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FORMULATION DEVELOPMENT, OPTIMIZATION AND PHARMACOKINETIC EVALUATION OF PRAZIQUANTEL LOADED SOLID SELF EMULSIFYING DRUG DELIVERY SYSTEM

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ABSTRACT
The current study was aimed to develop and optimize a solid self emulsifying drug delivery system for pediatric patients to improve the oral bioavailability and solubility of the anthelmintic drug, Praziquantel (PZQ). The optimized S-SEDDS tablet T3 batch showed minimum disintegration time and maximum drug release. *In vivo* pharmacokinetic activity in rats revealed that optimized S-SEDDS tablets (T3) had 2.14 folds higher bioavailability than marketed PZQ tablet and it produces rapid onset of action. The peak drug concentration (Cmax) of optimized S-SEDDS tablet T3 batch was approximately 1.76 fold higher than marketed tablet.
Keywords: Praziquantel, S-SEDDS, Pharmacokinetic Analysis, Distoside Tablet, Similarity Factor

INTRODUCTION:

Oral medicines are the usual method of treatment, because of their benefits, comfort in the administration of oral medicine, favored patients, economical efficacy and facility of large scale manufacture. Approximately 60% of currently available medicinal molecules are given via mouth. It is estimated nowadays that oral formulations account for about 90% of the worldwide market share of all human drug formulations. About 84% of best-selling medications, now worth 35 billion dollars, with an annual growth rate of 10%. Patients are often more likely than other parenteral methods to intravenous, subcutaneous, intramuscular and asthma injections. Oral wording is moreover; medicinal products given via oral procedure may cure pathological local illnesses such as colorectal abdomen, malignancies, infections, inflammation, bowel diseases, Gastroduodenum ulcers and reflux issues. [1-7]

Advantages of S-SEDDS:

- Spontaneous formation
- Ease of manufacture
- Thermodynamic stability and improved solubilization of bioactive materials
- More consistent temporal profiles of drug absorption
- Greater bioavailability
- Less drug needs to be used
- Faster release rates

MATERIALS AND METHODS

Materials: Praziquantel was kindly donated by Microlab Pvt. Ltd, Goa. All other chemicals used were of analytical grade.

Methods:

Formulation and development of solid self-emulsifying drug delivery system (S-SEDDS) tablets

The S-SEDDS tablets were prepared by using a direct compression method using several superdisintegrants including sodium starch glycolate, Crosscarmellose sodium and polyplasdone XL-10 at different dose as described in Table 1. S-SEDDS, povidone, microcrystalline cellulose, mannitol, magnesium stearate, doshion P-544 and aspartame, all accurately weighed prior to the combination and all the materials were screened by a 60 # screen. The final powder

was compressed into tablets by using a rotary tablet machine. The 3^2 factorial design was applied for the S-SEDDS tablet formulation of Praziquantel. [8,9]

Table 1. Formulation of 3^2 factorial design for Praziquantel S-SEDDS

Ingredients	T1	T2	T3	T4	T5	T6	T7	T8	T9
S-SEDDS	160	160	160	160	160	160	160	160	160
Sodium starch Glycolate	7.5	10	12.5	--	--	--	--	--	--
Crosscarmellose sodium	--	--	--	7.5	10	12.5	--	--	--
Polyplasdone XL-10	--	--	--	--	--	--	7.5	10	12.5
Povidone	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Microcrystalline cellulose	25	25	25	25	25	25	25	25	25
Mannitol	34	31.5	29	34	31.5	29	34	31.5	29
Magnesium Stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Doshion P-544	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Aspartame	1	1	1	1	1	1	1	1	1
Total (mg)	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**	**250**

Evaluation of tablets: [10, 11]

Hardness

The hardness of the tablet of each formulation was determined by using the Monsanto Hardness tester.

Thickness

The thickness was measured by using Digital Vernier calipers.

Friability

This test will assess capacity of tablets can withstand abrasion during packing, handling and transport. To determine friability by using the Roche friabilator, the following formula is employed,

$$\% \text{ Friability} = \frac{\text{Loss in weight}}{\text{Initial weight}} \times 100$$

Where, Loss in weight = weight of tablets before test - weight of tablets after test

Uniformity of weight

The average weight of the tablet was calculated from collective weight according to Indian Pharmacopoeia method.

