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Original Article

FAST DISSOLVING SUBLINGUAL PATCH OF PHENOBARBITAL SODIUM: FORMULATION AND *IN VITRO* EVALUATION

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ABSTRACT

Objective: To formulate and characterize. Phenobarbital sodium loaded sublingual patch using biodegradable, mucoadhesive, fast-dissolving natural polymer pullulan for immediate management of epileptic seizures.

Methods: Phenobarbital sodium loaded sublingual patches were prepared by the solvent casting method and were subjected to various physicochemical evaluation parameters to find the optimized sublingual patch. The *in vitro* drug release study and kinetic model of the optimized formulation was also carried out. The stability study of the optimized Phenobarbital sodium loaded sublingual patch was also done.

Results: From *in vitro* drug release study, it was found that Phenobarbital sodium loaded sublingual patch (S4) exhibited a maximum drug release of 96.24±1.27% at the end of 60 min compared to other formulations indicating a faster drug release from the formulation with release kinetics as Higuchi diffusion model. In fact, a notable release data was obtained between 0.5 to 8 min by all formulations, specifically S4 formulation (20.84±1.97% and 77.22±2.41% drug release at the end of 0.5 min and 8 min respectively) showed a better percentage release profile in comparison with other formulations. Such a trend is vital to deliver the drug at a faster rate to promote immediate effect for managing the fatal and complicated seizure. Considering the physicochemical property and *in vitro* drug release data, S4 formulation was regarded as an optimized one. The stability study also confirmed that S4 formulation is stable at refrigeration conditions.

Conclusion: The formulated Phenobarbital sodium loaded sublingual patch is an effective drug delivery carrier which enables faster drug release to manage epileptic seizure.

Keywords: Epilepsy, Phenobarbital sodium, Pullulan, Fast dissolving, Sublingual patch

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INTRODUCTION

Epilepsy is the third most common neurological disorder affecting almost 1% worldwide population in which brain activity becomes uncommon and is characterized by abnormal neuronal firing, which eventually results in unprovoked and unpredictable epileptic seizures and the recurrent episode of sensory disturbance [1, 2]. Epilepsy may occur by genetic predisposition or by brain injury such as trauma. This induces a brief episode of loss or disturbance of consciousness with or without characteristic body movement and sudden electrical storm, which may or may not lead to seizure. Seizure is a symptom for epilepsy associated with synchronously active neurons [3]. Typically used medications to subside seizure include oral and intravenous dosage forms. Presently the first-line drug for the ailment is benzodiazepine I. V. Along with this, pre-hospital management of epileptic seizure is achieved by rectal diazepam, intranasal and buccal midazolam solution. These benzodiazepines have a faster onset of action but possess short half-life, CNS depression and inability to differentiate postictal symptoms with that of the drug side effect. These reasons limit its use for therapy. The second line drug is phenytoin and fosphenytoin [3], whose dose given even though I. V is large (1.5g). The next choice of drug for the treatment comprises of Phenobarbital sodium, which is long-acting and cost-effective. But its current route of administration involves intravenous route that requires a skilled professional for administration and needs a sterile environment and also the oral administration possess delayed onset of action, poor bioavailability and interference of hepatic first-pass metabolism [4, 5]. High dose of Phenobarbital sodium (150 mg) is given intravenously to provide clinical benefit due to the inefficient delivery of drugs into the brain that leads to potential adverse effects [6].

Moreover, the oral tablet of Phenobarbital sodium takes at least 30 min to initiate its action. A rapid seizure control is mandatory to prevent the long term consequences in the brain, including neuronal damage, brain injury and, eventually, brain death. Unlike other routes, sublingual routes are superior due to its ability to absorb and produce action in seconds [7-9]. The degree of absorption is higher in the sublingual area when compared to other oral routes since the thickness of the sublingual area is 100-200 µm. Moreover, the polymer used is pullulan, which is biodegradable, non-hygroscopic, non-reactive, possess the mucoadhesive property and is a fast-dissolving polymer [10] and thereby providing management of epileptic seizure. The optimum brain concentration of Phenobarbital sodium for anticonvulsant activity is 7-9µg/ml [12]. It would be appreciable if dose reduction is done since only a minimal concentration is required for its anticonvulsant effect. Considering these, it is important to formulate a sublingual patch using adequate excipients along with the drug. Apart from pullulan, propylene glycol is used as a plasticizer to maintain its flexibility, clove oil used as a permeation enhancer and citric acid as saliva stimulating agent [13]. Using these agents, it was able to formulate a fast-dissolving sublingual patch of Phenobarbital sodium that showed a faster release pattern, which would be promising for the management of epilepsy [14, 15].

