Research Article

Formulation and Evaluation of Antiepileptic Non Aqueous Solution of Stiripentol

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ABSTRACT

Stiripentol (STP) is a narrative orphan drug that is used as adjunctive therapy for the treatment of severe myoclonic epilepsy in infancy (SMEI, Dravet syndrome). Due to the sudden onset of epileptic attack, it is necessary to formulate antiepileptics into such a delivery system, which provides immediate relief. For old and pediatrics, dysphagia (difficulty in swallowing) is a common complaint. A nonaqueous vehicle for oral pharmaceutical solution is described which has a satisfactory taste, low toxicity, good flow properties. The Stiripentol solution for pediatric oral usage (50mg/kg/day) was investigated to determine its physicochemical stability under different storage conditions. The purpose of this study is to develop and improve oral liquids formulations of Stiripentol for pediatric use. Five different formulations were developed, all of the formulations were physically, chemically stable for three months. The results of the stability studies determined. The developed solution evaluated for appearance, clarity, pH viscosity determination and test of stability study.

Keywords: Stiripentol, Oral solution, Caster oil, Miglyol, Stability of solution.

INTRODUCTION

The pharmaceutical industry is an important element of health care systems all over the world in order to discover, develop, manufacture and market medicines for human health. Oral liquids are homogeneous liquid preparations, usually consisting of a solution, an emulsion or a suspension of one or more medicaments in an appropriate vehicle. Oral liquids are intended for oral administration either undiluted or after dilution. Some patients, particularly pediatric and geriatric patients, have difficulty in swallowing solid dosage forms hence liquid dosage forms are needed. So drugs which are slightly soluble in water hence formulation of a solution will be most suitable but product may not be physically and chemically stable.[1]

Epilepsy is a chronic neurological disorder that affects between 0.5% and 1.0% of pediatric population[2]. It involves recurrent unprovoked seizures and it is the third most frequent neurological disorder, after cerebrovascular disease and dementia[3]. Typical pharmacological treatment includes antiepileptic drugs (AEDs) that control seizures when they are daily administered[3]. Stiripentol is white to pale yellow crystalline powder having Characteristic odour which is insoluble in water, soluble in acetone, ethanol, ether, acetonitrile, dichloromethane stable in cyclohexane, toluene, methanol. Stiripentol is indicated for the treatment of seizures allied with Dravet syndrome in patients 2 years of age and older taking clobazam. The dosage of Stiripentol is 50 mg/kg/day, administered by mouth in 2 or 3 divided doses. It is currently available as 250 and 500 mg tablets but unfortunately, no suitable liquid formulation for pediatric administration is commercially available[12]. The lack of pediatric liquid dosage forms represents a challenge for hospital and community pharmacists. Usually, children require smaller doses than adults which are adjusted by body weight. Thereby solid dosage forms must be fractionated in to fit pediatric dosages. This practice represents a concern issue because correct dosing must be ensured[5]. Preparing extemporaneous liquid formulations is one of the most common practices employed to adjust doses for paediatric patients. Moreover, children under 7 years old are unable to swallow capsules or tablets. Liquid formulations which are flavored aqueous solutions, syrups, or suspensions, are administered directly into the child's mouth by drop, spoon, or oral dispenser or incorporated into the child's food[6]. General dose volumes are ≤5 ml for children under 5 years and ≤10 ml for those of 5 years and over[7]

Stiripentol is a derivative of α -ethylene alcohol and has a chemical structure that is different from other currently marketed antiepileptic agents. Stiripentol (STP) is a novel antiepileptic drug (AED) structurally not related to other anticonvulsants used clinically to treat seizure disorders. It is an orphan drug as adjunctive therapy for the treatment of severe myoclonic epilepsy in infancy (SMEI, Dravet syndrome). STP reduces competently pharmaco-resistant seizures and status epilepticus.[8] STP has both direct and indirect anticonvulsant actions. Stiripentol was found to act through a sole site in a subunit-dependent manner. In spite of lower clinical utility of STP in adults, it is very effective in treating seizures in children due to its privileged improvement of α3-bearing receptors. STP has a good quality safety profile with relatively high therapeutic index. It is generally well-tolerated, even in epileptic children.[8, 10] STP's bioavailability is relatively low because of insolubility in water and biological fluids in addition to

