DRUG DISCOVERY

Development and Characterization of Tolvaptan HCl Fast Dissolving Tablets

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ABSTRACT

Objective: The purpose of present investigation to formulate, characterize the oral dissolving tablets (ODT) for Tolvaptan HCl. Tolvaptan HCl, a newer aquaretic sorvaptan. It mainly used for the effective management of Hyponatremia associated with Syndrome of inappropriate anti diuretic hormone (SIDAH), cardiac cirrhosis and congestive cardiac failure. *Methods:* ODT formulations of Tolvaptan HCl were prepared using different quantities of Ac-di-sol & Polyplasdone employed as Super-disintegrants by Direct Compression technique. Nine trials were formulated and evaluated for Pharmaceutical Product Performance. *Results:* Results shows that all the formulations were lie within the acceptance criterion and the *In-vitro* dissolution profiles were subjected to kinetic modeling. *Conclusion:* Formulation (TF_1) containing 50 mg of Ac-di-sol & 50 mg of Polyplasdone was found to be best one among all and also similar to the Marketed product (HYPONAT-O-30) (f2= 70.613, f1= 4.038 & No significant difference, t= 0.04738) to marketed product. Formulation (TF_1) follow first order, whereas release mechanism found to be nonfickian type (n= 0.863).

Keywords: Tolvaptan HCl, super-disintegrants, Polyplasdone, Ac-di-sol, Non-Fickian Diffusion.

1. INTRODUCTION

Oro Dispersible Tablets (ODT) occupy special role in pharmaceutical market. Oral dissolving tablets, melt-in mouth tablets were used frequently in the place of ODT (RK gunda et al., 2018).

Rapid disintegrating tablets can be readily avialble for disintegration, they breakdown in the mouth region within 60 seconds. Based on the method of manufacturing they exhibits variations in characteristic organoleptic properties such as sweetness/ taste masking and improved palatability. They also exhibit modulations in quality control; parameters such as breaking index, delivery of drug from formulation, stability, Clinical outcome. Many methods available for the preparation of ODTs , popular methods include cottoncandy process, granulation techniques, named technologies (Durasolv, Orosolv), spray drying, trituration, molding, lyophilization/ freeze drying, mass extrusion (Raghavendra G et al.,2016).

Tolvaptan HCl is a selective, competitive receptor blocker for vasopressin V_2 (antagonist) located in renal tubule. It mainly useful for treating hypervolemic, euvolemic hyponatremia and also associated with cardiac cirrhosis, Syndrome of inappropriate anti diuretic hormone (SIDAH) and congestive cardiac failure. It is available as uncoated tablets in the market with various strengths like 15 mg, 30 mg (Ramesh K et al., 2015; Sree Giri Prasad et al., 2015).

An attempt was made to achieve enhanced drug release from the dosage form by employing various concentrations of combination super disintegrants (Ac-di-sol, Polyplasdone) by formulating the Fast dissolving tablets for Tolvaptan HCl. Among various methods of manufacture techniques available, Tablets by Direct Compression techniques has unique nature in the form of less time consumption, rapid production, economy in the operational management (Gunda et al., 2016).

2. MATERIALS AND METHODS

2.1. Materials

Tolvaptan HCl was a gift sample procured from Konis Pharma Limited, Baddi, India. Lactose,Avicel, Polyplasdone, Ac-di-sol were procured from Aman Scientifics, Hyderabad. Other excipients were procured from LobaChemie Ltd, Mumbai.

2.2. *Preparation of Tolvaptan HCl Fast Dissolving Tablets*

Tolvaptan HCl ODT were manufactured as per direct compression method. The formulae presented as Table 1. To obtain the uniform mixed fine blend, all the contents were subjected to sifting using 40 mesh (#40). Lubricants were screened through #80, mix them with above mixture and compressed to get ODT with the help of Tablet minipress (8 stations) using 8 mm circular punches. Obtained tablets were subjected to IPQC tests. Final tablets were transferred to airtight, light resistance containers for storage and further processing (Jujjuru et al., 2017).