MATERIALS AND METHODS

Materials and excipients

Phenobarbital sodium API was gifted by Malladi Drugs and Pharmaceuticals Ltd, India and Pullulan were gifted by Gangwal chemicals pvt. Ltd, Bhiwandi. Propylene glycol was obtained from Choice Organochem Ltd, Mumbai, Citric acid was obtained from Fisher Scientific, the United States and Clove oil was obtained from Manohar Botanical Extracts pvt. Ltd. Kochi, All the chemicals used were of analytical grade [16].

Preformulation studies

Solubility

Solubility of the drug was checked in various solvents, including Methanol, Distilled water, Ethanol, Phosphate buffer saline (PBS) pH 6.8 [17].

Melting point

Melting point of the obtained drug sample indicates the purity of the sample. The presence of impurities in drug samples leads to a low melting point. Open capillary method was used to determine the melting point of the sample [19].

Partition coefficient

Partition coefficient of Phenobarbital sodium in n-octanol was found out [20]. The formed aqueous layer and organic phase were separated and the distribution of solute in both phase were determined by UV spectroscopy at 235 nm.

Formulation of phenobarbital sodium loaded sublingual patches

Phenobarbital sodium loaded sublingual patches were prepared by the solvent casting method [21-23]. From the preliminary physicochemical evaluation of the patches prepared, the suitable composition was used for the incorporation of Phenobarbital sodium. A natural polymer, pullulan was used as the main polymer along with the addition of propylene glycol as a plasticizer [24]. Clove oil was used as a permeation enhancer, and Citric acid was used as a saliva stimulating agent [25, 26]. Calculated amount of Phenobarbital sodium (1% (equivalent to 200 mg)) in methanol (9:1 ratio) was dissolved in the polymeric solution of pullulan (6.5-8.5%) and propylene glycol (4%). After complete dissolution of the drug, citric acid (0.005%) and clove oil (0.005%) was added and stirred using a magnetic stirrer for 30 min at 600 rpm to form a homogeneous solution [27, 28]. The solution was casted on petridish, initially coated with glycerin, then kept in a hot air oven at temperature 45±5 °C for 24 h [29]. The patch thus formed was cut into a size of 1×1 cm^2 diameter [30]. The formulation compositions of Phenobarbital sodium loaded sublingual patches were shown in table 1.

Table 1: Formulation composition of Phenobarbital sodium loaded sublingual patches

S. No.	Formulation code	Phenobarbital sodium (%)	Pullulan (%)	Propylene glycol (%)	Citric acid (%)	Clove oil (%)	Distilled water(ml)
1.	S1	1	6.5	4	0.005	0.005	qs.20
2.	S2	1	7	4	0.005	0.005	qs.20
3.	S3	1	7.5	4	0.005	0.005	qs.20
4.	S4	1	8	4	0.005	0.005	qs.20
5.	S5	1	8.5	4	0.005	0.005	qs.20

Preparation of backing membrane

A solvent casting film method was used to prepare the PVA-Aluminium backing membrane, is an impermeable substance that protects the product during use [31]. It was then casted on aluminum foil in a petridish at 50 °C by pouring 5 percent w/v aqueous solution of PVA and left for 8 h so as to get dry patch of drug impermeable backing membrane [32]. The patches of the appropriate size were then cut and stored in a suitable condition.

Physicochemical evaluation of prepared Phenobarbital sodium loaded sublingual patches

The Physico-chemical evaluation studies of prepared Phenobarbital sodium loaded patches are enlisted below

Thickness uniformity of the patches

The thickness of the prepared patches of each formulation of size 1×1 cm^2were measured using a screw gauge with least count at three different sites, and the average value was calculated [33].

Uniformity of weight of the patches

Three patches of each formulation of size 1×1 cm^2 were randomly subjected to weight variation by individually weighing the selected patches and the average was determined [34].

Folding endurance

Three patches of each formulation of size 1×1 cm^2 were sliced using a sharp blade. The folding endurance of patches was determined by folding a patch continuously at the same place until it appeared to crack. It was calculated as the number of times the patch is folded in the same position to either split the patch or produce noticeable cracks. The mean value with standard deviation was then determined [35, 36].

Surface pH determination

The surface pH was determined to keep the pH as close to neutral as possible. For this purpose, a combined pH-electrode was used. Patch of each formulation of size 1×1 cm^2 had been slightly wet with 1 ml of distilled water. The pH was determined by making the electrode came in contact with the patch surface. The procedure was carried out in triplicate, and standard deviation was reported on average [37].

Percentage swelling index

Three patches of each formulation were cut into 1×1 cm^2 and initially weighted and kept immersed in 50 ml PBS pH 6.8. Taken out and weighed at time intervals of 5, 10, 30 and 60 min until a constant weight was obtained [38].