Drug content

The accurate weight of powder was dissolved in 0.1 N HCl with 2 mg per ml of sodium lauryl sulphate, the solution was properly filtered and diluted. UV-visible spectrometer was used for analyzing drug content at 263 nm.

***In-vitro* drug release study**

The USP type-II device was used for the research of *in-vitro* drug releases. The dissolution test was performed by using 900 ml 0.1 N HCl with per ml of 2 mg sodium lauryl sulphate as the dissolution media at 37°C±0.5°C. 5 ml aliquots, at intervals of 2, 5, 10, 15, 20, 25 and 30 minutes, were withdrawn, filtered and replaced with 5 ml of fresh dissolution medium. The % drug release was measured by using a UV-Visible spectrometer at 263 nm.

Comparison of *In-vitro* dissolution study of a prepared tablet with marketed formulation

In-vitro dissolution research is used to compare a produced tablet with the marketed tablet formulation. (Distoside Tablet).

Similarity factor

The *in vitro* dissolution data of the optimized tablet formulation and marketed tablet formulation studies was compared by using similarity factor f_2. The optimized tablet formulation was considered as test formulation and Marketed formulation was considered as reference formulation. Dissolution profiles are considered as similar if f_2 value is found

in between 50-100. A Bioanalytical approach was created for the optimized Praziquantel S-SEDDS tablet to assess several Pharmacokinetic Parameters after ingestment of the optimized Praziquantel tablet (T3).

Experimental animals

In vivo study was conducted in accordance with the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA, Government of India) guidelines and approved by Institutional Animal Ethics Committee (IAEC),-Gourishankar Institute of Pharmaceutical Education and Research, Limb, Satara (Approval No. GIPER/IAEC/2020-21/02). In this experiment, male healthy white albino rats (weighing 150±20 grams) were used. The rats were bought from prestigious local retailers and are maintained in the Pharmaceutical Education and Research Institute of Gourishankar in Limb, Satara-415004. The cage was maintained at 25°C constantly. The venous blood samples (0.2 mL) were collected in a heparinized-coated micro-centrifuge tube with the retro orbital plexus of albino rats with a capacity of 2 mL. Different intervals of the samples were taken: 0, 0.15, 0.5, 1, 2, 4, 8, 12, 20, 24 hours following dosing. These samples were then centrifuged at 12000 rpm for 15 minutes and the plasma was extracted very carefully. Each heparinized tube containing sample preparation was administered 8.25% perchloric acid to precipitate plasma protein. The graph between time and the measured plasma concentration was produced after calculation of the pharmacokinetic parameters. The area under curve (AUC) was calculated by using the linear trapezoidal technique. Some pharmacokinetic parameters have been observed, such as concentration (Cmax), the time at which Cmax was observed (Tmax) etc. [12,13]

Preparation of rat plasma sample preparation

1. Praziquantel was isolated from plasma in the rat by using the liquid-liquid extraction method.
2. Upon oral administration of Praziquantel S-SEDDS tablet at 20 mg/kg dosing then blood samples were collected. Before administering the animals were kept fasted for overnight (~12 hr.). During fasting animals had free access to water.
3. Blood samples (0.2 mL) were collected and placed in heparin covered perchloric acid tube for plasma protein precipitation. Samples of retro orbital plexus 0, 0.15, 0.5, 1, 2, 4, 8, 12, 20 and 24 hours were taken and vortexed at 12000 rpm for 15 minutes by centrifugation. After samples were collected.
4. Simultaneously in 1.5 ml of centrifugal tubes with diazepam and a blank (200 µl of plasma without Praziquantel and Diazepam), at a fixed concentration.
5. These samples then transferred into auto sampler vials for injection.
7. For the calculation of r^2 and the linear regression equation, this data was used.

