusion through the human epidermis, with increases in both leading to higher drug flux. Among penetration enhancers, N-methyl-2-pyrrolidone (NMP) can effectively promote the diffusion of the drug through the human epidermis and can be used as SPEs. Increasing the concentration of NMP decreased the flux of (RS)-PRH, while (S)-PRH was 100 times more effective than its corresponding (R)-enantiomer. Therefore, a patch with a 50 mm thick methacrylic matrix containing 8% (S)-PRH and 15% NMP can provide continuous, non-irritating drug release over 48 hours.[76]

Cristina Padula et al developed a polymer film containing PRH using polyvinyl alcohol and an acrylic polymer as the matrix. This film exhibits bioadhesion only when applied to the skin, enabling exceptionally high local drug concentrations and short lag times. The study results indicated that drug permeation through barrier-impaired skin increased dramatically, reaching up to 40% within 24 hours. Occlusive conditions enhanced stratum corneum hydration, increasing the permeation of propranolol when the film was applied to intact skin, though the skin retention rate (8.8%) was lower than the permeation rate (10.8%). Under non-occlusive conditions, the skin retention rate of propranolol (3.5%) exceeded its permeation rate (1.7%). These findings suggest that the film can ensure a high proportion of the drug remains within the skin, thereby reducing the risk of systemic side effects and serving as an effective alternative to semisolid formulations.[77]

Similarly, penetration enhancers can be added to films to promote drug penetration. Federica et al designed transdermal films based on HPMC or carboxymethyl cellulose (CMC), using oleic acid and polysorbate 80 as skin penetration enhancers. The results showed that CMC had a higher water uptake than HPMC, but HPMC showed greater cumulative drug permeation amount, possibly because hydrated CMC exhibited higher intrinsic viscosity. Films containing both oleic acid and polysorbate 80 had greater permeability compared to films without enhancers or with only one enhancer. This experiment demonstrated that by adjusting the type of cellulose and enhancer used in the film preparation, the permeability of PRH can be easily modulated.[78] In the same year, researchers reported a novel green nontoxic

excipients - ionic liquids (ILs). These are organic salts composed of asymmetric organic cations and inorganic/organic anions, characterized by high thermal stability, low volatility, low toxicity, and high biodegradability. Researchers incorporated sodium dioctyl sulfosuccinate (a type of ILs) into a PRH amorphous melt for use in transdermal patches. This transdermal patch formulation reduces skin irritation and enhances the transdermal permeability of propranolol.[79]

Liposomes/Nanoparticles

Preformulated liposomes are dense aqueous dispersions of commercial liposomes that can quickly and effectively encapsulate both hydrophilic and lipophilic active pharmaceutical ingredients. Phosphatidylcholine and propylene glycol are added to enhance skin permeability. Antigone Nifli et al incorporated PRH into preformulated liposomes, which demonstrated good stability, sustained release kinetics, and significantly improved skin penetration of PRH. This formulation method is quick and easy, can be executed in the laboratory of community pharmacy laboratories without specialized equipment, and has potential applications in compounding pharmacies.[80]

Nanostructured lipid carriers (NLCs) consist of solid and liquid lipids forming lipid nanoparticles that enhance drug loading capacity, control drug release, and protect the contents from light irradiation. Jessika L. Rocha et al loaded PRH into NLCs for the topical treatment of IHs. NLCs restricted PRH penetration to the skin layers and showed at least 5-fold less drug accumulation in deeper layers compared to the drug solution. Interestingly, IHs lesions often appear in skin areas with lower follicular density. In hair follicle-deficient porcine skin, PRH permeability increased due to enhanced surface drug concentration from follicular blocking. This increase facilitated a higher permeation gradient, improving drug penetration through the stratum corneum into deeper layers, which minimized systemic absorption and adverse effects.[81]