Table 1: Formulae for the Preparation of Tolvaptan Oral dispersible tablets

Ingredients	Quantity of Ingredients/ Tablet								
	TF_1	TF_2	TF_3	TF_4	TF_5	TF_6	TF_7	TF_8	TF_9
Tolvaptan. HCl	30	30	30	30	30	30	30	30	30
Lactose-DC	34	39	44	39	44	49	44	49	54
Avicel pH 101	34	39	44	39	44	49	44	49	54
Polyplasdone	50	50	50	40	40	40	30	30	30
Ac-di-sol	50	40	30	50	40	30	50	40	30
Magnesium stearate	2	2	2	2	2	2	2	2	2
Total Weight	200	200	200	200	200	200	200	200	200

2.3. Evaluation of Tolvaptan HCl fast dissolving tablets

2.3.1. Hardness

It was carried out with the help of Monsanto Tablet Hardness Tester (Raghavendra Kumar Gunda et al., 2020).

2.3.2. Friability/ Durability

Twenty tablets were weighed (cumulatively) recorded as W_0 (Initial weight). Then the tablets were subjected to dedusting using Roche Friabilator for 4 min with a rotation rate of 25 rpm and weight was noted as Final weight (W). Percentage friability was determined from following equation (%Friability ≤1).

$$\text{Friability (\%)} = (W_0 - W) / W_0 \times 100$$

2.3.3. Assay

20 tablets were selected on the unbiased manner and pulverized. The powder equivalent to 100 mg Tolvaptan HCl was weighed and transferred to 100 mL volumetric flask containing 60 mL of methanol and sonicated for 10 min to solubilise the drug completely then dilute the methanolic solution with water to make up the final volume. From that prepare further dilution of 2 mL aliquot in 100 mL of 0.1 N HCl. The obtained solution was filtered through Whatman filter paper and absorbance of solution as measured at 268 nm with the help of UV-Visible spectrophotometer.

2.3.4. Thickness

Thickness was determined with the help vernier calipers (Manchineni PR et al., 2020).

2.3.5. Wetting time

Tablets to be tested for Determination of wetting time were placed on a petridish containing paper soaked in 5mL of distilled water (2.5inch internal diameter). Time taken by the tablet to wet was recorded in seconds.

2.3.6. *In-vitro* Dissolution Study

Tolvaptan HCl oral disintegrating tablets subjected to dissolution test with the help of USP XXIII type-II tablet dissolution test apparatus using 900 ml of pH 1.2 buffer as per official method specified in monograph. Absorbance for samples was noted at 268 nm using UV Visible spectrophotometer (after suitable dilutions if necessary).

2.3.7. Kinetic modeling of drug release

The dissolution profile of all the formulations was subjected to kinetic modeling (Higuchi et al., 1963; Peppas NA et al., 1985).

2.3.8. Disintegration test

This test was performed as per the provisions of modified disintegration test for tablets. A cylindrical vessel with 10 # was placed in such way that only 2 ml of medium would be placed below the sieve. Disintegration time was recorded (Raghavendra Kumar Gunda et al., 2016).

3. RESULTS AND DISCUSSION

9 Tolvaptan HCl fast dissolving tablets formulations were prepared by direct compression method using various proportions of super-disintegrants combination as per the formulae presented in Table 1. Developed formulations were evaluated for pharmaceutical product performance tests. Data was presented in Table 2.

All tablets found to have good mechanical strength and less friable. The prepared tablets were within the standard limits for uniformity of weight as well as drug content uniformity.

Table 2: Post-Compression Parameters

Formulation	Hardness (Kg/Cm^2)	Thickness (mm)	Friability (%)	Average Weight (mg)	Drug Content (%)	Wetting Time (Sec)	Disintegration Time (Sec)
TF_1	4.1±0.3	3.2±0.01	0.53±0.07	199.32±0.54	98.29±1.61	23.12±2.03	27.35±1.67
TF_2	3.9±0.1	3.2±0.01	0.6±0.04	199.48±0.59	98.8±2.4	24.52±2.62	29.78±2.25
TF_3	4.1±0.3	3.2±0.01	0.7±0.03	198.71±0.54	98.4±1.46	26.5±2.20	31.69±2.30
TF_4	4.2±0.2	3.2±0.02	0.6±0.02	200.10±1.1	99.47±1.13	25.4±1.18	29.57±1.45
TF_5	3.9±0.2	3.1±0.02	0.55±0.03	200.21±0.54	99.42±2.81	26.24±1.67	30.82±2.03
TF_6	4.1±0.3	3.3±0.01	0.64±0.01	199.71±0.98	99.84±1.97	28.66±1.35	33.83±1.18
TF_7	4.2±0.3	3.2±0.02	0.61±0.04	200.48±0.67	99.2±1.59	27.2±2.80	31.89±1.1
TF_8	4.0±0.4	3.2±0.01	0.57±0.03	200.38±0.51	99.27±2.83	28.5±2.4	33.55±1.48
TF_9	4.2±0.3	3.3±0.02	0.62±0.4	200.62±0.45	99.49±2.81	30.82±1.18	35.57±1.43