RESULTS AND DISCUSSION

Evaluation of S-SEDDS tablets

In the below Table 2 shows the assessment criteria for T1 to T9 batches. The hardness of tablets was ranged from 3.53±0.57 kg/cm^2 to 3.83±152 kg/cm^2. These are all tablets have very good mechanical strength. These tablets have a thickness of 2.60±0.152 mm to 3.13±0.208 mm. The friability of all formulations was found to be less than 1.0 % and was in the range of 0.13 ±0.026% to 0.67± 0.225 % indicating a good mechanical resistance of tablets. The uniformity of weight was found to be in the range of 249.00±1.000 mg to 251.33±1.527 mg. The % drug content of tablets was found to be between 95.53±0.894% to 99.71±0.098%. All these characteristics were verified acceptable and compliance with the Praziquantel tablet criteria. The disintegration time for batch T3 was found to be 10 sec. Compared to previous batches; this tablet has the quickest disintegration time. *In vitro* drug release results for T1 to T9 batches are shown in figures 1 (a) and 18 (b). While all batches to produce 56.79% to 73.78% of drug release after 5 minutes and 73.78% drug release of T3 batch in 5 minutes at a higher rate than the other batches. Therefore, the batch T3 was regarded as the optimized batch and used for further research.

Table 2. Evaluation parameters for Praziquantel S-SEDDS tablets

Formulation code	Hardness (kg/cm2)	Thickness (mm)	Uniformity of Weight (mg)	Friability (%)	Disintegration time (sec.)	Drug Content (%)*
T1	3.56±0.057	2.83±0.057	251.00±1.000	0.33±0.040	15.66±1.527	98.89±0.375
T2	3.66±0.115	3.13±0.208	249.33±0.577	0.20±0.035	12.33±0.577	99.34±0.110
T3	**3.53±0.057**	**2.90±0.100**	**250.00±1.000**	**0.13±0.026**	**10.00±1.000**	**99.71±0.098**
T4	3.80±0.100	2.60±0.152	251.33±1.527	0.39±0.057	38.33±1.527	97.48±0.490
T5	3.60±0.100	2.93±0.152	249.00±1.000	0.36±0.124	29.33±0.152	97.84±0.444
T6	3.76±0.152	2.86±0.115	250.00.±1.732	0.28±0.020	25.00±1.000	98.65±0.502
T7	3.73±0.152	2.76±0.057	250.66±1.527	0.67±0.225	42.00±1.00	95.53±0.894
T8	3.70±0.173	2.73±0.057	250.33±1.527	0.49±0.155	31.66±1.154	97.06±0.456
T9	3.83±0.152	2.66±0.115	249.66±1.732	0.42±0.217	26.33±1.527	97.33±1.176

Data expressed as mean ± SD (n = 3)