Percentage of moisture absorption

To evaluate the physical stability of the patches under high humidity conditions, the accurately weighed 3 patches of size 1×1 cm^2 and was placed in a desiccator containing saturated Aluminium chloride solution (79.5 % w/w relative humidity) for 3 d [39, 40].

Drug content uniformity

Patch from each formulation of size 1×1 cm^2 was dissolved in methanol and continuously shaken until the patch dissolved. After filtration, followed by proper dilution of methanol, the absorbance was measured at a wavelength of 235 nm and percentage drug content was then calculated. Methanol alone is the blank solution. The drug content determination was carried out in triplicate for all the formulations and the average percentage value with standard deviation was recorded [41].

Disintegration time

The disintegration time, in this case, is the time when an oral patch or film begins to break when it comes in contact with saliva or sublingual pH. The disintegration time should be in the range 5-30 sec for a fast-dissolving film or patch. United State Pharmacopoeia (USP) disintegration apparatus can be used to study disintegration time. In another method, the disintegration time can be visually determined by dipping the drug-loaded patch of size 1×1 cm^2 into 25 ml of PBS pH 6.8 buffer in a beaker. The beaker should be shaken gently, and the time when the film or patch begins to break or disintegrate was noted and the triplicate value was taken [42].

***In vitro* drug release study**

The studies of *in vitro* drug release of various formulations of Phenobarbital sodium loaded sublingual patches were done using static dissolution method. The apparatus was assembled by introducing an open-end tube vertically aligned to a beaker containing 50 ml of PBS pH 6.8, which acts as a receptor compartment [43]. The one end of the open end tube was tied with a cellophane membrane (molecular weight 12000-14000 D) which resembles the membrane acting as a barrier within the body so that only the tip touches the buffer solution surface. Reaction conditions have been standardized throughout the study. In the donor compartment, 1×1 cm^2 of the Phenobarbital sodium loaded sublingual patch was placed. The beaker was placed on a magnetic stirrer for 30 min and 1 ml of sample was taken at regular intervals. For each withdrawal, 1 ml of

fresh PBS pH 6.8 was replaced in the beaker and the samples collected were diluted using the same. The cumulative percentage of drug released in to the receptor medium at regular intervals was spectrometrically evaluated at 239 nm using a UV visible spectrophotometer. All these studies were done in triplicate [44].

Kinetic models of *In vitro* drug release study

In order to examine the release mechanism of the drug from the optimized sublingual patch, the percentage cumulative drug release values were fitted into various kinetic models such as Zero-order kinetics, First-order kinetics, Higuchi model and Korsemeyer–Pappas release kinetics to identify the in which model of release does the formulation is best fitted [45].

RESULTS AND DISCUSSION

Preformulation studies

Solubility

Phenobarbital sodium is freely soluble in distilled water and soluble in methanol ethanol and PBS pH 6.8 [46].

Partition coefficient

Partition coefficient of the drug was found to be 2.14, indicating that the drug possesses optimum lipid solubility [47].

