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DEVELOPMENT AND EVALUATION OF TOPICAL GABAPENTIN HYDROGEL

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ABSTRACT

According W.H.O., Epilepsy is an ongoing non-transferable sickness of the mind that influences individuals, everything being equal. Around 50 million individuals worldwide have epilepsy, making it perhaps the most widely recognized neurological sicknesses internationally. This research focuses on designing and formulation of topical gabapentin hydrogel with different and suitable polymers with different ratio of mixing and evaluation of same by following standard parameters such as physical parameters, pH level, viscosity, % drug release and skin permeation test. In Results, it showed as a transparent and complex hydrogel was formed. The pH was found near to neutral. The viscosity was optimum that confirms for its viscous flow. Skin permeation was found maximum in which permeation agents were incorporated to prepare. In conclusion, it assures that hydrogel of gabapentin exhibited an admirable potential in all the parameters evaluated. This research comes under the New Drug Delivery System (NDDS) that enhances the new approach in frequent dermal delivery of loaded gabapentin hydrogel. It would be very impactful with easier, adequate sustained dosing at desired site with minimal systemic side effects in individual's sensations of fits and convulsions. Extra investigations are needed to investigate the pharmacokinetic and pharmacodynamic reactions to topically applied gabapentin in additional detail.

KEYWORDS: Gabapentin, hydrogel, Epilepsy, NDDS.

INTRODUCTION

According W.H.O., Epilepsy is an ongoing non-transferable sickness of the mind that influences individuals, everything being equal. Around 50 million individuals worldwide have epilepsy, making it perhaps the most widely recognized neurological sicknesses internationally (WHO, 20 June 2019). In view of the all-out extended populace of India in the year 2001, the assessed number of individuals with epilepsy would be 5.5 million. The quantity of new instances of epilepsy every year would be near a large portion of 1,000,000. Since rustic populace comprises 74% of the Indian populace. The quantity of individuals with epilepsy in provincial territories will be - 4.1 million (Sridharan & Murthy, 1999). Roughly 20–30% of the epilepsy populace have more than one seizure for every month. (Forsgren et al. 2005).

Gabapentin is an antiepileptic drug with an obscure system of activity obviously unlike that of other antiepileptic specialists, and having some attractive pharmacokinetic qualities. Despite the fact that gabapentin is a primary simple of the synapse γ-aminobutyric corrosive (GABA), which doesn't cross the blood-cerebrum boundary, gabapentin enters into the CNS and its movement is apparently particular from GABA-related impacts (Goa & Eugene, 1993).

During the middle of 1990s, it was notable that antiseizure drugs improved neuropathic torment not receptive to conventional drugs like narcotics. Because of a nearly positive wellbeing profile, gabapentin presented restricted dangers to patients close by successful torment the executives; as needs in 2001. (Peckham et al. 2018). Gabapentin is an anticonvulsant drug that lessens synaptic transmission by diminishing presynaptic voltage-gated Ca2+ and Na+ channels. Besides, gabapentin decreases exocytosis and the release of synapse from presynaptic terminals (Quintero, 2017).

It's anything but processed and doesn't instigate hepatic catalysts or hinder digestion of other antiepileptic drugs. (McLean, 1994). The disposal half-life of gabapentin is 5 to 7 hours, and it requires two days for the body to clear gabapentin from its framework (Yasaei et al. 2020).

Gabapentin use is contraindicated in patients suffering with myasthenia gravis (MG) or myoclonus. (Quintero, 2017).

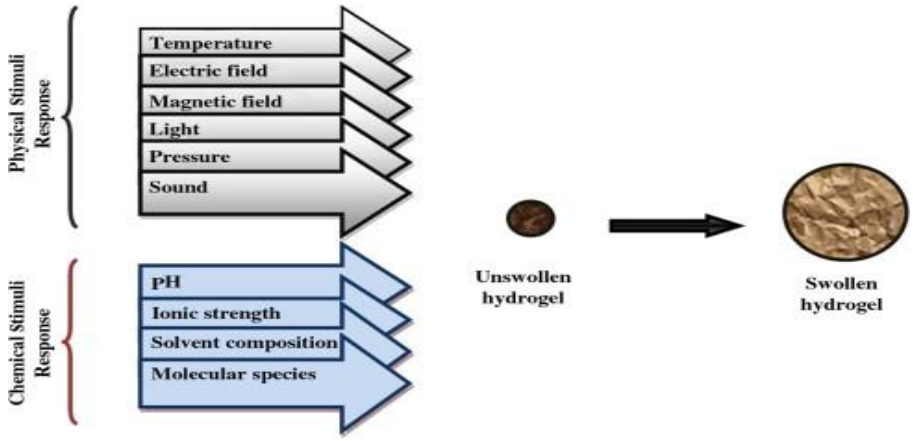

Fig. 1: Stimuli response swelling hydrogel (Ahmed, 2015).

