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Design, Evaluation Optimization Of Oro Dispersible Film Of Valsartan Using Response Surface Method: In Vitro Characterization

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ABSTRACT

The present work aimed at preparing quick release films of Valsartan with the purpose of developing a dosage form for a very quick onset of action, which is beneficial in managing of hypertension, aiding in the enhancement of bioavailability, and is very convenient for administration, without the problem of swallowing and using water.Valsartan Oro dispersible films prepared by using solvent casting technique by using different film forming polymers.All prepared films were evaluated for its weight variation, disintegrationtime, thickness, drug content, pH, dissolution study, and folding endurance. The drug-excipients compatibility study was done using differential scanning calorimetry (DSC) and Fourier transform infrared (FTIR). DSC and FTIR showed no interaction between the Drug and polymers. Formulation F3 is considered as the optimized formulation as it showed good folding endurance (>300), faster disintegration rate (32 s), and maximum in vitro drug release (98.36%) within 30 min. Fast oro dispersible films of valsartan can be considered suitable for clinical use in the treatment of hypertension, where a quicker onset of action for a dosage form is desirable along with the convenience of administration.

Keywords: Valsartan, Oro dispersible films, Solvent casting technique, film forming polymers, In vitro drug release studies

1.INTRODUCTION

Fast dissolving drug delivery is rapidly gaining interest in the field of formulation technology. These systems either dissolve or disintegrate within a minute, on contact little quantity of water or by chewing. This delivery system consists of a thin film, which is simply placed on the patient's tongue or mucosal tissue, instantly wet by saliva; the film rapidly dissolves. Then it rapidly disintegrates and dissolves to release the medication for oral mucosal absorption. [1,2]Orally disintegrating films (ODFs), when placed on tongue, immediately hydrates by soaking saliva following disintegration and/or dissolution releasing active pharmaceutical agent from the dosage form. ODFs are kind of formulations which are commonly prepared using hydrophilic polymers enabling rapid dissolution upon contact with saliva. Oral disintegrating

tablets (ODTs) and oral disintegrating films (ODFs) are the typical examples of orally disintegrating drug delivery systems.[3]Valsartan is an angiotensin II receptor antagonist used in the management of hypertension[4]. It improves symptoms and quality of life in patients with chronic heart failure.Valsartan is rapidly absorbed following oral administration.Valsartan (VAL), an antihypertensive and being a BCS Class II moiety, it is soluble only in alcohols. Pharmacologically VAL is an angiotensin II receptor antagonist with has high affinity towards the type I (AT1) angiotensin receptor[5]. Hence, it requires rapid absorption and high bioavailability in patient point of view. VAL is absorbed over 4 hours, and its bioavailability is only about 20 to 25%. Fed conditions delay the absorption of VAL[6]. The main objective of the study was to formulate and evaluate oro dispersible film containing valsartan usingfilm-forming polymers by solvent casting method it is used in the treatment of hypertention.

2.MATERIALS AND METHODS

Valsartan was collected as a gift sample from Hetero labs, Hyderabad and various excipients likepolymers and other excipients were purchased from Synpharma Research Labs, Hyderabad.

2.2 METHODOLOGY

Drug-Excipient Compatibility Study by FTIR[7]

In the formulation of ValsartanOro dispersible film formation, API and Excipient may interact as they are in close communication with each other, which could lead to the instability of drug. FT-IR spectroscopy was employed to ascertain the compatibility between valsartan and the selected polymers. The pure drug and drug with excipients were scanned separately.

Drug-Excipient Compatibility Study by DSC [8]

Possible interaction of drug with various excipients to be used in prototype formulation was checked by using differential scanning calorimetry (DSC). DSC study of pure drug, proposed excipients and their combination used in prototype formulation was carried out using DSC instrument (DSC-60, Shimadzu, Kyoto, Japan). In this process, samples (3–5 mg) were put into aluminium cell and scanned at 50–300 °C, at 10°C per minute rate under nitrogen atmosphere against blank DSC aluminium cell as a reference.