Table 3: Statistical Parameters

Formulation Code	Statistical Parameters											
	Zero order			First order			Higuchi			Korsmeyer-peppas		
	a	b	r	a	b	r	a	b	r	a	b	r
TF_1	31.460	1.182	0.847	1.872	0.016	0.974	13.073	11.063	0.962	0.566	0.863	0.843
TF_2	28.591	1.202	0.871	1.892	0.015	0.979	10.650	11.072	0.974	0.529	0.878	0.855
TF_3	28.683	1.201	0.869	1.890	0.015	0.979	10.699	11.073	0.974	0.530	0.878	0.852
TF_4	25.815	1.221	0.892	1.910	0.015	0.984	8.275	11.082	0.984	0.488	0.896	0.865
TF_5	30.006	1.149	0.848	1.859	0.013	0.970	12.091	10.761	0.965	0.548	0.865	0.847
TF_6	26.778	1.091	0.861	1.874	0.011	0.964	10.148	10.132	0.971	0.531	0.854	0.851
TF_7	24.069	1.111	0.885	1.895	0.011	0.974	7.872	10.143	0.981	0.490	0.872	0.862
TF_8	24.089	1.114	0.883	1.894	0.011	0.972	7.791	10.183	0.981	0.486	0.875	0.860
TF_9	21.379	1.134	0.905	1.914	0.011	0.980	5.514	10.194	0.989	0.440	0.896	0.871
HypoNat-O-30	26.148	1.381	0.888	1.925	0.020	0.993	6.237	12.554	0.981	0.404	0.978	0.866

Table 4: Dissolution/ Kinetic Parameters

Formulation Code	Dissolution Parameters				
	$t_{10\%}$ (Min)	$t_{25\%}$ (Min)	$t_{50\%}$ (Min)	$t_{75\%}$ (Min)	$t_{90\%}$ (Min)
TF_1	2.857	7.801	18.798	37.596	62.466
TF_2	2.982	8.142	19.62	39.24	65.197
TF_3	2.997	8.182	19.717	39.433	65.518
TF_4	3.113	8.498	20.478	40.957	68.049
TF_5	3.423	9.345	22.519	45.038	74.831
TF_6	4.156	11.346	27.34	54.681	90.852
TF_7	4.201	11.469	27.636	55.273	91.836
TF_8	4.204	11.477	27.656	55.311	91.9
TF_9	4.248	11.598	27.948	55.896	92.871
Hyponat-O	2.416	6.597	15.897	31.794	52.826

Wetting time for all the formulations varied from 23.12±2.03 to 30.82±1.18 sec. The Disintegration Time of tablets was in the range of 27.35±1.67 to 35.57±1.43 sec and the same was represented as Fig. 1-2.