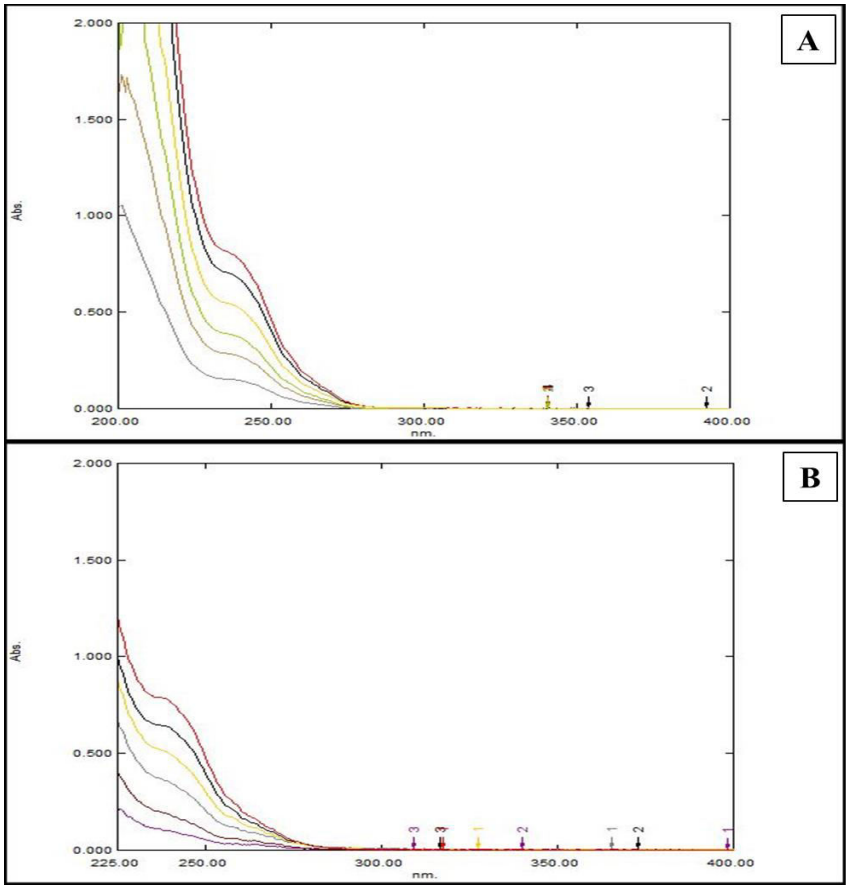

Fig. 1: (A) Absorption maxima of phenobarbital sodium in PBS pH 6.8, (B) Absorption maxima of Phenobarbital sodium in methanol

Lambda max of the phenobarbital sodium in phosphate buffer saline (PBS) pH 6.8

The Lambda max of the drug in phosphate buffer saline (PBS) pH 6.8 was found to be 239 nm, and was in accordance with the official standard. The absorption maxima of Phenobarbital sodium in PBS pH 6.8 were shown in fig. 1(A)

Lambda max of the phenobarbital sodium in methanol

The Lambda max of the Phenobarbital sodium in methanol was found to be 235 nm and was in accordance with the official standard [48]. The absorption maxima of Phenobarbital sodium in methanol were shown in fig. 1(B)

Preparation of calibration curve of phenobarbital sodium in PBS pH 6.8

The absorption values of the standard Phenobarbital sodium drug solution containing 20-120µg/ml of drug in pH 6.8 at the maximum wavelength of 239 nm is plotted. PBS of pH 6.8 provided similar pH as that of the sublingual fluid; thus it facilitates comparison of the results to *in vivo* conditions. The concentration used was in accordance with beer-lambert's law [49]. The calibration curve was shown in fig. 2(A)

Preparation of calibration curve of phenobarbital sodium in methanol

The calibration curve was found to be linear in the concentration range of 20-120µg/ml at a wavelength of 235 nm [fig. 2(B)]

Formulation of phenobarbital sodium loaded sublingual patches

In this study, Phenobarbital sodium loaded sublingual patches were prepared by the solvent casting method using biodegradable natural polymer pullulan. Priya *et al.* (2016) [50] described the perks of using pullulan as a film former. Apart from these advantages, it has a mucoadhesive property, which could help in retaining the formulation upon administration. It has been identified that the clove oil has a higher permeation index, which would accounts for the immediate permeation of drugs through the sublingual area to encourage instant therapeutics. In order to stimulate the production of saliva, an agent should be incorporated, which was citric acid. Propylene glycol acts as a good plasticizer that helps in maintaining the flexibility of the patch.

These factors led to the selection of pullulan, clove oil, citric acid and propylene glycol as excipients in the formulation [51]. The patches were prepared with polymer concentration varying from 6.5-8.5 %. Patches with concentration below 6.5% were found to be sticky and were unable to be peeled out from the petridish. The varying concentration of pullulan above 6.5% with an optimized concentration of propylene glycol gave flexible and easily removable patches. The fig. 3 showed the picture of the Phenobarbital sodium loaded sublingual patch. A Backing membrane of PVA-Aluminium was also made using the solvent casting method. It is impermeable in nature and protects the patch formulation during its use, which follows a unidirectional drug release pattern. Backing membrane being compatible provides a good bond with the drug reservoir, thus preventing the drug from leaving the dosage through top.

