Original Article

FORMULATION AND EVALUATION OF IMPLANTABLE DRUG DELIVERY OF DISULFIRAM

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Abstract

Disulfiram is widely prescribed to discourage alcoholics from drinking alcohol. The effectiveness of oral disulfiram as a treatment for alcoholism is severely limited due to its poor bioavailability and poor patient compliance. To minimize the failure of the orally administered drug, efforts have been made to prepare alternative dosage form of subcutaneously implantable disulfiram pellets or tablets. In the present study an attempt has been made to design and evaluate a disulfiram implant using plain drug. The disulfiram implants have been formulated by direct compression and the effect of parameters like pH of site of administration (6.0 and 7.4) and sterilization were studied on in-vitro release of implantable disulfiram pellets. In- vitro release has been studied by vial and rotary flask shaker methods. The release kinetic mechanism from all the formulation was found to be zero order. The in vitro release data of all the formulations was compared with that of marketed disulfiram implant (Esperal). In contrast to other formulation in vitro release from marketed formulation appeared to be independent of hydrodynamics of diffusion (volume of dissolution media and agitation speed). The present study had revealed that, in-vitro drug release from implants is unaffected by pH of site of administration and gamma ray sterilization. Both the methods (Vial Method & Rotating Flask Method) of in vitro dissolution testing are found significantly different for formulations prepared in laboratory but not for marketed formulation, indicating the different mechanism of release of marketed formulation.

Keywords: Implant, Local medication, Disulfiram.

INTRODUCTION

Drug delivery systems that can sustain pharmacologically effective therapeutic drug levels for long periods of time while also permitting "dosing-on-demand" would be immensely useful in modern medicine. Physicians can choose from a variety of precision delivery options, such as local or systemic circulation, while still ensuring appropriate dose over the duration of treatment with implantable drug delivery systems. These systems have several advantages, including focused local medication delivery at a steady and predetermined pace, which reduces the amount of drug required and potential side effects while boosting therapeutic efficacy. These systems are especially useful for conditions including cardiovascular disease, tuberculosis, diabetes, cancer, and chronic pain management, to mention a few, that require long-term medication or face issues with patient compliance. Disulfiram is widely prescribed to discourage alcoholics from drinking alcohol, since alcohol and disulfiram interact to produce a subjectively unpleasant experience characterized by facial flushing, nausea, tachycardia and hypotension etc “DER / DAR” Reaction 1,2. The effectiveness of oral disulfiram as a treatment for alcoholism is severely limited due to its poor oral bioavailability and by the willingness of patients to take the drug every day, many stop taking their tablets so that they might resume drinking alcohol as soon as the effect have worn off. So, the frequent failures with the orally administered drug have stimulated interest in parenteral therapy with subcutaneously implanted disulfiram pellets. The approach in designing of implant is directly compressing the plain disulfiram by tablet machine (Cadmach). The objective of present study was to development of an implant for clinically effective pellets by directly compress plain disulfiram drug. The release pattern of in vitro release (Up to or above 45 days) of subcutaneously implantable disulfiram pellets at different pH values dissolution medium (pH 7.4 and pH 6.0) by two methods i.e. (Vial method and Rotary flask Shaker) etc to study effect of pH and method. The present investigation made to check the effect of sterilization as some papers suggests sterilization process affects some drug properties and hence the in vitro release is affected.

Materials and method:

The drug Disulfiram USP was procured from Yarrow chem Products Mumbai. The different materials i.e. 0.2 M Sodium hydroxide, Potassium dihydrogen phosphate, Magnesium stearte, Copper (II) Chloride (dihydrate), Methanol AR, was purchased from SD fine Pvt. Ltd. The various instruments i.e. Tablet machine (Cadmach), Micrometer Screw gauze (Japan), Monsanto hardness tester (Cadmach, Ahemedabad, India), Single pan digital electronic balance (AB204, Mettler – Toledo), Rotary Shaker, U.V. spectrophotometer (Shimadzu UV-250 1PC double beam spectrometer) were used for proposed method. The various software i.e. NGSS, USA, Sigma-stat statistical software version 2.03 and Prism statistical software, and Microsoft Excel were used for the calculation, graphs and data treatment of the results obtained.

Preformulation of drug sample was used without further purification. Characterization of drug was done using physicochemical methods. The details are as given below.