possible hepatic first pass. It shows an anomalous dissolution profile in gastric and intestinal fluids due to its poor water solubility. Absorption of the drug can be influenced by oral fast dissolving dosage form; this may have effectiveness for epilepsy in pediatrics and those having difficulty in swallowing tablets/capsules resulting in improved patient compliance.[11] Additionally, epileptic patients have to carefully follow the dosage regimen for the prevention of sub-therapeutic concentration, The very limited solubility of stiripentol in water suggests that this drug will be not easy to abuse by IV injection.

The most common reason for the formulation of a solution for reconstitution is the inadequate chemical stability of the drug in the nonaqueous vehicle. The objective of the present study was to design a stable and effective solution of stiripentol that utilize for the seizures.

An ideal dosage form should be:

1. It should be safe and easy to administer.
2. It should be easy to handle.
3. It should be easy to produce and manufacture
4. Provide high patient compliance.
5. Should be physically and chemically stable.
6. It should maintain its therapeutic activity throughout the shelf life.

Advantages of oral route of administration:[13]

1. It is most easy and safest route for administration of drug for patients.
2. It is most convenient for patients.
3. This route can be used for large variety of dosage forms.
4. Nursing for administration is not required.
5. It is economical to the patients.

MATERIALS AND METHODS

Stiripentol purchased Nuray Chemicals, all other materials, reagent and chemicals used were of analytical grade.

Experimental Preformulation Study

Solubility[14]

1mg Stiripentol was dissolved in 100ml of different solvents like water, Propylene glycol, Miglyol and Kolliphor separately and was tested for solubility as per BP 2000.

Determination of λmax[15]

A solution of Stiripentol containing the concentration 10 µg/ ml was prepared in Methanol and UV spectrum was taken using Shimadzu UV double beam spectrophotometer. The solution was scanned in the range of 200 to 400 nm.

Preparation of standard and sample solutions

STP stock solution (1mg/mL) was prepared by dissolving 25 mg of STP reference standard material into 25mL methanol in a 25mL volumetric flask and completing the volume properly. This stock solution was later diluted with methanol to produce a working standard solution of 100μg/mL. Working solution wasstoredat4◦C until required for analysis.[15]

Preparation of calibration samples

An eight-point calibration curve (2, 4, 6, 8, 10, 12 μg/mL) was constructed by plotting the peak area of STP (y) versus STP nominal concentration(x). Analysis of calibration sample sat each concentration was performed in triplicates. Slope, intercept, and $r2$ values were calculated as regression parameters by linear regression. The linear regression equation was used to calculate the concentrations of STP in aqueous solutions and dosage form based on their peak area.

Standard calibration curve of stiripentol

Table 1: Absorbance data of stiripentol in methanol

Conc. in ppm	Absorbance
0	0
2	0.1392
4	0.2882
6	0.391
8	0.5382
10	0.6626
12	0.774

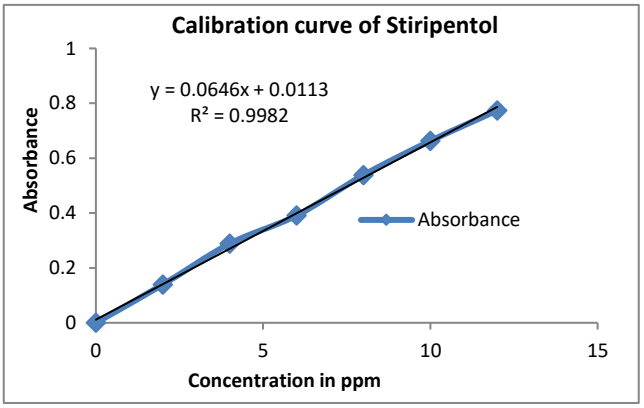

Figure 1: Standard calibration curve of stiripentol in methanol

Formulation development

Procedure: Using the evidence available from literature and practical work where a solution of stiripentol was prepared.