Formulation design

Preparation of Oro dispersible film

Table-1: Formulation Design of Valsartan Oro dispersible film

Ingredient(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Valsartan	40	40	40	40	40	40	40	40	40
HPMC E2V5	2	4	8	-	-	-	-	-	-
CMC	-	-	-	2	4	8			
HPC	-	-	-	-	-	-	2	4	8
PEG400	20	20	20	20	20	20	20	20	20
Citric acid	5	5	5	5	5	5	5	5	5
Saccharin	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Sodium starch glycolate	5	5	5	5	5	5	5	5	5

Valsartan Oro dispersible films were prepared by solvent casting method. Briefly, Polymer was added in purified water; and it was allowed to dissolve completely for 30 min at slow stirring and then valsartan was added under continuous slow stirring and allowed to stir for 10 min at slow stirring speed. PEG400, citric acid and saccharin were added subsequently to this beaker under continuous gentle stirring and dispersion was allowed to stir after each addition. After addition of all excipients, dispersion was allowed to stir for 15 min. After complete removal of bubbles, dispersion was cast on glass petriplate . The glass petriplate was kept in controlled temperature oven at 50°C for 5 h. After drying, films were peeled and cut into 3.5 cm × 3 cm (10.5 cm2) and store in triple laminated Alu pouch. These films were further subjected to various evaluation tests.

Evaluation of Oro dispersible films

Physical appearance[9]

All the prepared Oro dispersiblefilm were observed for color, clarity, flexibility, and smoothness.

Thickness[10]

A thickness of the film was measured by micrometer screw gauge. Film was measured at three positions i.e. left, right and central corners and the mean value of thickness was calculated.

Weight uniformity[11]

The prepared films are to be dried at 60^0C for 4hrs before testing. A specified area of 4.52 cm^2 of film is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

Moisture absorption studies[12]

The films were weighed accurately and placed in a desiccators containing aluminium chloride to maintain 79.50% RH. After 3 days, the films were taken out and weighed. The percentage of moisture uptake was calculated using the following formula.

$$\text{Perentage moisture uptake} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Moisture loss studies[13]

Three films were weighed individually and kept in a desiccator containing calcium chloride at 37^0C for 24 hrs. Then the final weight was noted when there was no further change in the weight of the patch. The percentage of moisture loss was calculated using the following formula.

$$\text{Percentage moisture loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$$

Folding Endurance[14]

Folding endurance of the film was measured by folding the film at the same point until it was broken. The number of folds before the film breaking is the folding endurance of the film.

Tensile strength[15]

The tensile strength of an oro dispersible film (ODF) is determined by measuring the force required to break a film sample under tension, and then normalizing that force by the film's cross-sectional area. This procedure generally involves preparing film samples of a specific size and shape, then using a tensile testing machine to apply a controlled tensile force until the

film breaks. The force at break and the film's dimensions are then used to calculate the tensile strength.

Drug content[16]

The assay was determined by dissolving one film of dimension 3.5 cm × 3 cm containing 40mg of Valsartan in 6.8 phosphate buffer in 100 ml volumetric flask under continuous shaking for about 20 min. If any large undispersed fragments of film were seen, sonication was performed for 5 min to disperse film fragments residues. The above solution was further diluted to get concentration of valsartan and the absorbance was measured at 250 nm using UV-visible spectrophotometer. The experiments were carried out trice and average values of three assays were recorded.

In Vitro Disintegration Time[17]

The in vitro disintegration time is the time at which the film starts to break. The disintegration time was measured in a beaker containing 20 ml deionized water. The time at which film starts to break was measured as disintegration time of film. The time at which the film completely dissolves was considered as dissolution time or solution time. In vitro disintegration time and solution time were evaluated in USP dissolution apparatus fitted with basket rod at 50 RPM maintained at 37 ± 0.5ºC.Basket portion of the assembly was separated from rod and it was fitted in USP dissolution apparatus. This rod was used to give stirring effect to film during disintegration. Disintegration test assembly containing rotating rod.

In vitro dissolution study[18]

The *in-vitro* study of drug permeation through the Dialysis membrane was performed using a modified Franz type glass diffusion cell. The modified cell having higher capacity is (10 ml) is used to maintain sink condition. The samples were analyzed for drug content spectrophotometrically. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal.

