A transdermal edaravone patch as a novel parenteral therapeutic system for amyotrophic lateral sclerosis: preparation method using calcium silica

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We are looking for partners for the promotion of this study to try to apply 505b(2) regulatory pathway. Please contact us.
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【 Background 】

Edaravone : Effective drug to inhibit the progression of functional disability in amyotrophic lateral sclerosis (ALS), which is designated as an intractable disease[1)]

Disadvantages of Oral Formulations
➢Affected by food
➢ Danger of aspiration

Disadvantages of injectable formulations
➢ Pain
➢ Hospital visits and hospitalization for dosing
➢ Frequent dosing for long periods of time

By making a transdermal formulation

➢ Can be used in patients with impaired swallowing
➢ Not affected by food
➢ Improved disadvantages of intravenous infusion

Target permeability

Since the relationship between the efficacy and pharmacokinetics of edaravone, as well as its absorption rate from the skin, are unknown, we assumed an AUC equivalent to that of an oral suspension and no loss within the skin after stratum corneum permeation. Namely,

Formulation	Dose (mg)	$AUC_{0\sim\infty}$ (ng･h/mL)	CL_{tot} (L/h)
RADICUT®ORS (Liquids for Oral Administration)	105	2165±673	35.9

https://pins.japic.or.jp/pdf/newPINS/00070732.pdf

Mean plasma concentration (ng/mL) = 2165 (ng･h/mL) ÷ 24 (h) = 90.20 (ng/mL)
Continuous infusion velosity (μg/h) = Css × Cltot = 90.20 (ng/mL) ×35.9(L/h) = 3231(μg/h)

When we design a transdermal formulation with an application area of 100 cm²,
3231(μg/h)÷100(㎠)＝32.3 μg/㎠/h
It is necessary to achieve a transmission rate of 775.4 μg/cm²/24 h. In this study, we aimed for this rate.

Preliminary studies

Preliminary studies have shown that the use of a commonly used adhesive reduced the amount of edaravone permeation (Fig. 1) .

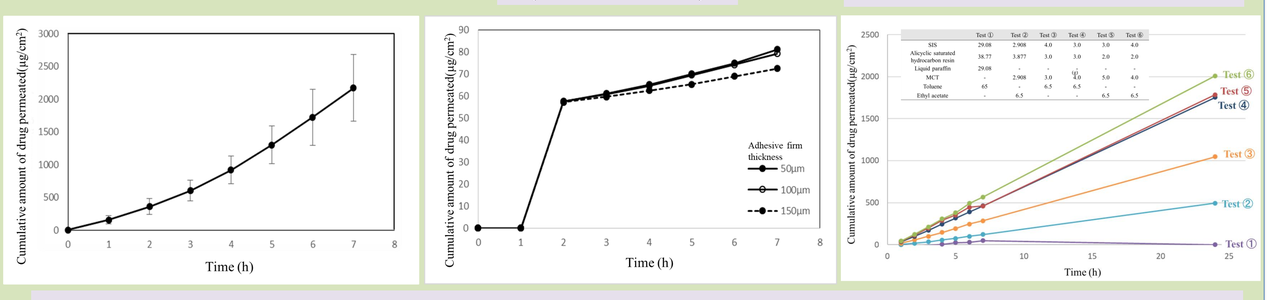


Fig. 1. Effect of applying adhesive layer (50μm) on the permeability of edaravone from 100 mg/mL Edaravone-propylene glycol (PG) solution

【Objective】

･To apply edaravone formulation to tape formulation
･To improve permeability through adhesives