Momentarily, hydrogels hold fantastic biocompatibility. Its water adoring surface has less penchant for cells and proteins to adhere to these surfaces (Akhtar et al. 2016). Hydrophilic gels that are normally alluded to as hydrogels are organizations of polymer chains that are here and there found as colloidal gels (water scattering medium). (Ahmed, 2015). Hydrogels have played a key job in is drug conveyance innovation (Monica & Gautami, 2014). Martin et al. (2017) studied an assortment of effective gabapentin plans including Carbopol hydrogels containing different saturation enhancers.

On the basis of literature survey, I found that hydrogel of gabapentin can be developed with different polymers to facilitate dissolution, bioavailability and stability of the topical formulation. This research focuses on designing and formulation of topical gabapentin hydrogel with different and suitable polymers with different ratio of mixing and evaluation of same by following standard parameters.

MATERIALS AND METHODS

1. Experimental requirements

Gabapentin, Carbopol, methyl hydroxybenzoate, propyl hydroxybenzoate, sodium methyl hydroxybenzoate and sodium ethyl hydroxybenzoate. Phosphate-buffered saline (PBS) 0.01M. An oil-in-water (o/w) base Lipoderm. All the materials were procured from the certified suppliers and of analytical grade only.

2. Preparation of hydrogel (Martin et al. 2017)

Initially, gabapentin is dissolved into the required mass of de-ionized water. Hydrogels are prepared as follows-

A. For blank- Carbopol and 0% ethanol gels, sodium methyl and ethyl hydroxybenzoate are also dissolved in de-ionized water.

B. For hydrogels- containing a permeation enhancer, methyl and propyl hydroxybenzoate are dissolved in the required mass of permeation enhancer solvent. Permeation enhancers included dimethyl sulfoxide (DMSO), dimethyl isosorbide (DMI), isopropyl myristate (IPM) or propylene glycol (PG). The permeation enhancer mixture is added to the aqueous mixture and pre-mixed for 5 min.

Then, the mixture A and mixture B are transferred to a STD 1 Silverson mixer fitted with a square hole high shear screen. A required amount of Carbopol (powder) is dispersed within the solution and mixed for approximately 30 min. Residual gel is removed from the working head and the formulation is kept at room temperature for approximately 1 h. Finally, a sufficient quantity of neutralizing agent is added in a drop-wise manner and mixed at low shear to cross-link each gel and provide appropriate viscosity.

3. Production of formulations utilizing different bases

Some specified quantity of gabapentin powder is triturated into one of the following bases and mixed by hand: Versatile cream, Doublebase gel or Lipoderm base. Each formulation is prepared as a 10% (w/w) product, and mixed by hand or automated paddle until thoroughly mixed. Formulations are packaged into aluminium tubes and crimped for proper storage under ambient conditions (prior to use) (Martin et al. 2017).

4. Evaluation parameters

4.1 Physical parameters

The hydrogel was examined for its color, size and shape.

4.2 Viscosity

Roughly 200 g of plan are put into a uniquely designed round and hollow plastic holder. The plans are then examined utilizing a Contraves Rheomat LG108 Viscometer. Each gel broke down was set into a water shower set to 32 ±2ºC and equilibrated for approximately 30 min before analysis (Martin et al. 2017).

4.3 pH of hydrogel

The formulated hydrogel was recorded for its pH using digital pH meter.

4.4 In-vitro drug release

The *in-vitro* drug release is performed by Franz diffusion (FD) cell using phosphate buffer at pH 7.2 scale.

Cellophane membrane is used as semi-permeable membrane for diffusion. Receptor compartment up is filled with 20 ml medium up to the mark of collection limb. Then membrane is kept on the receptor compartment.

Accurately weighed 1 gm of emulgel and placed on the membrane in between donor and receptor compartment and fit them firmly. The rotation per minute (rpm) of magnetic stirrer in the donor compartment and external stirrer are adjusted in such a way to make laminar flow in the medium. The temperature of FD cell was maintained at 37°C by circulating water jacket. 5 ml of sample was collected on different time intervals from the collection limb and replace the same volume with buffer medium. Then the samples were analyzed by UV-spectrophotometer at 276 nm wavelength and thus concentrations are determined (Pani et al. 2014).

4.5 Preparation of skin membrane

Subcutaneous fat is removed by blunt dissection and each skin sample cut into sections of approximately 1.5 cm^2. Sections are immersed in a water bath at 60ºC for 55 s before the epidermis was removed by forceps. Epidermal membranes were wrapped in aluminium foil and frozen at -20ºC prior to use; all membranes were used within three months of preparation (Abraham & Donald, 1989.

RESULTS AND DISCUSSION

4.1 Evaluation of physical features of hydrogel

Initially, the hydrogel was prepared following the standard procedure as follows-

The formulated hydrogel was evaluated for different physical features as following-

Table 5.1 Physical features of hydrogel.

S. N.	Physical features	Observation
1.	Color	Transparent
2.	Shape	Matrix- oriented
3.	Odor	Pleasant

The above table confirms for the color, shape and odor of the hydrogel of gabapentin. In all the factors, it showed an excellent form of formulation in terms of physical features that it has better color, well needed shape and fragrance in odor. Most of the hydrogels follow the above-mentioned physical features.

It also predicts for the uniformity of API and additives added; may indicate for better drug release and thus optimum bioavailability.