Percentage of drug release was determined using the following formula.

$$\text{Perentage drug release} = \frac{\text{Da}}{\text{Dt}} \times 100$$

Where, Dt = Total amount of the drug in the film

Da = The amount of drug released

Drug release kinetics[19]

The amount of drug released from the pharmaceutical dosage form and its processes is an essential but which is intricate process in matrix systems. Zero order or first order kinetics were used to characterize the sequence of drug release from matrix systems. The Higuchi diffusion model was used to investigate the mechanism of drug release from matrix systems. The Korsmeyer- Peppas equation also categorized drug release mechanisms as Fickian/nonFickian/anomalous. The release exponent 'n' value is utilized in the Korsmeyer-Peppas equation to characterize distinct release processes from the dosage form

Stability Study[20]

The stability study of the prepared FDF was carried under different environmental conditions. The six film strips were first wrapped separately with butter paper and followed by alluminium foil. The film strips were stored in stability chamber at two different storage conditions of 40 °C/ 60% relative humidity (RH) and 60 °C/ 75% RH. The film strips were evaluated for the appearance, weight, drug content and in vitro drug release after 45 days.

3. RESULTS& DISCUSSION

Drug - excipient compatibility studies

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied. The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components.

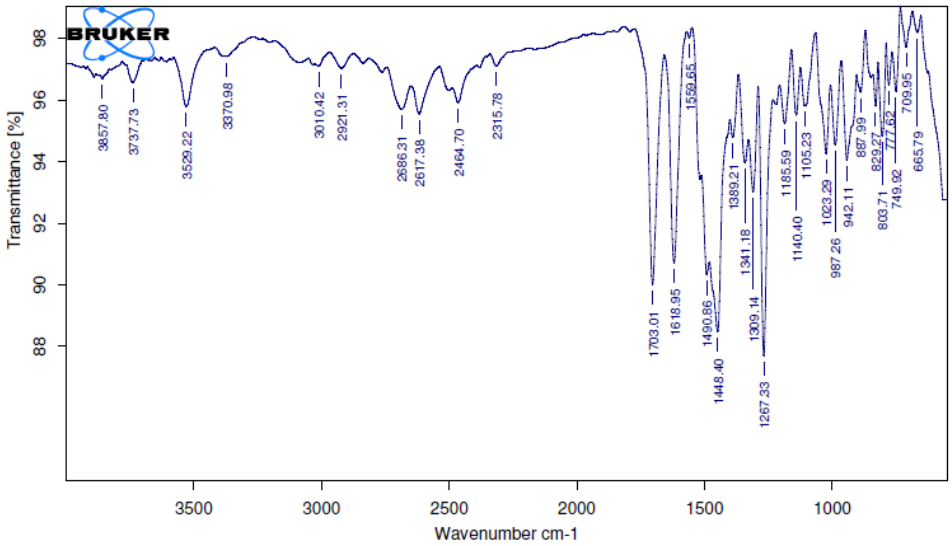

Fig-1: FT-IR Sample for Valsartan

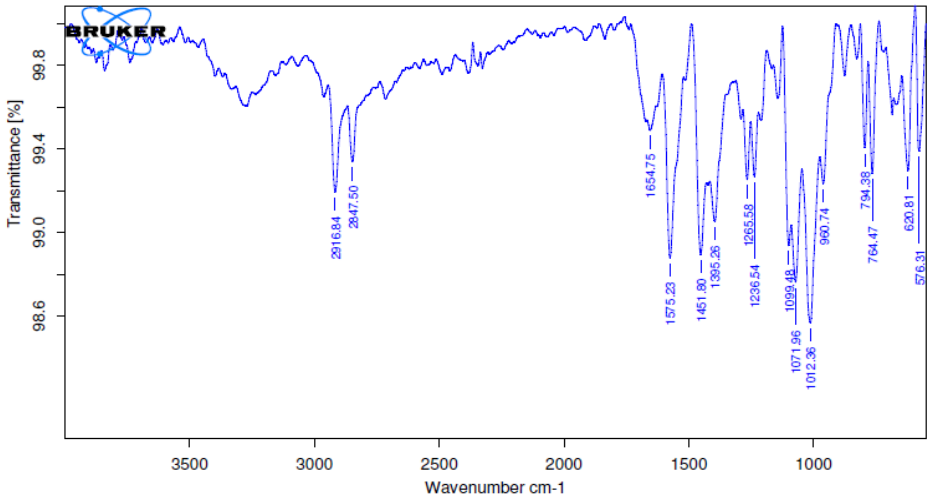

Fig-2: FT-IR Sample for Optimized Formulation

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of Pure drug and physical mixture of drug and excipients were studied. The characteristic absorption of peaks were obtained as above and as they were in official limits (±100 cm^{-1}) the drug is compatible with excipients.