【Materials & Method】

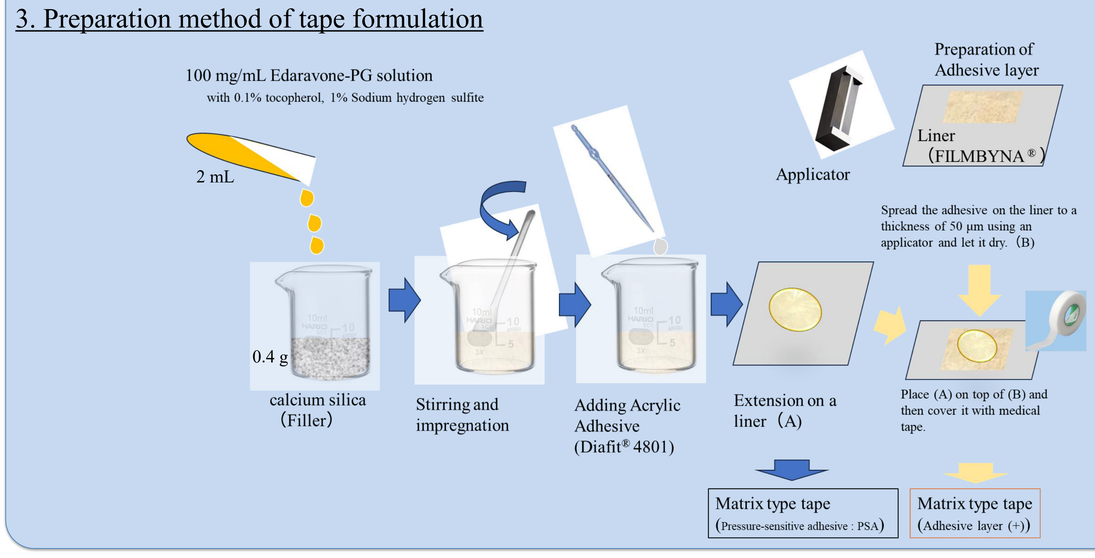
1. Materials

API : Edaravone (3-Methyl-1-phenyl-5-pyrazolone, Tokyo Chemical)
Adhesive : Diafit 4801(Daido Chemical), Styrenic Thermoplastic Elastomers (SIS, ENEOS Materials), Hydrocarbon resin (Regalite R1100, Synthomer), Medium Chain Triglyceride (Palmester 3595, KLK OLEO)
Solvent : Propylene glycol
Liner: FILMBYNA®(BD, Zacros)
Sodium hydrogen sulfite, Tocopherol, Calcium Silicate

2. Permeability test

The edaravone skin permeability was evaluated *in vitro* using a Franz-type vertical diffusion cell system with an artificial membrane (Strat-M™ 25mm Disc, Merck Millipore Co.) or mouse skin at 32.0±1.0℃. 1% Sodium hydrogen sulfite for Strat-M™ , and isotonic 36.5mM Phosphate buffered 0.73% Sodium hydrogen sulfite-0.08% NaCl (pH7.4) for mouse skin were used for receptor solution, respectively. Edaravone concentration of the sample from the receptor chamber was determined by a reverse phase HPLC method.

3. Preparation method of tape formulation

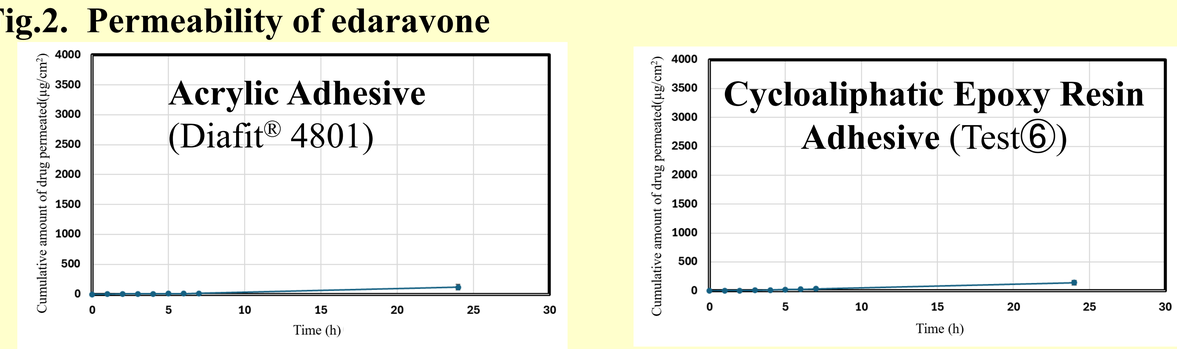


【Results】

1. Investigation of PSA tape-type adhesive patches with edaravone dissolved in the adhesive (without filler)

In tests of PSA tape-type transdermal patches containing dissolved edaravone, formulations were prepared using a simple formula consisting only of adhesive and edaravone, and a transparent appearance and good adhesive strength were confirmed. Permeability tests showed that neither acrylic nor cyclic aliphatic epoxy resin adhesives allowed for significant permeability of edaravone (Fig.2). The absence of edaravone crystals in the resulting adhesives suggests that edaravone was dissolved as a solid solution within the adhesive, indicating a strong intermolecular bond with the adhesive.

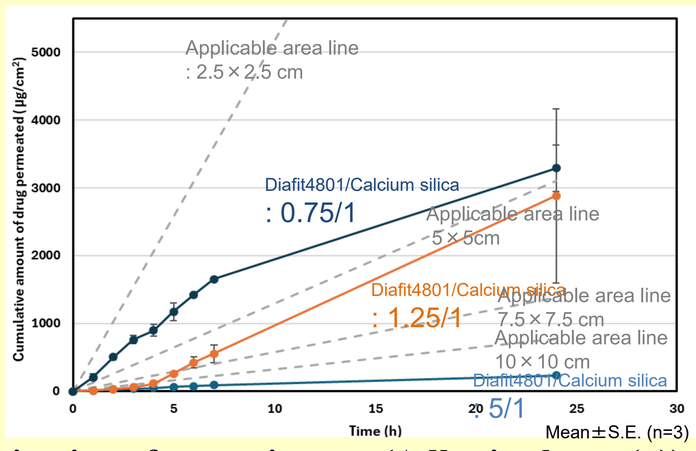
Fig.2. Permeability of edaravone



2. Investigation of pressure-sensitive adhesive (PSA) tape type using acrylic adhesive (with filler)

The results of the permeability test showed that increasing the proportion of porous microparticles improved permeability, suggesting that the target edaravone blood concentration could be achieved with a formulation having an application area of 25 cm² or less at an adhesive/calcium silica ratio of 0.75/1 (Fig.3). However, the resulting formulation did not exhibit sufficient adhesion.