Researchers have developed a 1% propranolol nanoemulsion (NE) using Pluronic F127 as the matrix, with a particle size of 26 nm. Ex vivo permeation studies have shown that the NE significantly retains within the epidermis and dermis due to the nanoscale droplets' large surface area enhancing skin contact. The retention in the dermis is higher for 1% NE compared to 0.5% NE, highlighting the importance of drug concentration for dermal retention. The NE predominantly remains in the skin, with minimal systemic absorption. No cytotoxic effects were observed in skin cells, confirming the NE's local safety. Further studies on skin irritation and clinical trials are required to validate safety and efficacy.[82]

Microneedles

An increasing number of physical devices and methods, such as microneedles (MNs), iontophoresis, sonophoresis, magnetophoresis, electroporation, and photomechanical waves, have been developed to enhance skin permeation.[101–103] MNs technology allows drug delivery across the stratum corneum to underlying layers with minimal invasiveness. The length of the needle is only 0.2–1.5 mm, and it can be self-administered like a patch, with the advantages of a simple delivery mechanism, painlessness, and minimal invasiveness.[104] In 2018, researchers loaded propranolol into a nanoemulsion and incorporated it into solid MNs. Experimental results showed that MNs pretreatment significantly increased skin concentrations for all formulations and notably increased the skin-to-receiver ratios.[83] However, solid MNs are made of silicon or metal, and can cause severe skin damage if the needle tips break off. Dissolving MNs are composed of water-soluble matrix materials such as polyvinylpyrrolidone (PVP), hyaluronic acid (HA), maltose, dextran, albumin, and chondroitin sulfate. Dissolving MNs, on the other hand, are created by encapsulating drugs into biodegradable polymers and consist of water-soluble matrix materials such as PVP, HA, maltose, dextran, albumin, and chondroitin sulfate. Upon insertion into the skin, the needle tips dissolve by absorbing interstitial fluid, and releasing their drug payload. Dissolving MNs address several issues encountered by solid MNs due to their operating mechanism, fundamentally reducing the risk of injury from needle sticks after use. Additionally, manufacturing dissolving MNs is relatively easier compared to other types of MNs.[105]

Building on this, He et al loaded propranolol into dissolving MNs composed of HA and PVP-K90. The prepared MNs have a pyramidal shape and can pierce the SC and reach the dermis, with good penetration, high skin delivery efficiency and excellent mechanical strength (Figure 3). Moreover, the cumulative permeation and skin retention of PRH in dissolving MNs were much higher compared to skin treated with PRH solution alone or with solid MNs. The drug exhibited sustained release, showing substantial advantages in transdermal delivery of hydrochloride propranolol. Nevertheless, further animal experiments are necessary to assess the pharmacokinetics and pharmacodynamics of MNs for successful application.[84]