DSC Analysis

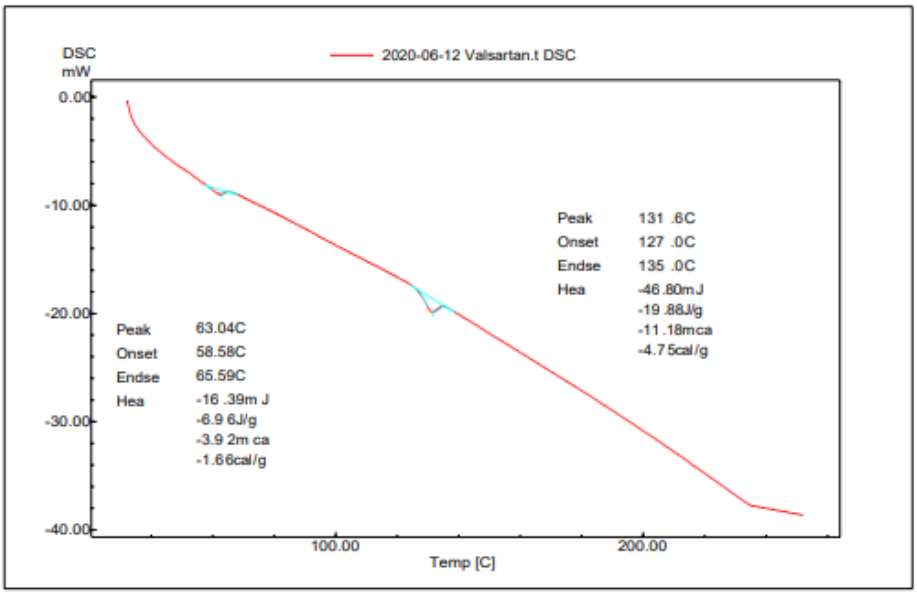

Fig-3: DSC Analysis of Valsartan

The DSC scans of ODF of the Valsartan as compared with the individualfilm excipients are displayed. Valsartanindicates an exothermic sharp peak at 65.59^{0}C, because of the drug decomposition. Moreover, the endothermic heightappeared at 127^{0}C is attributed to the melting of Valsartan degradation product.

Evaluation of Oro dispersible films formulation

Physical appearance

The prepared patches were found to be uniform, smooth, flexible and homogenous.

Folding endurance

The folding endurance numbers of all the Valsartan Oro dispersible films are 279 to 298. The folding endurance number gives the mechanical property of the patches, high folding endurance number indicate that has high mechanical property. These results indicated that the patches would not break and maintain their integrity with general folding when applied.

Thickness of the film

Thickness was changed from batch to batch in individual strips of medicated films carry uniform thickness, which indicates that total medicated film carriesuniform thickness.

Weight uniformity

The weights are in the range of 69.38 to 81.20. The F3 formulation patches showed maximum weight.

Tensile strength

For ODFs, an ideal tensile strength range is usually 13.69–15.39MPa

Drug content

The drug content analysis of the prepared formulations has shown that the process employed to prepare the patches was capable of giving uniform drug content with minimum batch variability. All the films were found to have drug content in the range of 90.32 to 98.36%. So, the method employed i.e. solvent evaporation method is satisfactory for the preparation of

Valsartan Oro dispersible films.

In vitro disintegration time

It was observed that in vitro disintegration time varies from 32 to 52s for the all formulations. The disintegration time for F3 was the lowest. This can be explained as the higher concentration of the polymer, the thicker gel will produce on contact with the media, which require a longer time to disintegrate

Table-2: Physicochemical evaluation of Valsartan oro dispersible films

F. code	Weight Variation (mg)	Thickness (mm)	Folding endurance	Drug content (%)	% Moisture loss	% Moisture absorption	Disintegration time (Sec)	Tensile strength(Mpa)
F1	80.91	0.09	298	91.86	7.15	9.63	45	14.59
F2	79.86	0.07	283	95.90	7.35	8.95	38	13.69
F3	81.2	0.12	279	98.36	7.50	7.81	32	15.25
F4	78.93	0.10	295	96.37	6.18	6.98	46	14.55
F5	76.89	0.08	286	93.24	8.12	8.68	50	15.82
F6	80.81	0.11	292	90.32	8.16	8.24	39	14.12
F7	69.38	0.08	288	95.86	7.10	7.89	52	15.39
F8	70.54	0.13	296	97.71	6.99	7.21	49	14.98
F9	75.38	0.09	290	96.38	7.08	7.26	48	14.57

***In vitro* release study**

All the nine formulation of Valsartan Oro dispersible films were subjected to in vitro release studies these studies were carried out using dissolution apparatus. The dissolution medium consisted of 900 ml of Standard buffer pH 6.8 for period of time.