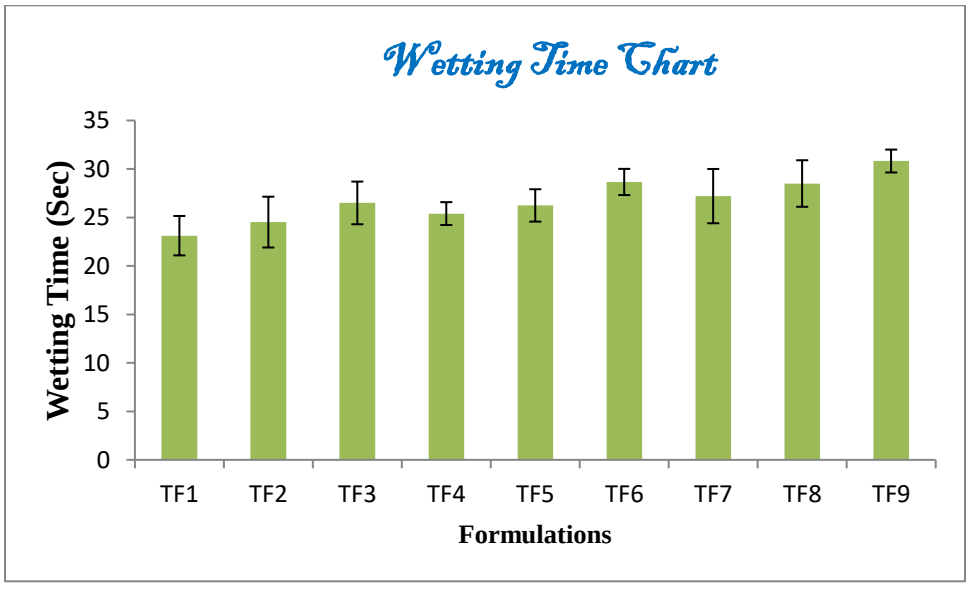

Fig.1 Wetting Time Chart

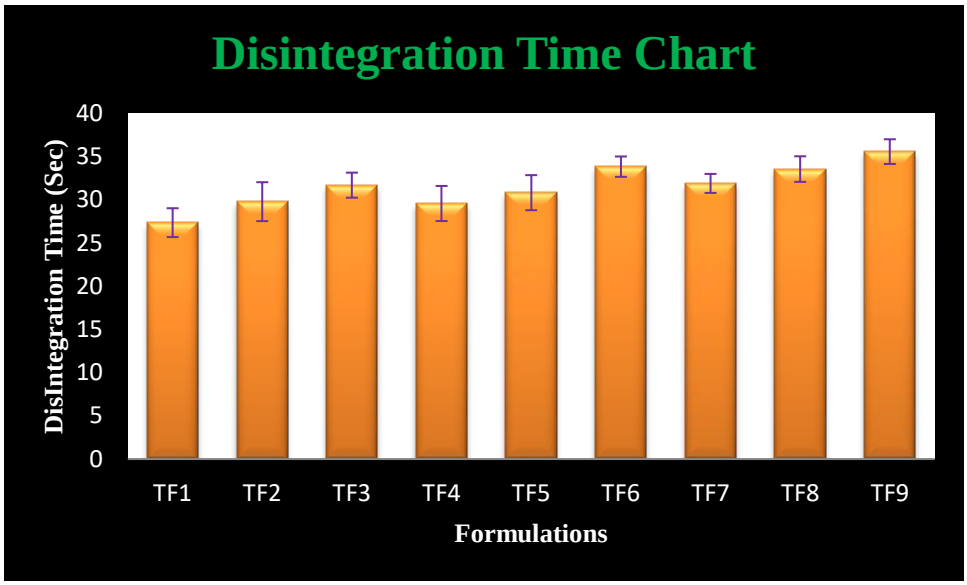

Fig.2 Disintegration Time Chart

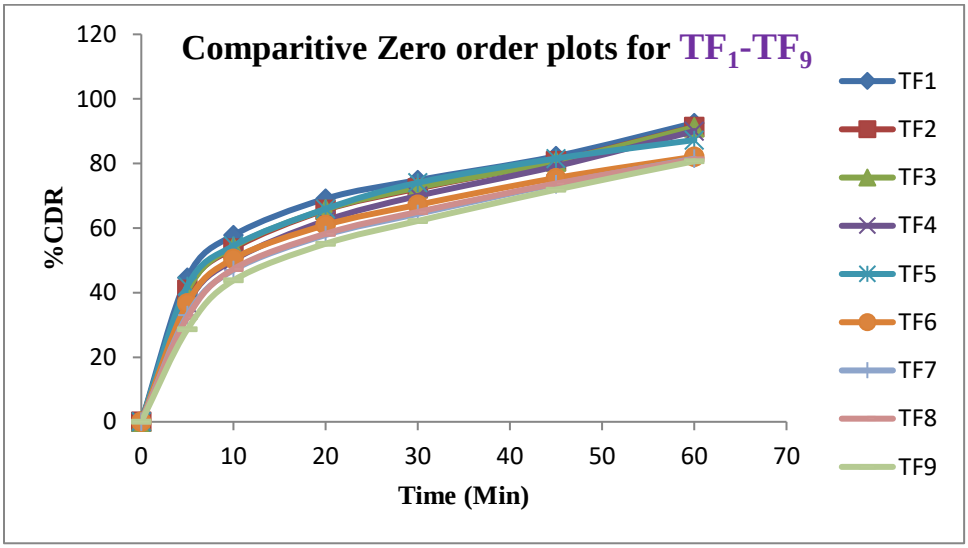

Fig.3 Comparative Zero order plots