Fig.3. : Effect of adhesive/calcium silica ratio on permeability of edaravone



3. Investigation of a matrix-type (Adhesive layer (+)) using a cyclic aliphatic epoxy resin adhesive (with filler).

Adhesive layer of Test ⑥ was used. The permeability of edaravone across the skin-model membrane was influenced by the thickness of the adhesive layer. 50μm layer provided an applicable area of 25 cm² or less to achieve target permeability (Fig.4). Although the permeability through mouse skin was lower, an applicable area was estimated to be 100 cm² of our target (Fig.5). The drug permeability using filler was higher than that of solution. It indicates that the impregnaing drug solution into calcium silicate can provide not only the solidification of large amount of solution but also enhancement of drug penetration through skin.

Fig.4. Effect of adhesive layer's thickness on permeability of edaravone

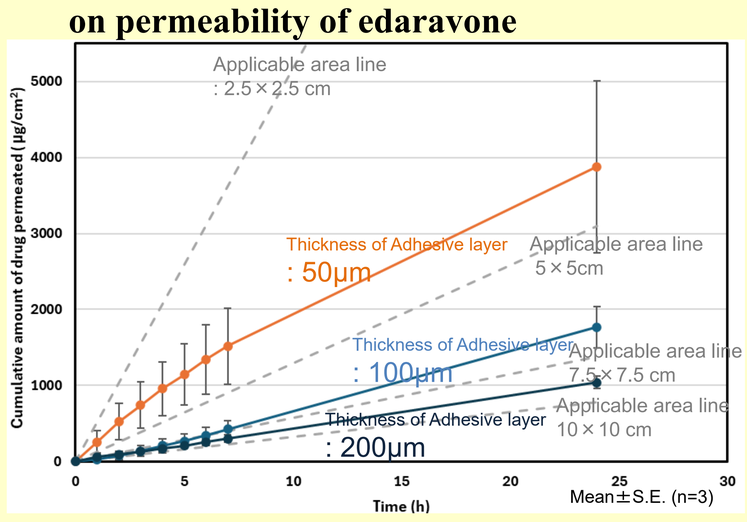
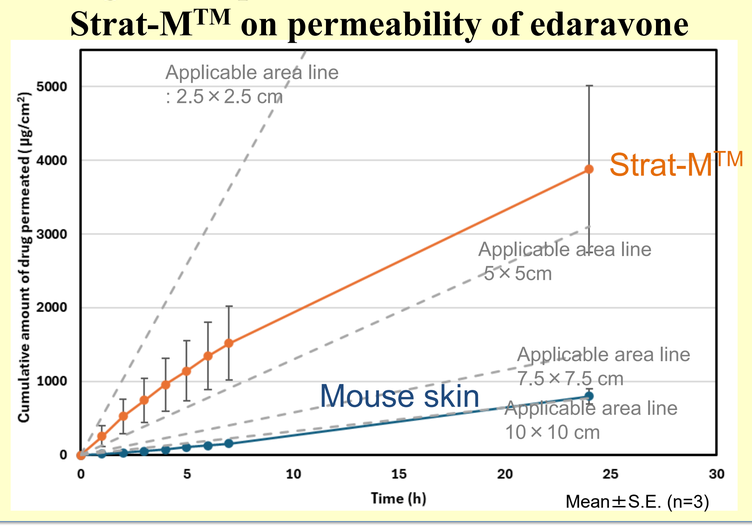


Fig.5. Comparison of mouse skin with Strat-M™ on permeability of edaravone



【 Discussion】

Prediction based on the previous clinical trial data with the oral edaravone preparation indicates that a patch with the minimum permeability can provide AUC comparable to the oral edaravone formulation [1)] . This suggests that approximately 100 cm² (10×10 cm) meets the criteria and can be developed as an effective edaravone TTS for ALS patients.

【Conclusion/Implication】

This study demonstrated the potential of edaravone in tape formulation. The development of edaravone TTS is expected to contribute to improving the QOL of ALS patients for commercialization. This formulation is expected to be applicable to the 505b(2) regulatory pathway as an improved formulation that can overcome the drawbacks of oral suspensions.

【Acknowledgements】 This research was supported in part by financial assistance from Shima Trading Company Ltd.

【References】 (1) Hidetoshi Shimizu, *et al*., Evaluation of Pharmacokinetics, Safety, and Drug-Drug Interactions of an Oral Suspension of Edaravone in Healthy Adults, *Clinical Pharmacology in Drug Development* (2021).