Table-3: *In vitro* drug release profiles of Valsartan Oro dispersible films (F1-F9)

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	6.93	10.28	11.21	9.63	12.28	8.95	10.75	9.99	10.45
10	28.39	25.93	29.38	25.34	27.81	34.61	33.28	24.75	28.96
15	39.31	40.18	43.56	37.58	38.95	40.12	41.09	43.56	40.58
20	51.25	53.19	62.84	55.64	60.25	59.14	54.79	58.74	60.12
25	75.89	78.92	80.17	81.27	79.80	85.28	74.15	82.45	78.46

30	90.14	93.14	98.95	93.58	94.25	96.32	92.84	94.71	97.36

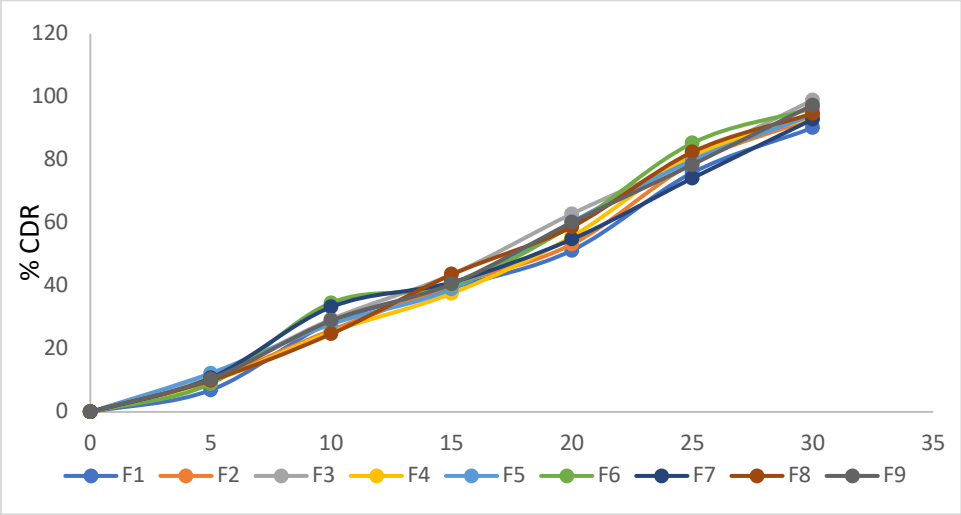

Fig-4: Drug release for all formulations

Kinetic models:

Dissolution data of above two methods was fitted in Zero order, First order and Higuchi equations.

Table-4: Drug Release Kinetics of Formulation F3

Time (min)	%CDR	SQARE T	LOG T	LOG%CDR	ARA	LOG%ARA
0	0	0	0	0	0	0
5	11.21	2.236068	0.69897	1.049605613	88.79	1.846742
10	29.38	3.162278	1	1.468051791	70.62	1.816805
15	43.56	3.872983	1.176091	1.639087871	56.44	1.844363
20	62.84	5.477226	1.477121	1.798236176	37.16	1.77745
25	80.17	7.745967	1.778151	1.904011884	19.83	1.67169
30	98.95	10.95445	2.079181	1.995415799	1.05	1.63349