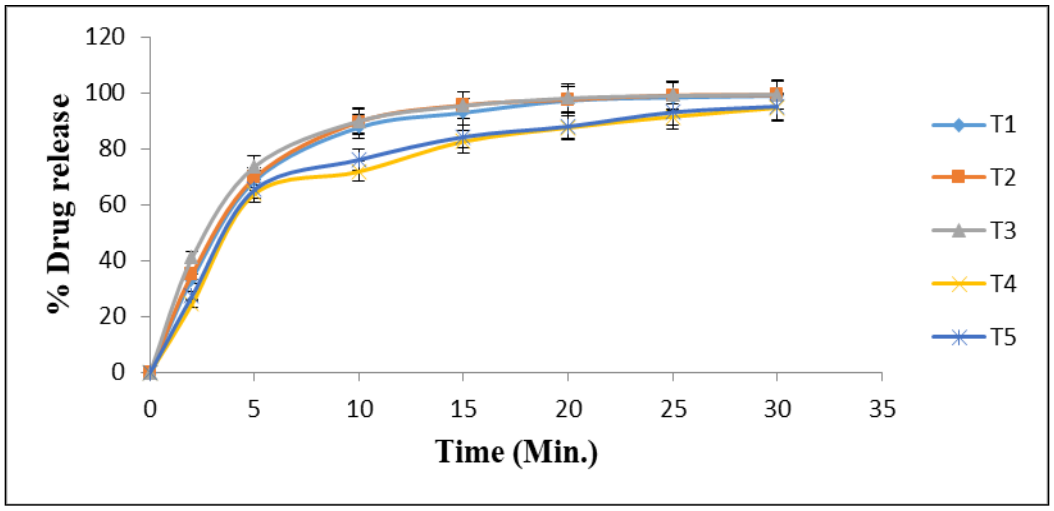

Figure 1 (a). *In-vitro* drug release profile of formulations T1 to T5

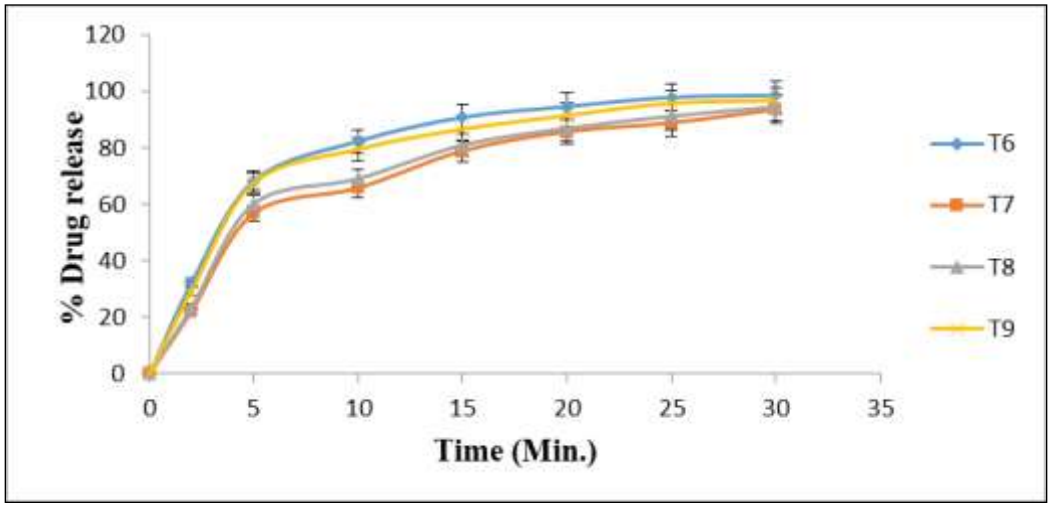

Figure 1(b). *In-vitro* drug release profile of formulations T6 to T9

Comparison of *In-Vitro* dissolution study of optimized batch T3 with marketed formulation (Distoside Tablet)
In-vitro drug release of optimized T3 batch was compared to the marketed tablet, i.e. (M). In 15 minutes, batch T3 shows 95.54% of drug release in 0.1 N HCl containing 2% SLS, whereas marketed formulation shows 53.86% of drug releases by 15 minutes as shown in figure 2. These results clearly demonstrate the solubility enhances and dissolution was increased of S-SEDDS Praziquantel tablet.

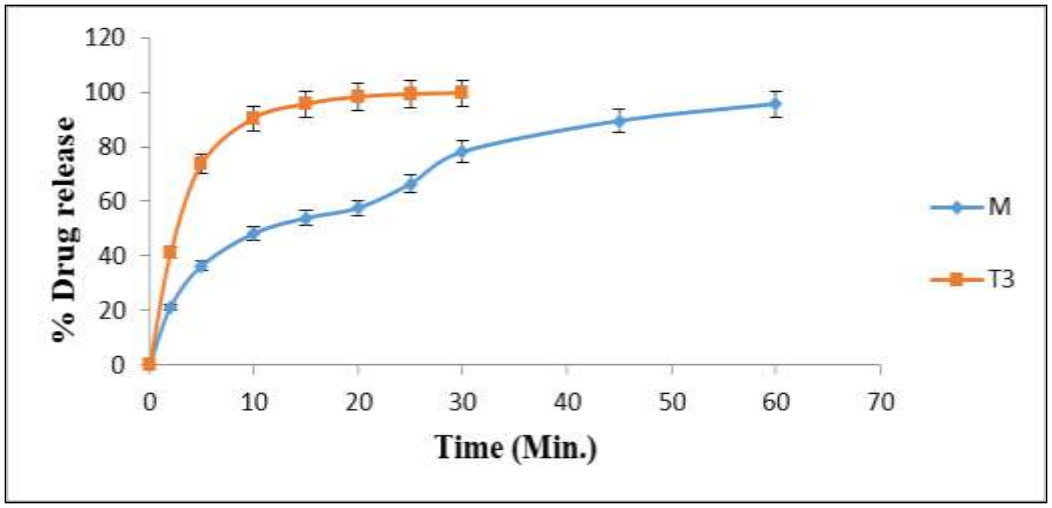

Figure 2. *In-vitro* drug release comparison of T3 & marketed sample (M)