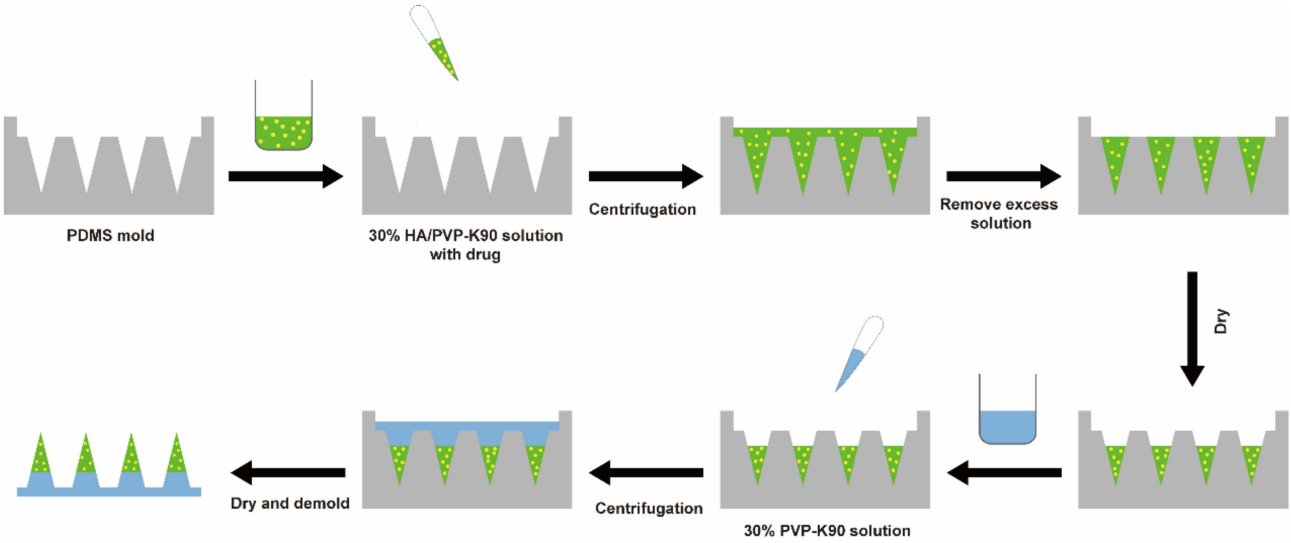

Figure 3 Schematics of the fabrication process of propranolol hydrochloride loaded MNs. Reproduced from He J, Zhang Z, Zheng X, Li L, Qi J, Wu W, Lu Y. Design and Evaluation of Dissolving Microneedles for Enhanced Dermal Delivery of Propranolol Hydrochloride. *Pharmaceutics*, 2021. 13(4). © 2021 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license.[84]

Injectable Formulations

Due to the wide range of locations where IHs can grow, including both superficial skin layers and deep internal vascular tumors, intravenous propranolol treatment has been proven successful for some infants with life-threatening diffuse neonatal hemangiomatosis.[106] Due to the prolonged treatment duration required for IHs and the lack of targeting and sustained release properties in conventional injectable formulations, which are often associated with numerous adverse effects, it is crucial to develop biocompatible scaffolds as sustained-release carriers for nanoparticles. These scaffolds can help maintain the biological activity of the drug at the targeted site.[107] The newly developed PRH injectable formulation can be used both for intralesional injection to treat superficial skin-layer hemangiomas and for intravenous or intraperitoneal injection to treat deep vascular tumors (Table 3).

Guo et al developed various nanoparticles loaded with propranolol to reduce systemic adverse effects and extend dosing intervals through intralesional injection. Utilizing the specific expression of VEGFR2 in IHs, they developed

Table 3 Summary of Studies on PRH-Targeted Injection Formulations for the Treatment of IHs

Main Materials	Preparation Methods	Physicochemical Properties	Experimental Model	Main Effects	Year[Ref]
PLGA-PEG-MAL; PVA; Mouse anti-human VEGFR2 monoclonal antibody	Double emulsion method; conjugating thiolated	PS: ~116.7nm; PDI<0.2; ZP: ~-19.2mV; EE: ~65.9%; DL: ~6.7%	HemECs; HUVECs; BALB/c nude female mice	Targeted delivery and sustained release for 8 days; inhibited the expression of VEGF; reduced adverse reactions, with good safety	2017[108]
PLGA -PEG-COOH; PVA; A15 aptamers	Double emulsion method; EDC/NHS technique	PS: ~143.7nm; PDI: 0.16; ZP: ~-20mV; EE: ~51.8%; DL: ~5.9%	HemSCs; mice	First report on developing aptamer-conjugated nanoparticles for IHs treatment; targeted delivery and sustained release for 8 days; clinically safe; reduced frequency of administration	2017[109]
PLGA-PEG-PLGA; PVA; chitosan; DSPC; CHOL	Film hydration method; modified double emulsion method	PS: ~77.8nm; PDI: 0.26; EE: ~23.9%; DL: ~1.2%	HemSCs; mice	Targeted delivery and sustained release for 40 days; safety and reduced the frequency of administration	2017[110]

(*Continued*)

Table 3 (Continued).