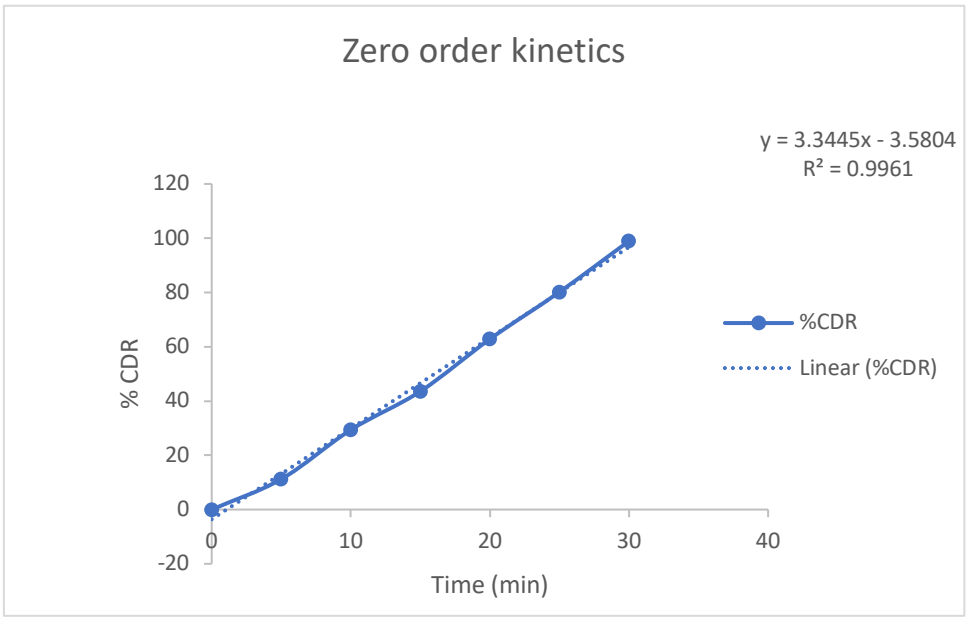

Fig-5: Zero order kinetics of optimized formulation

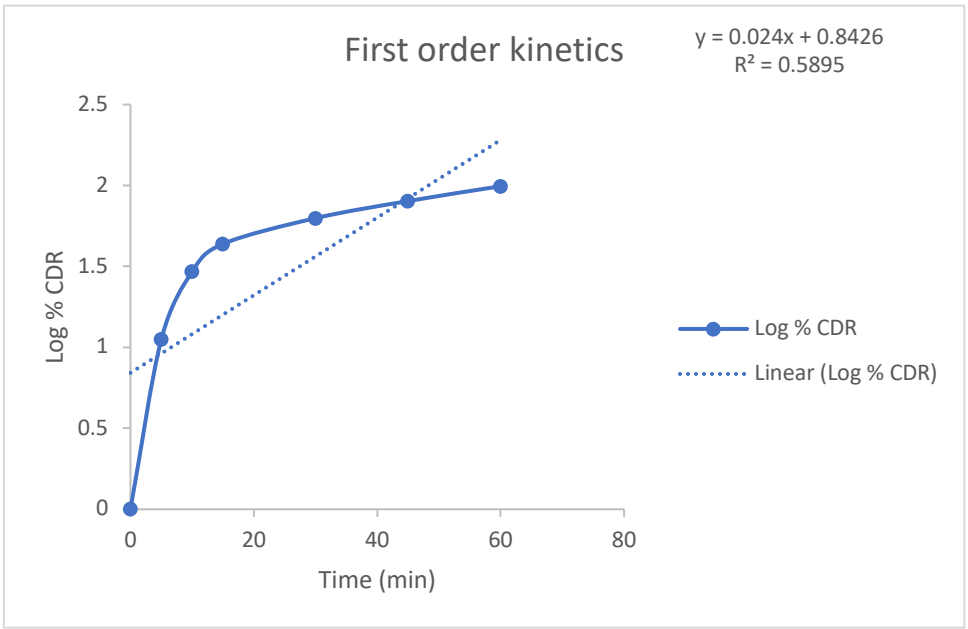

Fig-6: First order kinetics of optimized formulation

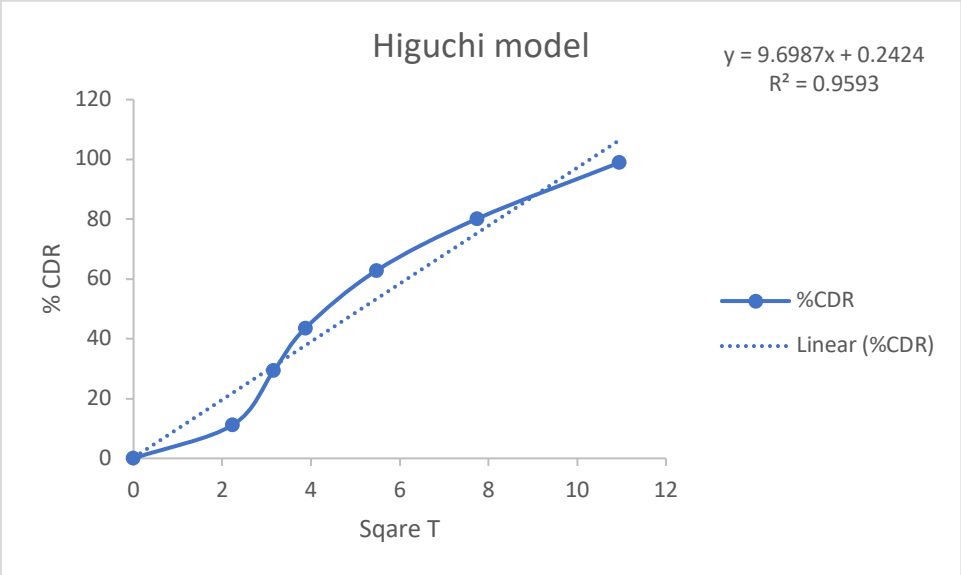

Fig-7: Higuchi model of optimized formulation

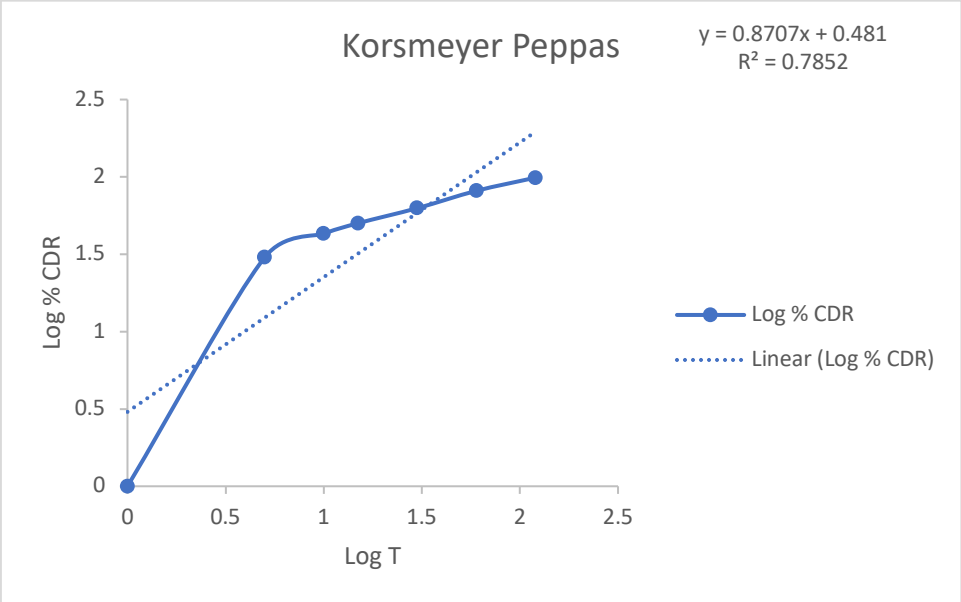

Fig-8: Korsmeyer peppas of optimized formulation

The values of in vitro release were attempted to fit into various mathematical models. Plots of zero order, first order, Higuchi model, KorsmeyerPeppas.

Regression values are higher with Zero order release kinetics. Therefore, all theoro dispersible film follows Korsmeyer peppas.

Stability studies

There was no significant change in physical and chemical properties of the oro dispersible films of formulation F-3 after 90 days. Parameters quantified at various time intervals were shown.

Table-5: Stability studies of all formulations

F.no	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-3	25^{0}C/60%RH % Release	98.95	98.10	97.16	96.85	Not less than 85 %

F-3	**30^0C/75% RH % Release**	98.95	98.12	97.45	96.12	**Not less than 85 %**
F-3	**40^0C/75% RH % Release**	98.95	98.14	97.86	96.05	**Not less than 85 %**

4. CONCLUSION

The present investigation will be helpful to provide patient friendly unique dosage forms. This formulation enhances patient compliance because patient can take it by simply putting it in oral cavity without need of water at any time and at any place. Valsartan fast dissolving film is unique taste-masked flash release formulation. The developed fast dissolving film formulations ofdrug will provide the alternative route for providing quick onset of action.

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