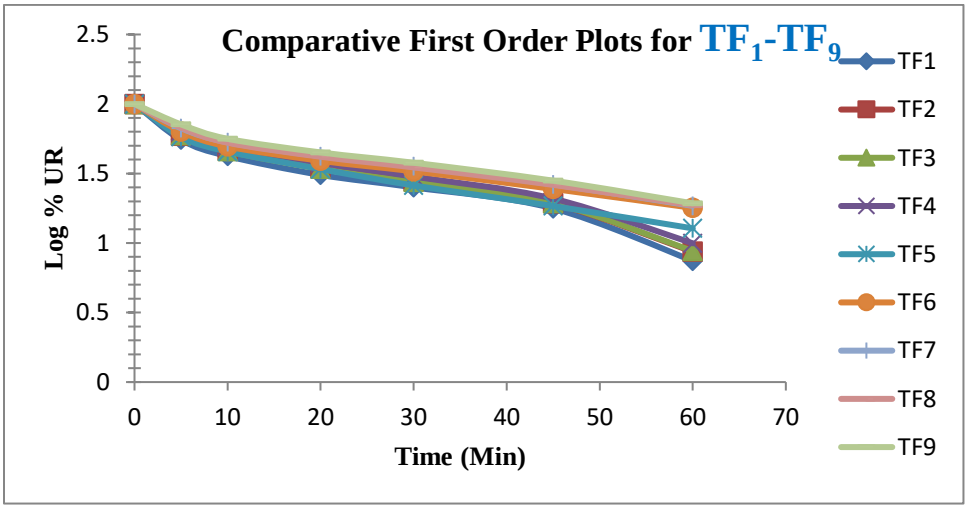

Fig.4 Comparative First order plots

Dissolution profiles of Tolvaptan HCl fast dissolving tablets were well fit to kinetic modeling, results presented in Table 3 and the same was shown in Fig. 3-6.