Main Materials	Preparation Methods	Physicochemical Properties	Experimental Model	Main Effects	Year[Ref]
PVA; CTAB; TEOS; $NH_3 \cdot H_2O$; EG	Direct co-condensation method; Physisorption	PS: 133.7nm; ZP: −3.59mV; EE: 58.8% ±7.2%	HemSCs; BALB/c-nu mice	Sustained and controlled drug release; enhanced cytotoxicity and apoptosis rates in HemSCs; induced autophagy dysfunction with excessive autophagosome accumulation to improve PRH therapy efficacy; reduced PRH dosage and administration frequency	2019[111] 2020[112]
PLGA; PVA	Double emulsion emulsification solvent evaporation	$t_{1/2}$: 5.16 h; AUC: 411.59 g·h/mL; apoptosis rate: 59.43%	BALB nude mice	The mechanism of PLGA-PP nano-targeted delivery for treating hemangiomas involves down-regulating the Id-1 gene, inhibiting HemECs hproliferation, and promoting apoptosis	2021[113]

Abbreviations: poly(lactic-co-glycolic acid)(PLGA, 20 kDa)-poly ethylene glycol (PEG, 5 kDa)-maleimide (PLGA-PEG-MAL); PVA, polyvinyl alcohol; VEGFR, Vascular endothelial growth factor receptor; PS, particle size; PDI, polydispersity index; ZP, zeta potential; EE, encapsulation efficiency; DL, drug loading; HemECs, Human hemangioma endothelial cells; HUVECs, Human umbilical vein endothelial cells; EDC, carbodiimide, NHS, N-hydroxysuccinimide; HemSCs, Hemangioma-derived stem cells; DSPC, DistearPropranolol hydrochlorideoyl-l-phosphatidylcholine; CHOL, cholesterol; CTAB, Cetyltrimethylammonium bromide; TEOS, Tetraethyl orthosilicate; EG, ethylene glycol.

propranolol-loaded PLGA nanoparticles (PNP) and conjugated PNP with anti-VEGFR2 antibodies (PNP-VEGFR). The drug loading capacity of PNP-VEGFR was 6.7%, with an in vitro release time extending up to 192 hours. In Human umbilical vein endothelial cells (HUVECs) cell experiments, the IC50 of PNP-VEGFR after 72 hours was 2.4 times and 3.8 times that of PNP and propranolol, respectively; after 120 hours, it increased to 2.9 times and 4.8 times. Similar results were observed in HemECs cells, indicating a significant increase in cytotoxicity with PNP-VEGFR. After 35 days of intralesional injection in mice, the PNP-VEGFR group showed a significant reduction in hemangioma volume, weight, and microvessel density compared to the propranolol and PNP groups. PNP-VEGFR demonstrated superior therapeutic effects, with targeting and sustained release properties, making it a promising candidate for treating IHs.[108]

Aptamers are short single-stranded DNA or RNA molecules that can bind to target molecules with high selectivity and affinity. Compared to antibodies, aptamers have lower immunogenicity and better availability.[114] Hemangioma stem cells are CD133-positive cells isolated from IHs. Some researchers believe these cells are the origin of IHs.[32] A15 is an RNA aptamer that binds specifically to CD133 and has been successfully used as a targeting ligand for tracking CD133-positive cancer cells. Guo et al developed propranolol-PLGA nanoparticles containing CD133 aptamer (PPN-CD133). The experimental results demonstrated that PPN-CD133 also exhibited an excellent release duration of 192 hours in vitro. Propranolol, PPN, and PPN-CD133 showed a dose-dependent inhibition of VEGF-A mRNA expression in HemSCs. Additionally, PPN-CD133 significantly outperformed propranolol and PPN in inhibiting both bFGF mRNA and protein expression. When injected intralesionally into mice, PPN-CD133 treatment led to a 76% reduction in hemangioma volume, compared to 57% and 34% reductions with PPN and propranolol treatments, respectively. Furthermore, the average weight of hemangiomas in the treatment group was significantly lower than in the other groups, and all treatments were well tolerated by the mice. These results indicate that PPN-CD133 is a promising system for targeted delivery and sustained release. However, the study has limitations: due to the tendency of PLGA nanoparticles to load hydrophobic drugs, the drug loading capacity of propranolol in PPN-CD133 is relatively low (5.9%), and the reduction of side effects by PPN-CD133 is difficult to analyze through the mouse model.[109]