Step: I Firstly we have to prepare a solvent system.

Step: II To the above solvent system to add Stiripentol API.

Step: III After that add the sweetening agent and flavoring agent as the specified amount and the pH was measured.

Following ingredients were selected to develop the desired formulation.

Table 2: Composition used in the formulation of solution:

Ingredients (g)	S1	S2	S3	S4	S5
Stiripentol	500mg	500mg	500mg	500mg	500mg
Propylene Glycol	5ml	-	-	1.5ml	-
Caster oil	q.s.	5ml	1ml	2.5ml	2.5ml
Miglyol	-	-	4ml	-	-
Sorbitol	-	-	-	1.5ml	2.5ml
Sweetener	100mg	100mg	100mg	100mg	100mg
Flavour	q.s.	q.s.	q.s.	q.s.	q.s.

Formulation Appearance

Formulation appearance of each batches

S1 Batch

Appearance: In this formulation, a clear solution appeared, after the addition of castor oil.

Inference: It should be not acceptable because of unpleasant rough taste.

S2 Batch

Appearance: In this formulation, a clear solution appeared but in thick form.

Inference: There is so viscous formulation, therefore it should not suitable for administration.

S3 Batch

Appearance: In this batch, the solution is formed but slightly viscous.

Inference: It is suitable for administration as compared to other formulation and taste comparison.

S4 Batch

Appearance: In this formulation, the solution is phase dispersion occurred.

Inference: The solution is in a turbid form and not suitable for administration and taste.

S5 Batch

Appearance: In this formulation, the solution is phase dispersion occurred as well as turbidity occurred.

Inference: The solution is in a turbid form and not suitable for taste.

RESULTS AND DISCUSSION

Preformulation studies

Difference Scanning Chromatography

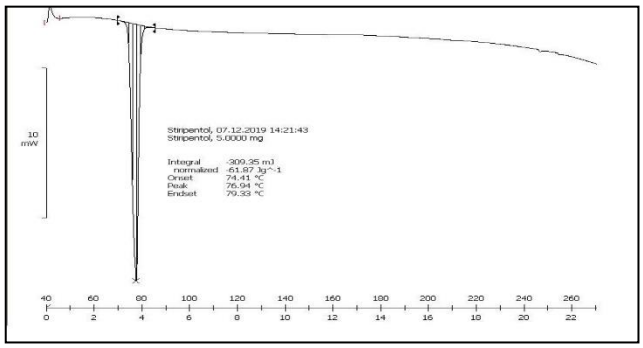

Figure 2: Represent the DSC of samples of stiripentol API

FT-IR analysis

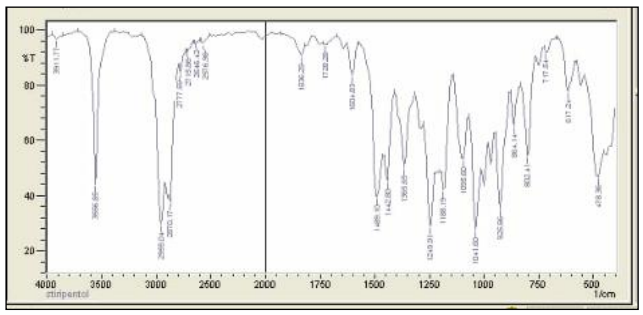

Figure 3: Represent the FTIR spectra of samples of stiripentol API

The IR spectrum of Stiripentol was interpreted and identified. The chief absorption bands of the drug are present in the Stiripentol with the same degree of sharpness and position it indicates that there is an absence of physical and chemical interactions among active component.

Evaluation of solution

1. pH [16]

pH is measure the negative logarithm base 10 of hydrogen ion concentration. Determination of pH: pH of solution was determined by using pH meter. pH of the syrup also contributes to stability and characteristics of formulations. So pH of the syrup was recorded from time to time.