Similarity Factor

Similarity factor was obtained after comparison of dissolution profile of optimized formulation T3 and marketed formulation. Comparison of drug release profile of test (T3 Optimized formulation) and reference (Marketed formulation) as shown in figure 2.

Similarity Factor *f*2:- 54.45.

The value of *f*2 value was found to be between 50 to 100. Hence, it indicated similarity between the dissolution profiles of reference and test products.

Extraction of Praziquantel with different concentrations as shown in below tables

Table 3. % Recovery with Methanol at 100 ng/mL

Concentration (ng/mL)	AUC	Conc. Found	Recovery %
100	71.45	85.61759777	85.6175978
100	70.65	84.81759777	84.8175978
100	69.12	83.28759777	83.2875978

Table 4. % Recovery with Methanol at 500 ng/mL

Concentration (ng/mL)	AUC	Conc. Found	Recovery %
500	385.67	399.8375978	79.9675196
500	387.6	401.7675978	80.3535196
500	379.03	393.1975978	78.6395196

Table 5 % Recovery with Methanol at 1000 ng/mL

Concentration (ng/mL)	AUC	Conc. Found	Recovery %
1000	846.11	860.2775978	86.0277598
1000	833.26	847.4275978	84.7427598
1000	821.76	835.9275978	83.5927598

Table 6. % Recovery with Acetonitrile:Methanol at 100ng/mL (60:40 v/v)

Concentration (ng/mL)	AUC	Conc. Found	Recovery %
100	73.87	88.03759777	88.0375978
100	72.35	86.51759777	86.5175978
100	71.89	86.05759777	86.0575978

Table 7. % Recovery with Acetonitrile:Methanol at 500ng/mL (60:40 v/v)

Concentration (ng/mL)	AUC	Conc. Found	Recovery %
500	396.23	410.3975978	82.0795196
500	384.11	398.2775978	79.6555196
500	396.46	410.6275978	82.1255196

Table 8. % Recovery with Acetonitrile:Methanol at 1000 ng/mL (60:40 v/v)

Concentration (ng/mL)	AUC	Conc. Found	Recovery %
1000	856.11	870.2775978	87.0277598
1000	864.24	878.4075978	87.8407598
1000	846.32	860.4875978	86.0487598

Table 9. % Recovery with Acetonitrile:Methanol:Water at 100ng/mL (50:10:40 v/v)

Concentration (ng/mL)	AUC	Conc. Found	Recovery %
100	76.56	90.72759777	90.7275978
100	77.11	91.27759777	91.2775978
100	76.89	91.05759777	91.0575978

Table 10. % Recovery with Acetonitrile:Methanol:Water at 500 ng/mL (50:10:40 v/v)

Concentration (ng/mL)	AUC	Conc. Found	Recovery %
500	438.11	452.2775978	90.4555196
500	437.09	451.2575978	90.2515196
500	436.77	450.9375978	90.1875196

Table 11. % Recovery with Acetonitrile:Methanol:Water at 1000 ng/mL (50:10:40 v/v)

Concentration (ng/mL)	AUC	Conc. Found	Recovery %
1000	899.21	913.3775978	91.3377598
1000	897.56	911.7275978	91.1727598
1000	890.17	904.3375978	90.4337598

Using chromatographic analysis by using 0.45 µm membrane filter paper, the mobile phases of Acetonitrile-Methanol-Water (50:10:40 v/v) have been filtered. The flow rates were at 1.0 ml/min for mobile phases and at 217 nm eluent detected. Inject 2 mL volume with a 10 minute running time.