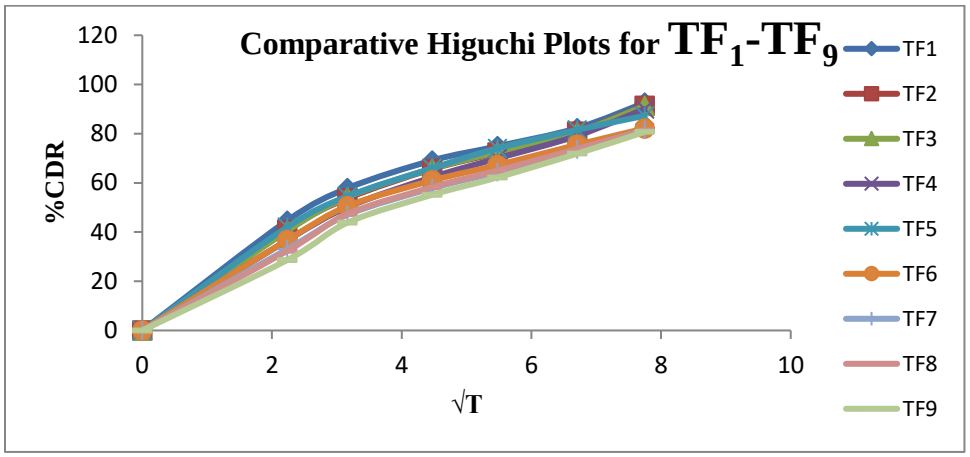

Fig.5 Comparative Higuchi plots

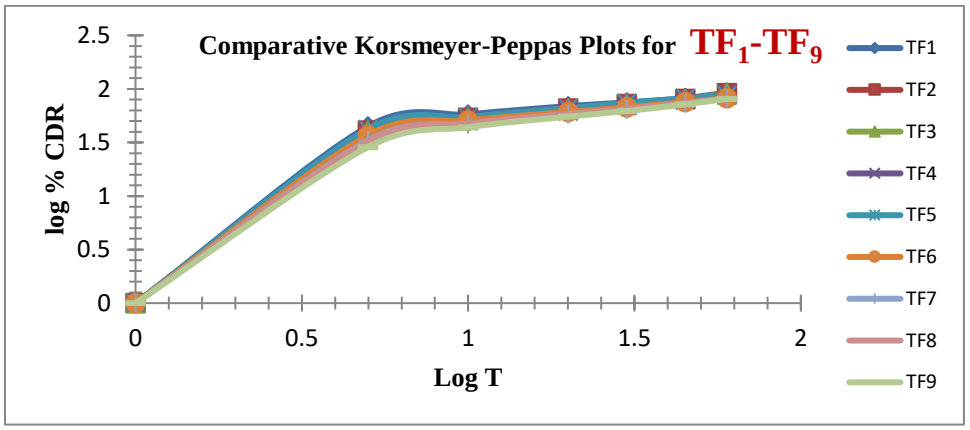

Fig.6 Comparative Korsmeyer-Peppas plots

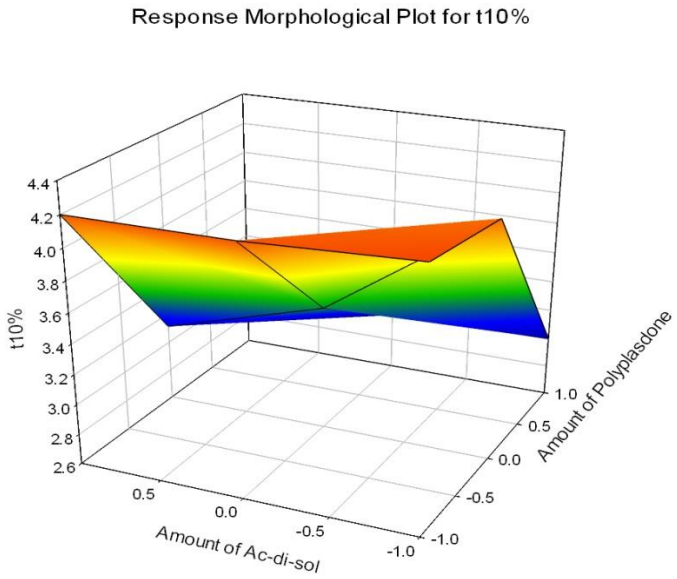

Fig.7 Response Morphological Plot For $t_{10\%}$

Based on the desirability, TF_1 is considered as best formulation among all batches. TF_1 composed of both Ac-di-sol and polyplasdone in equal quantity i.e 50 mg each, produced promising dissolution characteristics, which helps in meeting the purpose of research by faster disintegration& rapid dissolution (optimum delivery of drug from dosageform). Data for derived kinetic parameters were summarized in Table 4.

The effect of combination super-disintegrants on the wetting time, release profile were studied with the help of Response surface methodology using Sigmaplot software. RSM plots were shown as Fig. 7-11. TF_1 is compared with Marketed product (HYPONAT-O-30) tablets, shows similarity f2= 70.613; f1= 4.038 and the same was presented as Fig. 12.