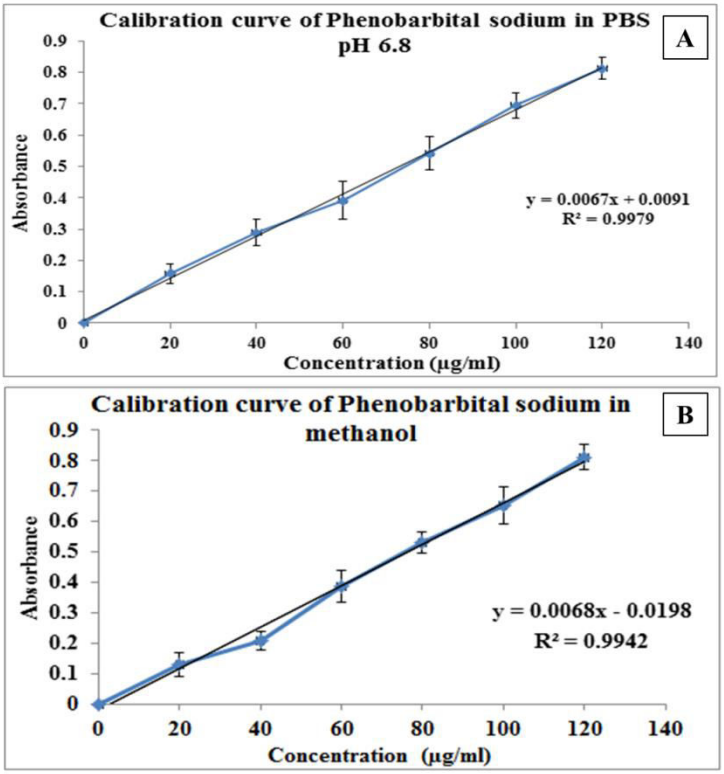

Fig. 2: (A)The standard calibration curve of the pure drug of Phenobarbital sodium in PBS pH 6.8 with slope, intercept and regression coefficient, (B) The standard calibration curve of the drug phenobarbital sodium in methanol with slope, intercept and regression coefficient, (Values are expressed as mean±standard deviation, n=3)

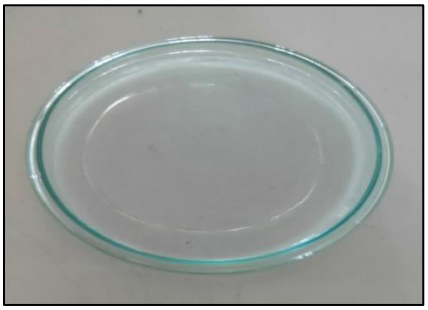

Fig. 3: Formulation of phenobarbital sodium loaded sublingual patch

Physicochemical evaluation of prepared Phenobarbital sodium loaded sublingual patches

Physicochemical properties

The physicochemical evaluation data were tabulated in the table 2

Thickness uniformity of patches

The thickness of the prepared sublingual patches varied from 0.23±0.62 mm to 0.39±0.69 mm [fig. 4(A)]. The patches were evenly distributed in the petridish. The thickness of S4 is 0.29±0.89 mm, which is adequate to be placed in the sublingual area [52].

Uniformity of weight of patches

The average weight of the patches varied from 118 mg±0.75 to 133 mg±0.87 for S1-S5 formulations, of which S4 has an optimum average weight, which is 124±0.57 mg [fig. 4(B)].

Folding endurance

The folding endurance of various patches varied from 56±1.03 to 162±1.05. It has been found that a good patch should have folding endurance above 150, which was shown by S4 (162±1.05) [fig. 4(C)]. The folding endurance values did not change much when a comparison was made between bare patches and the drug-loaded patches. Furthermore, the obtained result promises that it will endure stresses that would be encountered in the area of administration.

Surface pH determination

The surface pH of all the formulations S1-S5 was found to in the range 6.41±0.69 to 6.76±1.06 [fig. 4(D)] indicating that all the formulations were non-irritant to oral as well as sublingual mucosa [53].

Percentage swelling index

The swelling index of the patches S1-S5 ranged from 13 %±0.84 to 34 %±1.38 [fig. 5(A)]. As the concentration of pullulan increased more than an optimum concentration, the swelling property decreased. S4 formulation (34 %±1.38) got a maximum swelling index.