To address this issue, researchers used microballoon liposomes (PLIM) to deliver PRH. PLIM was composed of liposomes (PLs) loaded with propranolol encapsulated within microballs made from poly(lactic-co-glycolic acid)-b-poly (lactic acid) copolymer (PLGA-PEG-PLGA), combining the advantages of both microballs and liposomes. Its drug loading capacity (23.9 ± 7.3%) was significantly higher than that of PPN-CD133 nanoparticles. PLIM achieved sustained

drug release for up to 40 days in vitro and effectively inhibited the proliferation of HemSCs, significantly reducing VEGF-A and bFGF levels in these cells. Upon intralesional injection in mice, PLIM demonstrated superior therapeutic effects on hemangiomas compared to propranolol and PL in vivo, effectively reducing the adverse effects and high dosing frequency associated with propranolol treatment for IHs.[110] Autophagy is a crucial biological process for maintaining cellular homeostasis. Low level of cell autophagy helps maintain its steady state. However, under various physical, chemical, or biological stressors, both endogenous and exogenous, the level of autophagy in cells often increases significantly. This "induced" excessive and abnormal autophagy can have negative effects on cells and may even lead to cell death.[115] Wu et al developed a propranolol delivery system based on mesoporous silica nanoparticles (PRN@MSN), targeting HemSCs derived from CD133-positive hemangioma tissues (Figure 4). The apoptosis rate of HemSCs treated with PRN@MSN (20 μM PRN) was significantly higher than that of free PRN. The ROS production induced by PRN@MSN contributed to autophagy induction. Additionally, by measuring the expression of autophagy-related proteins (LC3 and p62), it was confirmed that PRN@MSN could both induce the formation of autophagosomes and impair autophagic degradation. In vivo experiments also showed that the expression of LC3 and p62 in the PRN@MSN group was significantly higher than in other groups, indicating that these nanoparticles can inhibit hemangioma growth both in vivo and in vitro, enhancing the efficacy of PRN in treating hemangiomas with the advantages of high efficacy, low toxicity, and reduced dosing frequency.[111,112]