2. Viscosity:[17]

The viscometer was thoroughly cleaned with a mixture of warm chromic acid. It was then filled with distilled water and clamped vertically onto a stand. The viscosity of the liquid to be determined is delivered from a pipette into the limb with bulb E. The quantity of liquid should be such that, when it is sucked through the tube in the next limb, the upper level stands above the A mark and the lower level stands in the other limb at the bottom of bulb E. First, the distilled water was sucked until its upper meniscus in above A, it is level marked and allowed to flow down. The stop clock was started when it reaches A mark and stopped when the level reaches B mark. The flow time was noted down in seconds in the tabular column. The procedure was repeated untill the agreement values are obtained. The viscometer was cleaned again and an equal volume of liquid was taken and the flow time was determined in

second as above. The density of the liquid with a specific gravity bottle was determined and viscosity was calculated,

Time in seconds flow x viscometer factor x wt/ml of water x wt/ml of liquid.

3. In-vitro drug release

In-vitro release of all the batches was determined using USP Type II apparatus (Paddle) LABINDIA DS 8000 in 1000 ml of 6.8 Phosphate buffer &0.5% SLS at 37±0.5°C and at 75 rpm for 1.30 hr. The sample was withdrawn at specific time points (5, 10, 15, 30, 45, 60,90min). From these samples 1 ml was taken and diluted with media up to 50 ml to made 55.5 ppm solution. These samples analysed by spectrophotometrically at 262nm**.**

4. Assay

Accurately measured 10 ml of solution was transferred to a 100 ml volumetric flask. Volume was made up with Methanol. From the above 5ml of the solution was withdrawn and made upto 50ml with Methanol and sonicated for 30 min .The absorbance of the resulting solution was measured at 262 nm.

5. Stability test

The chemical stability of Stiripentol in oil solution and solid dosage form was evaluated under accelerated and stress conditions. Each sample, contained in a scintillation vial, was placed in stability chambers maintained at 25ºC/60%RH. At predetermined time points, samples were withdrawn and the drug remaining in the samples was analyzed by the LC–MS/MS method.

6. Study of Different Parameters of Formulations

Table 3: Study of various parameters of different formulations

Batches	P^H	Viscosity cP	% Drug release	Assay %
S1	8.98	86.6	87	109.74
S2	6.35	117	86	100.13
S3	6.58	88.18	88	99.7
S4	7.60	168.4	80	88.12
S5	6.88	180.4	76	89.17

7. Comparative study of marketed formulation with optimized test product

Table 4: Comparative data

Sr. No.	Parameters	Results		Inference
		S3	Diacomit	
1	Appearance	Colourless solution	Pink Colored suspension	Complies
2	Ph	6.58	6.80	Complies
3	Viscosity	88.18 cP		Complies
4	Dissolution at 1.30hr	93%	87%	Complies
5	Assay	99.7%	99.3%	Complies

Table 5: Evaluation of accelerated stability study

Parameters	Initial	25ºC/60%RH		
		1M	2M	3M
Appearance	Colourless solution	Colourless solution	Colourless solution	Colourless solution
pH	6.58	6.58	7.04	7.01
Viscosity	88.18cP	87.23 cP	150.10 cP	151.25 cP
Dissolution at 1.30hr	90%	92%	88%	87%
Assay	99.7%	100.1%	103.5%	103.5

CONCLUSION

From the study which was carried out it was concluded that:

1. The S3 batch was selected as the best formulation based on the various evaluation studies.

2. The formulation S3 was compared with a marketed sample of Stiripentol Suspension and tablet and it was found that the drug release from the formulated solution matches the drug release profile of the marketed suspension sample. The drug release from the formulated solution was higher when compared with that of the marketed tablet sample.

3. Stability studies also concluded that the drug release profile or other parameters did not alter significantly after the accelerated stability studies.

4. Further work can be continued to make formulations with suitable excipients that can prevent crystallisation and to impart latest techniques to mask the bitter taste of the drug.

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