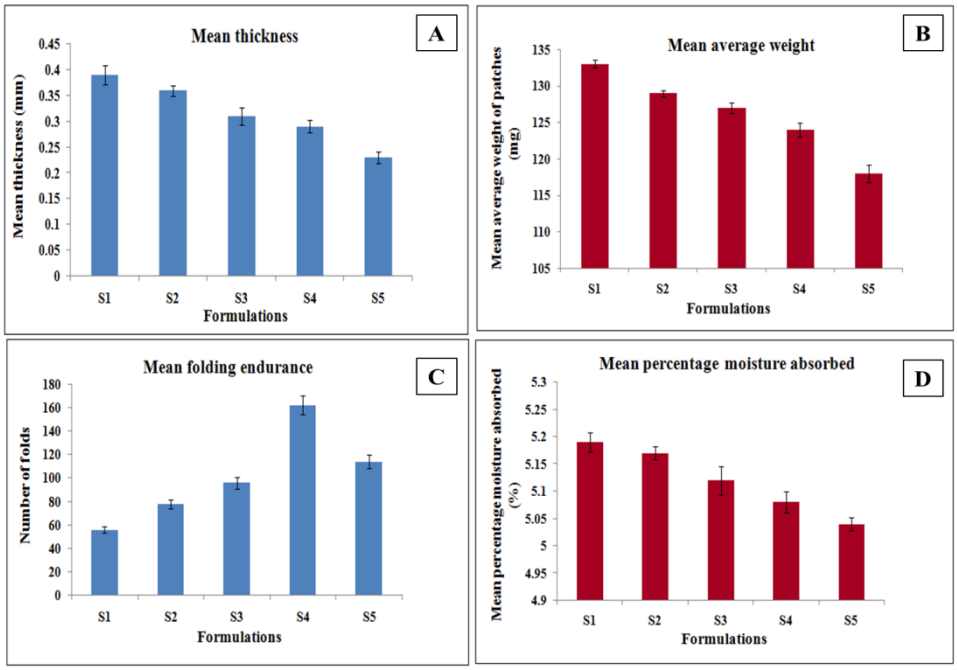

Fig. 4: (A) Mean thickness of various drug loaded sublingual formulations (S1-S5), (B) Mean average weight of formulations S1-S5, (C) Mean folding endurance of formulations S1-S5, (D) Mean surface pH of formulations S1-S5, (Values are expressed as mean±standard deviation, n=3)

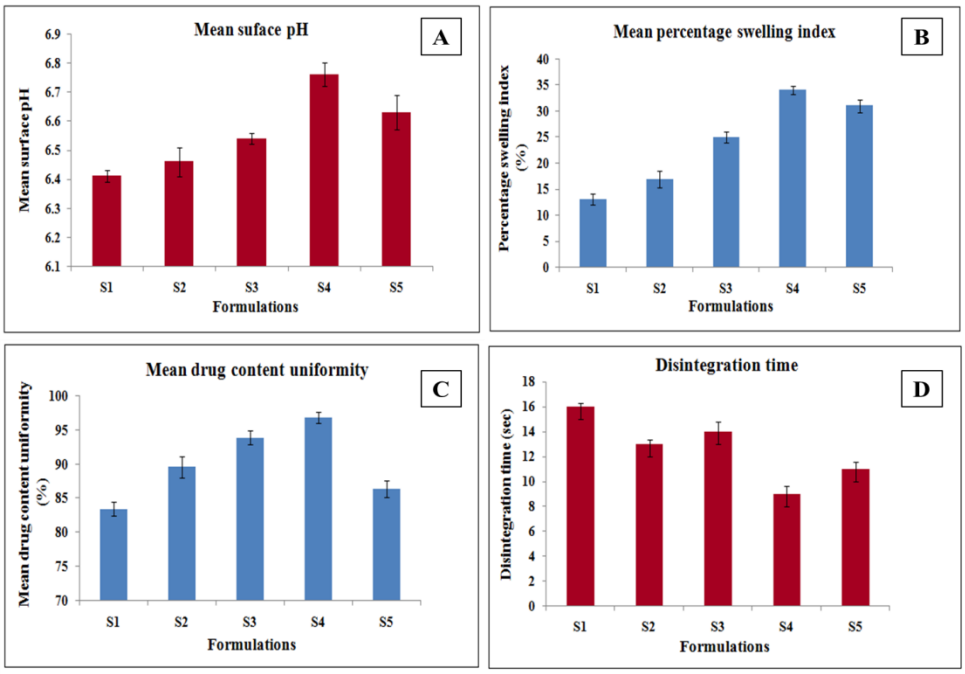

Fig. 5: (A) Disintegration time of the formulations S1-S5, (B) Mean drug content uniformity of the formulations S1-S5, (C) Mean % swelling index of formulations S1-S5, (D) Mean surface pH of formulations S1-S5, (values are expressed as mean±standard deviation, n=3)

Table 2: The physicochemical evaluation data of various drug loaded sublingual formulations (S1-S5), (values are expressed as mean±standard deviation, n=3)

Code	Mean thickness (mm)	Average weight (mg)	Folding endurance	Surface pH	% Swelling index (%)	% Moisture absorbed (%)	Drug content uniformity (%)	Disintegration time (Sec)
S1	0.39±0.62	133±0.87	56 ±1.03	6.41±0.69	13±0.84	5.19±0.76	83.39±0.91	16 ±0.87
S2	0.36±1.02	129±0.99	78±0.76	6.46±0.76	17±1.24	5.17±1.21	89.56±1.13	13±1.51
S3	0.31±1.32	127±0.65	96±1.34	6.54±0.90	25±1.13	5.12±0.87	93.89±1.02	14±2.18
S4	0.29±0.89	124±0.57	162±1.05	6.76±1.06	34±1.38	5.08±0.79	96.78±0.82	09±1.24
S5	0.23±0.69	118±0.75	114±0.45	6.63±1.09	31±1.99	5.04±1.14	86.34±0.89	11±1.94

Percentage of moisture absorption

The percentage moisture absorption of the Phenobarbital sodium encapsulated patch was found to be between 5.19 %±0.76% to 5.04 %±1.14 [fig. 5(B)]. All formulation possess percentage moisture absorption around 5%. The lesser the percentage moisture absorption the more the patches will be stable at humid conditions.