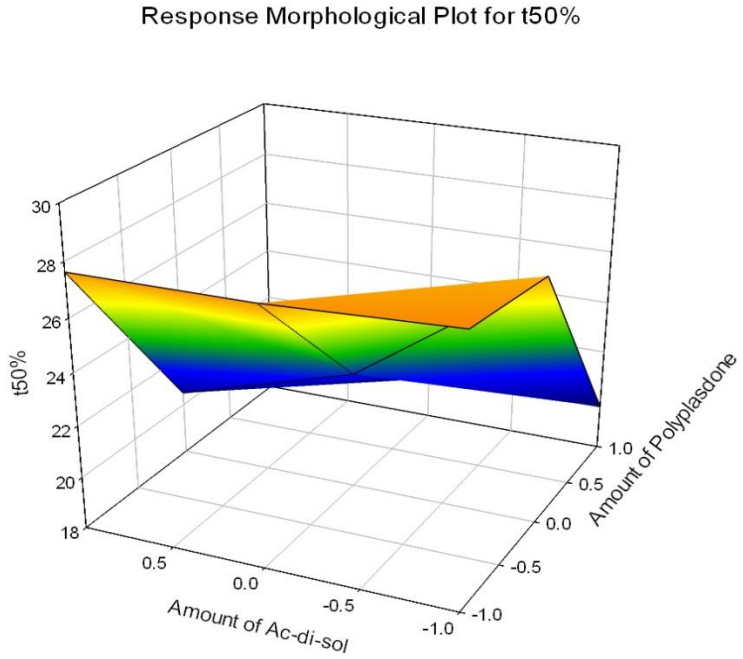

Fig.8 Response Morphological Plot For $t_{50\%}$

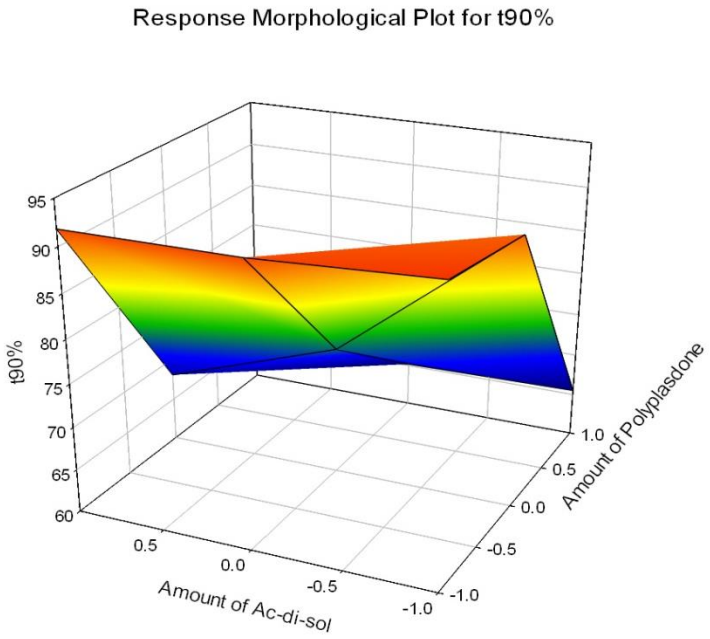

Fig.9 Response Morphological Plot For $t_{90\%}$

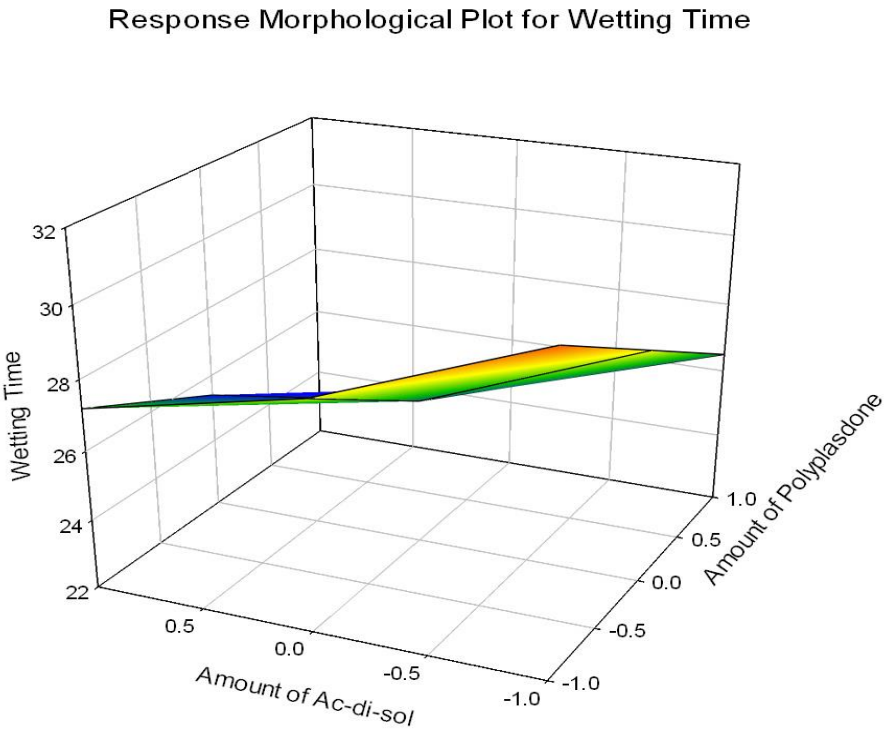

Fig.10 Response Morphological Plot for Wetting Time

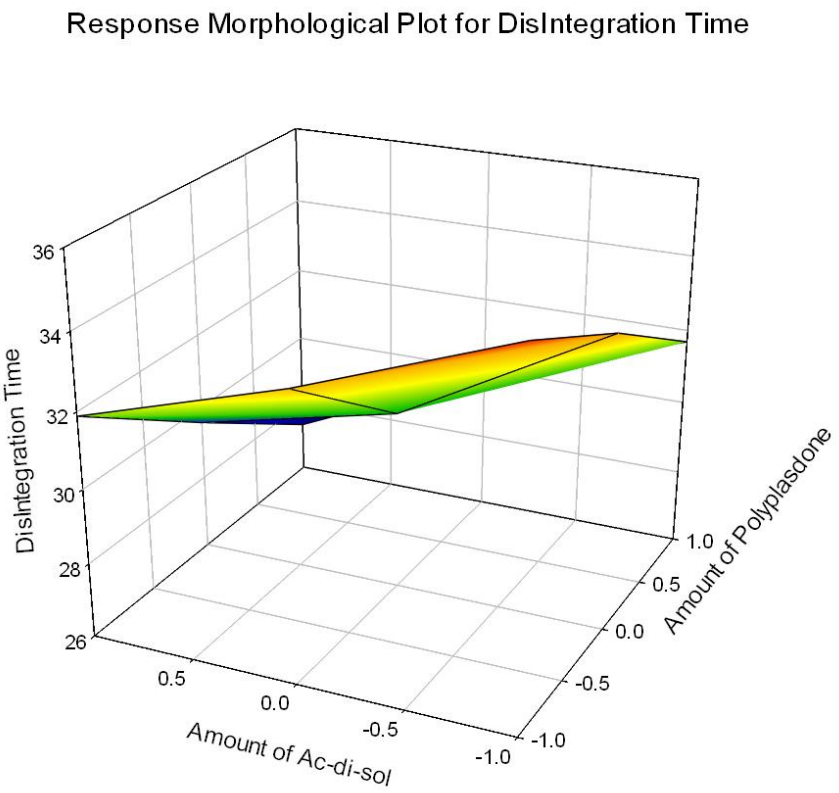

Fig.11 Response Morphological Plot for DisIntegration Time

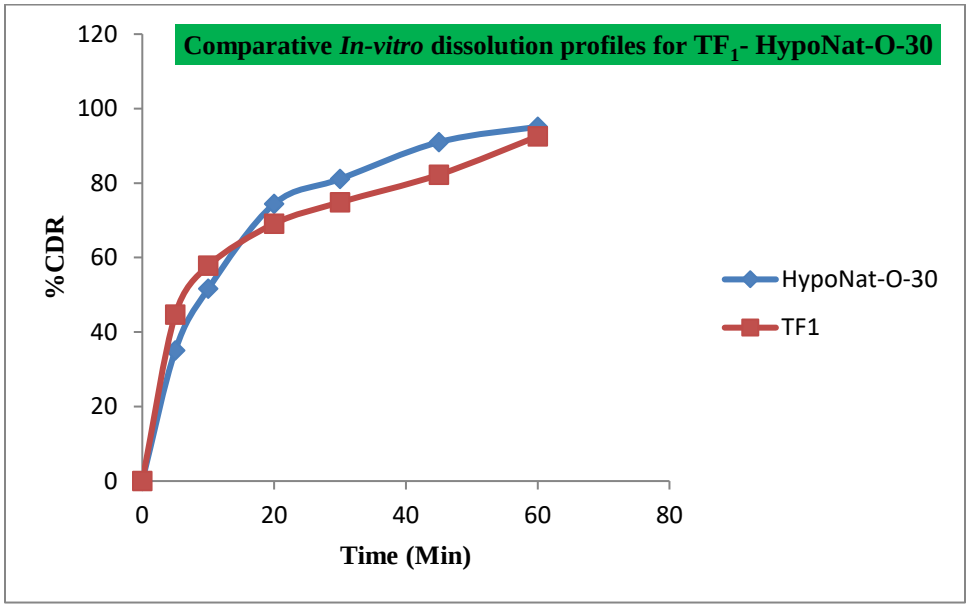

Fig.12 Comparative *In-vitro* Dissolution Profiles for TF_1, HypoNat-O-30

3. CONCLUSION

The current research investigation focuses about influence of utilization of super-disinterants such as Polyplasdone and ac-di-sol for the development of Tolvaptan ODT. TF_1 follows first order type of kinetics, higuchi type model where ad the mechanism of drug release follows nonfickian. On the basis of evaluation parameters, the optimized formulation TF_1 may be used for the effective management of hypervolemic, euvolemic Hyponatremia. This may improve the patient compliance and therapeutic outcome in case of hyponatremia associated with Cardiac cirrhosis, Congestive cardiac failure and SIDAH.

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Abbreviations

ODT	-	Oral Disintegrating Tablet
RSM	-	Response Surface Morphology
PEG	-	Poly Ethylene Glycol
IPQC	-	In-Process Quality Control
% CDR	-	Percentage Cumulative Drug Release
RPM	-	Revolutions per minute
BCS	-	Biopharmaceutical Classification
UR	-	Un Released
Min	-	Minute
°C	-	Degree Centigrade
$t_{10\%}$	-	Time taken to release 10% drug from dosage form
$t_{50\%}$	-	Time taken to release 50% drug from dosage form
$t_{90\%}$	-	Time taken to release 90% drug from dosage form
WT	-	Wetting time
DT	-	Disintegration time dissimilarity factor
f_1	-	Dissimilarity factor
f_2	-	Similarity factor

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The authors declare that there are no conflicts of interests.

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