54.2 Production of formulations utilizing different vehicles

The following table comprises data in terms of different vehicles used (diverse ratios) but percentage of gabapentin was kept same. In some formulations, permeation enhancer was added but in most of them none the same was utilized.

On the basis of different polymer or vehicle used the uniformity of mixture and color with odor was found changed. Odor occurred as per the odor of the permeation agent used.

Table 5.2: Formulations with different vehicles.

Vehicle (%w/w)	Gabapentin (API)(%w/w)	Permeation enhancer	Features
Lipoderm	10	None	Homogenous & off-white in color
Versatile	10	None	Homogenous & off-white in color
Doublebase	10	None	Homogenous & white in color
Carbopol	10	None	Homogenous, transparent
Carbopol (0.7)	10	Ethanol	Homogenous, transparent & ethanolic odor
Carbopol (1.5)	10	DMSO	Homogenous, off- white & DMSO characteristic odor
Carbopol (0.8)	10	PG	Homogenous & transparent

4.2 Viscosity

Following table represents the viscosity observed in the hydrogel made by different polymers used. It showed that hydrogel demonstrates a desired level of viscosity and may make the better drug release from its base.

Vehicle (%w/w)	Gabapentin (API) (%w/w)	Viscosity
Lipoderm	10	1.52
Versatile	10	2.27
Doublebase	10	2.43
Carbopol	10	2.59
Carbopol (0.7)	10	2.72
Carbopol (1.5)	10	3.13
Carbopol (0.8)	10	2.81

4.3 pH of hydrogel

The pH of different hydrogel was recorded using digital pH meter with electrodes- probes. The following table comprises the pH of diverse hydrogels.

Table 5.3: pH of hydrogel.

Vehicle (%w/w)	Gabapentin (API) (%w/w)	pH
Lipoderm	10	6.4
Versatile	10	6.6
Doublebase	10	6.7
Carbopol	10	6.3
Carbopol (0.7)	10	6.5
Carbopol (1.5)	10	6.8
Carbopol (0.8)	10	7

4.4 In-Vitro drug release

The in-vitro drug release study was recorded from 0.5 to 8 hrs. Formulation no. 1, 2 and 3 demonstrated a time dependent drug release. The optimum drug release was found at 8 hours.

Table 5.1.2 In-vitro drug release test.

Hydrogel	Time (hr)	% drug release
Lipoderm	2	11.52 ± 0.48
Versatile	2	12.02 ± 0.38
Doublebase	2	19.10 ± 0.78
Carbopol	2	24.01 ± 0.98
Carbopol (0.7)	2	30.12 + 0.12
Carbopol (1.5)	2	32.42 ± 0.48
Carbopol (0.8)	2	34.44 ± 0.23

4.5 Preparation of skin membrane

It showed that Carbopol (1.5% w/w) in gabapentin (10% w/w) exhibited an optimum level of skin penetration power using the DMSO as permeation agent. Another hydrogel formulation of Carbopol (0.8% w/w) in gabapentin 10% w/w showed maximum permeation power when polyethylene glycol was used as permeation agent. It's obvious that the formulation of hydrogel without containing any permeation agent used demonstrated the low rate of penetration across the hair-free membrane of rats. That's why permeation agent is required while formulating the hydrogel because permeation agent easily crosses the skin barrier in drug absorption.

CONCLUSION

This research comes under the New Drug Delivery System (NDDS) that enhances the new approach in frequent dermal delivery of loaded gabapentin hydrogel. It would be very impactful with easier, adequate sustained dosing at desired site with minimal systemic side effects in individual's sensations of fits and convulsions. Skin conveyance of gabapentin could give an elective treatment to oral conveyance of the dynamic for neuropathic torment conditions, with related decreased fundamental results; this is upheld by in vivo contemplates and observational clinical proof. Be that as it may, gabapentin is a polar particle and would not be relied upon to cross the layer corneum boundary without any problem (Martin et al. 2017).

The association between electrolytic polymers didn't frame a gel because of the inconsistent charge thickness, ionic strength and atomic load of the electrolyte polymers which utilized in the arrangement. The quaternary ammonium gatherings of copolymers and carboxylic gatherings in sodium alginate were found to upgrade the change in the swelling ratio. The micrograph for swollen models showed the presence of huge pores that sped up arrival of the medication to environment (Abdulmonaim & Haddad, 2018).

Effective conveyance of gabapentin could give an elective treatment to oral conveyance of the dynamic medication for neuropathic torment conditions, with related decreased foundational results. Gabapentin stacked chitosan transdermal film ready by dissolvable projecting technique utilizing glycerine and DMSO as plasticiser and entrance enhancer (Sayare et al. 2019).

It would be a great launch towards allopathic external applicable medicines to ease the life and millions. It may also be confirmed that its production at bulk level would be reasonable in terms of cost. It would be great deal for stability of formulated hydrogel. It will reduce the dosing frequency of the same gabapentin as it will provide for prolonged and desired action.

Extra investigations are needed to investigate the pharmacokinetic and pharmacodynamic reactions to topically applied gabapentin in additional detail.

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