Pharmacokinetic data analysis

Plasma concentration *vs.* time data of Praziquantel was analyzed by Pk solver version 2.0 to derive various pharmacokinetic parameters, *viz.*, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, C_{max}, t_{max} and $t½$ as shown in table 11,12 &13 and figure 3.

Table 12. Summary Table- Input Variable

Time In Hr	Time in Minutes	Plasma Drug Conc. Mcg/ml	Log Plasma Drug Conc. Mcg/ml
0	**0**	**0**	**0**
0.15	15	81.23	1.909716453
0.5	30	156.34	2.194070108
1	60	354.21	2.549260818
2	120	591.24	2.771763808
4	240	432.27	2.635755096
8	480	341.1	2.532881719
12	720	234.98	2.371030899
20	1200	115.23	2.061565562
24	1440	88.14	1.945173046

Table 13. Summary Table- Output

Time	Conc.	ln(C)	AUC	AUMC
0	0	0	0	0
0.15	81.23	4.39728464	6.09225	0.9138375
0.5	156.34	5.05203312	47.667	16.725875
1	354.21	5.86988996	175.3045	124.820875
2	591.24	6.38222203	648.0295	893.165875
4	432.27	6.06905039	1671.5395	3804.72588
8	341.1	5.83217569	3218.2795	12720.4859
12	234.98	5.4595004	4370.4395	23817.6059
20	115.23	4.74693013	5771.2795	44315.0459
24	88.14	4.47892646	6178.0195	53154.9659

Table 14. Pharmacokinetic Calculation Results

Parameter	Marketed Formulation	T3 Formulation
AUC (h ng/ml)	6177.90±1.73	13261.84±1.50
$t^{1/2}$ (h)	1.05 ±0.33	1.30±0.21
Cmax (ng/ml)	147.92±2.08	260.66±1.14
Tmax (h)	2.00±0.50	1.20±0.20
MRT (h)	11.74±1.13	13.47±0.55
Cl (ml h^{-1} g^{-1})	0.028±0.002	0.055±0.001

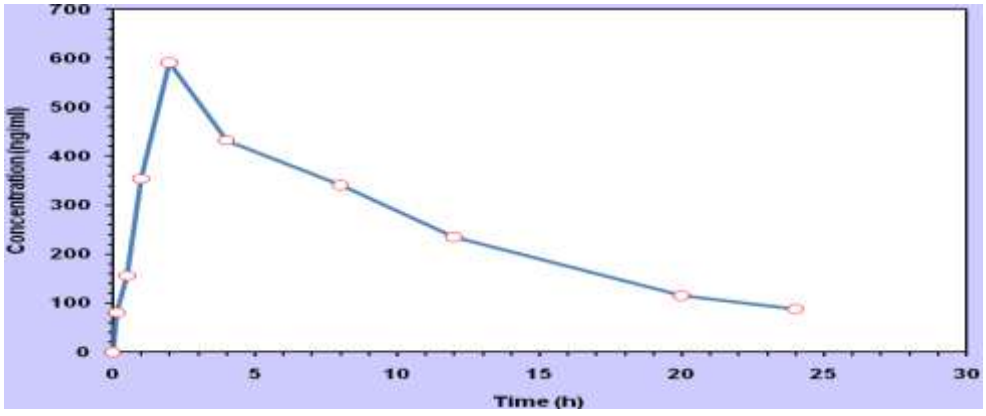

Figure 3. Time in (hr) Vs Concentration (µg/ml)

CONCLUSION

In this article, Pharmacokinetic profile of the optimized S-SEDDS tablet was studied in comparison with marketed tablet. The AUC for optimized S-SEDDS tablet T3 batch was found to be 13261.84±1.50 ng.h/ml and 6177.90±1.73 ng.h/ml for marketed tablet respectively. The peak drug concentration (Cmax) of optimized S-SEDDS tablet T3 batch was higher than marketed tablet. *In vivo* pharmacokinetic investigation in rats, demonstrated significantly higher AUC by the developed optimized S-SEDDS tablet. The value of *f*2 value was found to be between 50 to 100. Hence, it

indicated similarity between the dissolution profiles of reference and test products. Thus, it can be concluded that S-SEDDS would be a promising dosage form in the prevention of worm infections for pediatric patients.

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