Drug content uniformity

All the formulations exhibited good drug content. Among them, S4 exhibited the highest drug content, with 96.78±0.82 % [fig. 5(C)]. The obtained value depicts that the homogenous distribution of drug content has been achieved [54].

Disintegration time

The disintegration time of all formulation varied from 09±1.24 to 16±0.87 sec. Among them, S4 disintegrates at a faster rate (09±1.24). This suggests that the formulated patches will get fastly disintegrated in the sublingual fluid pH within few seconds and the drug will be then permeated instantly [fig. 5(D)].

***In vitro* drug release study**

The *in vitro* drug release study gave an idea regarding the amount of the drug that is available for absorption into the systemic circulation [55]. The release profile of drug predicts the *in vivo* behaviour of the drug in the circulation. The drug release study was carried out using a phosphate buffer solution (PBS) of 6.8 since the pH of the sublingual fluid is in this range. The cumulative percentage drug released from each formulation v/s time curve was plotted at different time intervals. The cumulative percentage drug released for all formulations varied from 75.97±2.48% to 96.24±1.27 % at the end of 60 min. A significant release was shown within first 30 seconds by all the formulation specifically by S4 formulation (20.84±1.97%) and about 50% of the drug was also released within 8 min of which S4 showed 77.22±2.4% release compared to other formulations. This drug release pattern is substantial as the drug could reach systemic circulation at a faster rate that ultimately results in rapid onset of action. After 60 min, the patch lost its stability and integrity and was not suitable for further studies. The S4 formulation showed a maximum release of 96.24±1.27 % when compared to other formulations. Upon analysing the release data and physicochemical parameters, the S4 formulation was considered to be the optimized one and was further selected for the remaining study. With the aid of biocompatible polymer pullulan and permeation enhancing the capability of clove oil may have resulted in accelerating the drug release from the formulation [56]. Finally, the kinetic model determination of the optimized formulation S4 was also carried out. The *in vitro drug* release data of prepared S1-S5 formulations were shown in fig. 6(A).

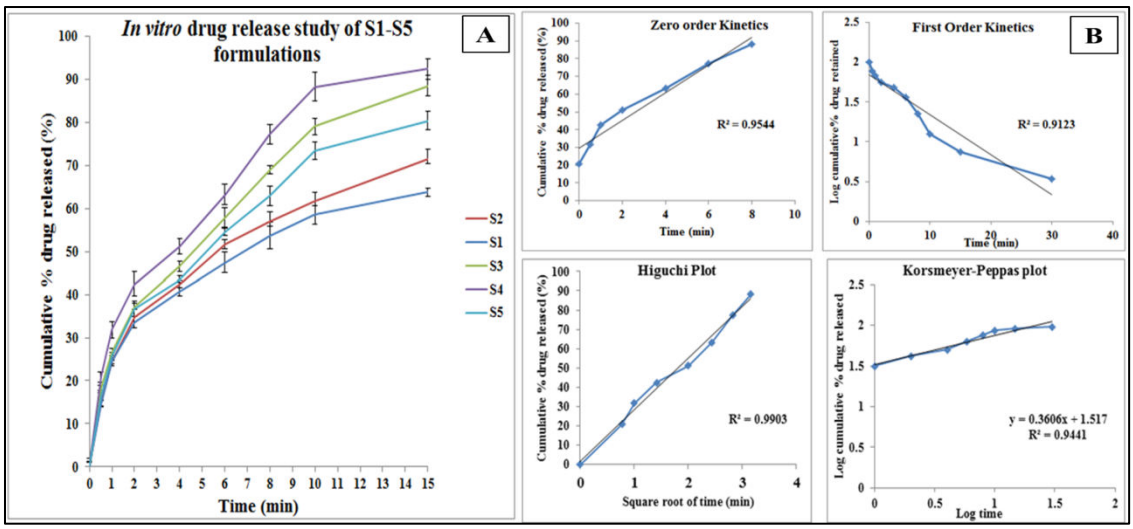

Fig. 6: (A) *In vitro* drug release of prepared S1-S5 formulations, (B) *In vitro* drug release model fitting data of optimized Phenobarbital sodium loaded sublingual patch (S4), (Values are expressed as mean±standard deviation, n=3)

Table 3: *In vitro* drug release model fitting data of optimized phenobarbital sodium loaded sublingual patch (S4), (values are expressed as mean±standard deviation, n=3)

Zero-order release plot	First-order release plot	Higuchi plot	Korsemyer peppas plot		Best fitted model
R^2R^2	R^2	R^2	n	R^2	Higuchi plot
0.9544	0.9123	0.9903	0.36	0.889	

Kinetic models of *In vitro* drug release study

The drug release profile of optimized Phenobarbital sodium loaded sublingual patch (S4) was attributed to different kinetic models like zero order, first order, Higuchi diffusion model and Koresmeyer Peppas plot to interpret drug release by kinetic modeling [57] [fig. 6(B)]. The release kinetics of the drug Phenobarbital sodium was found to be Higuchi diffusion model with the highest regression coefficient value, R^2= 0.9903. Hence we can conclude that the optimized formulation showed rapid release from the polymer matrix by diffusion as it was the best fit in the higuchi model [58].