The sample of Disulfiram was studied for organoleptic characters and it was found to be a white or almost white, odorless and tasteless crystalline powder. The melting point was determined by Open Capillary Method and the uncorrected melting point was found to be 70 - 740 C. The solubility of the Disulfiram was determined by adding excess amount of drug in the solvent and equilibrium solubility was determined by taking supernatant and analyzing it on Shimadzu UV 2501 PC, double beam, double monochromator spectrophotometer. The analytical study of drug sample as wavelength of maximum absorption (λmax) was done by UV spectroscopy. The method was given as prepare stock solution of Disulfiram in methanol of 20 µg/ml was prepared. To 5.0 ml of this solution 20.0 ml of 0.1% w/v solution of cupric chloride in methanol was added. The solution was thoroughly mixed and allowed to stand for 1.0 hour. The spectrum of this solution was recorded using Shimadzu UV 2501 PC, double beam, spectrophotometer at 1.0 nm slit width using methanol and water as solvent in the range of 300 – 600nm [3 - 5].

Preparation of Implants: The active ingredient was made into desired pellets by direct compression (Table 1.) The pellet S1 was compressed on 16 station rotary tablet machine equipped with 6.6 mm flat faced punch and die set. As this formulation was prepared to mimic the marketed formulation (M) hence the active ingredient was 100 mg without any excipients and this formulation was send for gamma ray sterilization. The formulation NS was non sterilized formulation which was not send for gamma ray sterilization as it was kept to study the effect of sterilization on release. Before compression, surfaces of the die and punch were lubricated with magnesium stearate.

Table 1: Formulations of Disulfiram Implant

S. No.	Formulation code	Active ingredients (mg)	Diameter (mm)
1	M	100	6.6
2	S1	100	6.6
3	NS	100	6.6

Evaluation of Implants: The compressed implant matrix was evaluated for thickness, weight variation test, hardness and drug content [6].

Thickness and Diameter variation Test: The thickness of implants was determined using a Micrometer Screw Gauge (Japan).

Hardness Test: For each formulation, the hardness of six implants (n = 6) was determined using the Monsanto hardness tester (Cadmach, Ahmedabad, India)

Weight Variation Test: To study weight variation, 20 pellets of each formulation were weighed using an electronic digital balance.

Drug Content: Five implants were weighed and powdered. The drug content was measured as per the following compendial procedure.

Standard Solution: 40 □g/ml of disulfiram in 0.1% w/v solution of cupric chloride in methanol.

Sample Solution: An accurately weighed amount of powder equivalent to 0.4 gm of disulfiram was dissolved in 75.0 ml of methanol; this solution was adjusted to 100.0 ml with methanol. The 5.0 ml of the resulting solution was again diluted to 100 ml with methanol. The solution was thoroughly mixed and filtered. To the 5.0 ml of the resulting solution sufficient 0.1% w/v solution of cupric chloride in methanol was added to produce 25 ml of the solution. The extinction of standard and sample solution was measured at 395.5 nm using blank solution prepared by diluting 5.0 ml of methanol to 25.0 ml with the cupric chloride solution.

Sterilization of Implant: The formulation S1 was send to gamma ray sterilization.

The radiation source used: Co-60

Duration of exposure: 5 to 7 minutes

Dose of Radiation: 2.5 Mrad which is equivalent to 25kGy (Kilogray)

The sterility test was carried out by using direct inoculation method. 20 units were directly transferred to sufficient volume of fluid thioglycollate medium. This fluid thioglycollate medium was incubated at 30 to 35 0C for 14 days. Media were observed visually for any turbidity and microbial growth after 14 days [7].

in vitro release study: The experimental design for in vitro drug release studies was done. In vitro-release was done by different two methods Vial Method [8 -11] and Rotary Flask shaker Method [12 - 14]. The study was done with quantity 10 ml or 1000 ml of phosphate buffer pH 7.4 and at pH 6.0 with 25 rpm agitation speed for 5 min. at 37°C + 0.5°C.