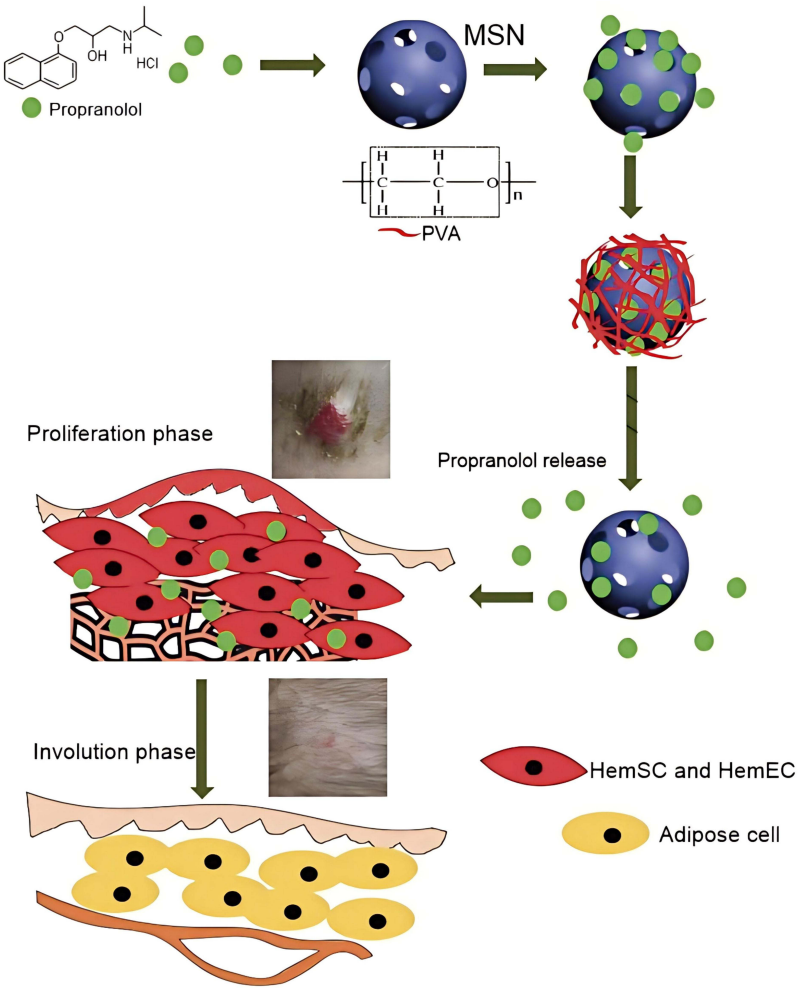

Figure 4 Scheme map of proposed PRN@MSN nanoparticles in treating IHs. Reproduced from Wu H, Wang X, Zheng J, Zhang L, Li X, Yuan WE, Liu X. Propranolol-Loaded Mesoporous Silica Nanoparticles for Treatment of Infantile Hemangiomas. *Adv Healthc Mater*, 2019. 8(9): e1801261. © *2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.*[111]

In 2021, researchers used PLGA nanoparticles as drug delivery carriers and employed the solvent evaporation method to prepare PLGA-propranolol (PLGA-PP) nanocarriers. Preliminary studies were conducted on their targeting ability and pharmacokinetics. Further investigation into the mechanism of action for treating vascular tumors was also carried out. The experimental results showed that PLGA-targeted nanospheres are more likely to bind with receptors highly expressed in HemECs cells and further facilitate the rapid internalization of PLGA-PP nanospheres into cells. The half-life ($t_{1/2}$) of PLGA-PP was found to be 5.16 hours, significantly longer than that of propranolol. Additionally, the AUC for PLGA-PP was 411.59 g·h/mL, which was 1.64 times greater than that of propranolol. The study also indicated that the mechanism of action of PLGA-PP involved the downregulation of the Id-1 gene, thereby inhibiting the colonization of HemECs and promoting apoptosis. Compared to propranolol, PLGA-PP offers significant advantages in terms of improved in vivo stability and prolonged circulation time. It not only reduces systemic side effects but also enhances drug accumulation at the tumor site, thereby further improving the efficacy of treating IHs.[113]

Conclusion

This article summarized various types of PRH formulations currently used and reported, using PRH as a model drug. It clarified the therapeutic effects of PRH and explored its potential clinical applications. An increasing number of researchers are focusing on the design and development of propranolol drug delivery systems. While various new dosage forms have been developed with promising potential applications, some issues require further investigation. For oral formulations, improving targeting, sustained release, and patient compliance are pressing issues that need to be addressed in clinical settings. Addressing surfactant-induced toxicity, enhancing stability, and increasing drug-loading capacity requires further study in topical formulations. The safety of carrier materials for targeted injectable formulations is an ongoing concern, and safer carriers need to be further explored. In addition, the cost control of new formulations in large-scale production and long-term safety and efficacy in clinical applications also need further validation. Finally, the disease mechanism of IH needs further investigation. Developing IH models is a key tool and strategy for studying the pathophysiology and treatment options of IHs, and the establishment of deep vascular tumor models is still under exploration. In addition to some oral preparations, other topical and injectable formulations are still in the research stage, and the formulations for clinical use are still limited. In the face of many difficulties, despite these challenges, new formulations of PRH that can provide sustained and effective anti-IH effects with low toxicity have become a research hotspot. With the development of new drug delivery technology and dosage forms, the research on new dosage forms of PRH will continue to be deepened. Through multidisciplinary collaborative innovation, optimization of existing technology, and development of safer, more efficient, and more convenient drug delivery systems, it is expected to improve the treatment effect of IHs further and bring greater patient benefits.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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