Stability study

The stability study of the optimized Phenobarbital sodium loaded sublingual patch (S4) was carried out for 3 mo at refrigerator temperature (4±2 °C) and its physical changes like colour, flexibility, texture and physicochemical characters like disintegration time and folding endurance were estimated at an interval of one month [59]. The physical appearance of the patch was retained and did not show any change after 3 mo on comparing with the freshly prepared patch at refrigeration. The disintegration time and folding endurance of the patch was determined for 0 mo, 1st, 2nd and 3rd month, respectively and was shown in fig. 7(A) and fig. 7(B). The results of the study indicated that there were no significant changes observed in the disintegration time and folding endurance when stored at refrigerated temperature even after 3 mo [60]. Thus the result of stability study confirmed that the optimized Phenobarbital sodium loaded sublingual patch S4 remained stable at refrigerated temperature (4±2 °C) for three months.

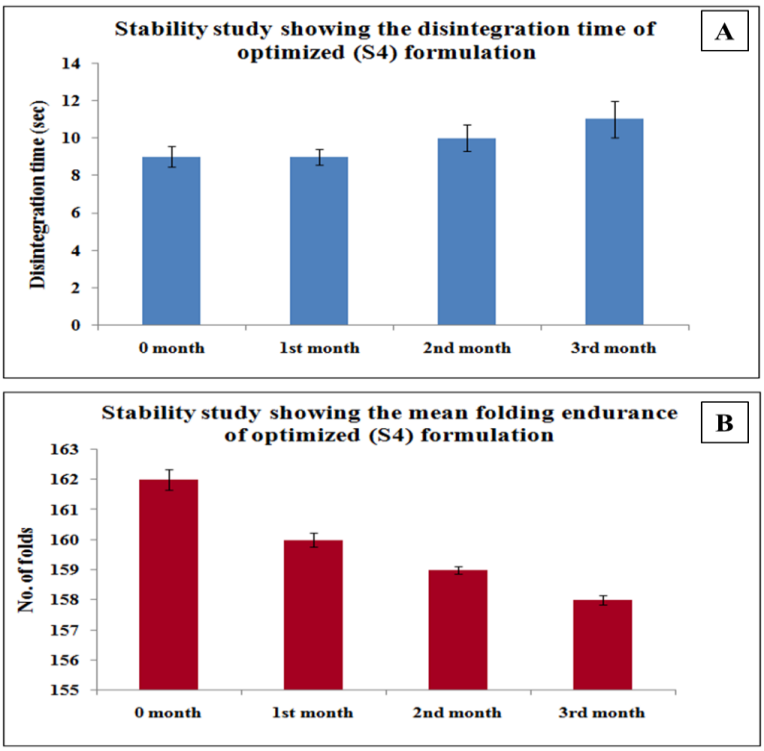

Fig. 7: (A) Stability data showing the disintegration time of optimized Phenobarbital sodium loaded sublingual patch (S4) formulation, (B) Stability data showing the Folding endurance of optimized Phenobarbital sodium loaded sublingual patch (S4) formulation, (values are expressed as mean±standard deviation, n=3)

CONCLUSION

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate seizures. Several routes for the administration of anti-epileptic drug have been identified but none seems to be completely effective. Sublingual patches gained applicability in drug delivery system as a novel, convenient and easily administrable form of the drug product. Furthermore, the degree of absorption through the sublingual route is higher when compared to other routes and hence could deliver the drug at much faster rate, which is mandatory in our ailment of interest. Phenobarbital sodium loaded sublingual patches were prepared by the solvent casting method using biodegradable, biocompatible natural polymer pullulan with clove oil as a permeation enhancer, propylene glycol as a plasticizer and citric acid as saliva stimulant. The optimised sublingual patches of Phenobarbital sodium (S4) provided a maximum drug release within short span of time with diffusion mediated release mechanism. The S4 formulation retained its physicochemical properties even when it was subjected to refrigerated condition, depicting its stable nature. Thus the optimized Phenobarbital sodium loaded pullulan based sublingual patch was found to be promising for the sublingual delivery of drug for the management of epileptic seizures, which requires further scientific scrutiny.

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Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

All authors have no conflicts of interests.

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