Result and discussion:

The characterization of Disulfiram was done by physicochemical parameters as well as by spectroscopic methods. The drug was found to be pure and was used in the study without any purification. Analysis of drug was done by compendial method for the entire work. The result of wavelength of maximum absorption (λmax) was found to be 395.5 nm. A standard curve was prepared by dissolving 10 mg of Disulfiram in 20 ml of methanol. It was further diluted with 0.1% w/v solution of cupric chloride in methanol to get the solution in range of 5 to 40 □g/ml. The absorbance of these solutions was determined spectrophotometrically at 395.5 nm. Calibration Curve Result Eq. of Line is Y= 0.0317X-0.0454 and r20.9961 (Figure 1 & 2). The drug was found to be slightly soluble in water and freely soluble in acetone and Tween-80. The solubility of drug in methanol 33.05 mg/ml, water 0.2 – 0.3 mg/ml, acetone 119.37 mg/ml, 0.1 M Phosphate buffer pH 7.4 0.25 – 0.35 mg/ml, Tween 80 more than 125 mg/ml. The results of evaluation of implants for thickness, weight variation, hardness, friability and drug content were studied. All the implants had uniform distribution of drug in all the formulations. The drug content is as shown in the Table 2. The microbiological testing of prepared implants was confirmed after 14 days incubation period on fluid thioglycollate medium suggesting the sterility of implant and there was no visual growth of microorganisms was seen. The in-vitro dissolution of disulfiram implants of of all the formulation by Vial and Rotary Flask shaker Method are as shown in the Table 3 - 4. These data were treated with various dissolution models to interpret and discuss the results obtained from the in-vitro release of different formulations of disulfiram Implants. the release kinetics of disulfiram was investigated for gain better insight into the mechanism underlying the release of disulfiram from subcutaneous tissue implants and their role in systemic delivery of disulfiram. The results were fitted to the zero order and first order model. The values of kinetic rate constant (K) and regression coefficient as calculated from zero order are shown in (Table 5-6 and Figure 3-4). From the regression coefficient it is clear that release of all the formulation by all the methods shows zero order kinectics. Hence for all the statistical interpretation, zero order release constants were selected. All the formulations contain pure drug which is very slightly soluble, obviously the best fit was obtained was for zero order. Higuchi square root and Korsemeyer peppas equations were not applied as no polymer was used in the formulations. The effect of pH aand sterilization by vial method at both pH (7.4 and 6.0) was done for zero-order release rate constant data of formulation S1 and NS (Table 7) was subjected to two-way ANOVA (Table 8). Whereas the effect of pH aand sterilization by vial method at both pH (7.4 and 6.0) was done (Table 9) was subjected to two-way ANOVA (Table 10). Literature survey of radiation [16] induced chemical changes in pharmaceuticals has indicated that many drugs decompose when irradiated with dose ranging from 10 to 60 kGy. The literature survey has also indicated that half of solids had not decomposed. The decomposition was on an average less than 2%. Decomposition was more in case of liquids. From the two ways ANOVA test it is evident that there is no significant difference in drug release from formulation S1 (Sterilized formulation) and NS (Non-Sterilized formulation). Thus, it can be concluded that sterilization has no impact on the

release rate of plain disulfiram implants. This can be attributed to one or more of following reasons. The dose of radiation was 20 kGy. At this level of dose, disulfiram implants were effectively sterilized without degradation of the drug. The % assay values of sterilized and non-sterilized implants were (93.40 + 0.037) and (94.69 + 0.065) respectively. Disulfiram implants does not contain hydrated water so there was no possibility of degradation of disulfiram due to formation of free radicals on exposure to gamma radiation. The effect of pH was studied due to the two ways ANOVA test and it is evident that there is no significant difference in drug release from formulation S1 and NS in release mediums of different pH values (7.4 and 6.0).

Table 2: Evaluation of different formulation of Disulfiram

Parameter	**S1**	**NS**	**MF**
Diameter (mm)	6.504 (±0.067)	6.571 (±0.078)	6.693 (±0.057)
Thickness (mm)	2.523 (±0.022)	2.603 (±0.034)	2.705 (±0.023)
Hardness (Kg/cm^2)	2.813 (±0.40)	2.962 (±0.72)	2.4 (±0.013)
Deviation in weight variation	2.241 (±0.251)	2.297 (±0.320)	2.105 (±0.050)
Drug content	93.40 (±0.037)	94.69 (±0.065)	96.15 (±0.018)

Table 3: The drug released from formulation M, S1 and NS at pH 7.4 and 6.0 by Vial method (n= 3)

Time (Days)	***% CUMULATIVE RELEASE***					
	pH 7.4			**pH 6.0**		
	M	**S1**	**NS**	**M**	**S1**	**NS**
5	8.99 (± 1.24)	19.20 (± 1.21)	18.56 (± 1.47)	7.52 (± 1.44)	19.08 (± 1.12)	18.9 (± 1.18)
10	16.51 (± 1.76)	28.62 (± 0.88)	27.39 (± 1.89)	17.32 (± 1.36)	28.15 (± 0.86)	27.15 (± 0.92)
15	21.87 (± 1.52)	37.31 (± 1.30)	36.90 (± 2.01)	26.90 (± 1.69)	36.90 (± 0.69)	35.89 (± 0.59)
20	30.67 (± 1.20)	51.31 (± 1.48)	50.91 (± 1.65)	32.84 (± 1.32)	50.97 (± 1.02)	51.47 (± 1.12)
25	43.47 (± 0.69)	68.58 (± 0.99)	67.91 (± 1.50)	41.83 (± 0.98)	68.10 (± 1.39)	67.06 (± 1.42)
30	53.28 (± 0.59)	87.46 (± 1.34)	86.72 (± 0.87)	57.76 (± 0.84)	86.92 (± 1.48)	85.80 (± 1.56)
35	65.10 (± 1.30)	94.60 (± 1.28)	93.92 (± 0.97)	69.04 (± 1.42)	94.01 (± 0.63)	95.37 (± 0.74)
40	78.54 (± 1.48)			83.84 (± 1.38)		
45	92.86 (± 1.61)			95.39 (± 1.60)		

Table 4: Drug released from formulation M, S1 and NS at pH 7.4 and 6.0 by R.F. method (n= 3)

Time (Days)	***% CUMULATIVE RELEASE***					
	pH 7.4			**pH 6.0**		
	M	**S1**	**NS**	**M**	**S1**	**NS**
5	12.34 (± 1.30)	21.33 (± 1.48)	19.19 (± 1.23)	11.09 (± 1.10)	20.82 (± 1.21)	19.24 (± 1.48)

10	18.51 (± 1.39)	38.75 (± 1.76)	35.12 (± 1.63)	17.91 (± 1.10)	38.12 (± 1.38)	36.94 (± 1.33)
15	24.28 (± 1.28)	54.64 (± 0.84)	52.90 (± 1.07)	24.88 (± 1.09)	54.32 (± 1.80)	53.46 (± 1.84)
20	38.08 (± 1.30)	73.91 (± 0.77)	72.01 (± 0.93)	38.67 (± 1.27)	73.49 (± 1.20)	78.68 (± 1.35)
25	51.30 (± 1.58)	95.86 (± 0.63)	94.28 (± 0.39)	50.93 (± 1.07)	95.48 (± 0.97)	94.0 (± 0.89)
30	57.12 (± 1.34)	98.20 (± 0.79)	97.36 (± 0.68)	57.93 (± 1.45)	98.06 (± 0.65)	98.72 (± 0.71)
35	64.10 (± 1.21)			63.97 (± 1.47)		
40	79.30 (± 1.18)			79.87 (± 1.32)		
45	94.26 (± 1.63)			94.16 (± 1.57)		

Table 5: Dissolution kinetic treatment to formulation M, S1 & NS by Vial & R.F. Method at pH 7.4

Formulation Code	**Equation of Line**	**Regression Coefficient**	**Release Rate Constant**
	Zero order	**Zero order**	**Zero order**
M (V)	Y= 2.1035x - 6.8767	0.9841	2.1035
S1(V)	Y= 2.1296x + 1.7043	0.9837	2.1296
NS(V)	Y= 2.6839x + 0.9371	0.9846	2.3703
M(R.F.)	Y= 2.0239x - 1.9292	0.9851	2.0239
S1(R.F.)	Y= 3.9854x + 6.2867	0.9780	3.9854
NS(R.F.)	Y= 3.6568x + 3.066	0.9801	3.6568

Table 6: Dissolution kinetic treatment to formulation M, S1 & NS by Vial & R.F. Method at pH 6.0

Formulation Code	**Equation of Line**	**Regression Coefficient**	**Release Rate Constant**
	Zero order	**Zero order**	**Zero order**
M (V)	Y= 2.2008x – 1.9292	0.9879	2.2008
S1(V)	Y= 2.1296x + 3.6062	0.9834	2.0133
NS(V)	Y= 2.3703x + 2.360	0.9834	2.6681
M(R.F.)	Y= 2.0291x - 1.9175	0.9851	2.0291
S1(R.F.)	Y= 3.9854x + 5.6367	0.9788	3.9477
NS(R.F.)	Y= 3.3703x + 3.860	0.9824	3.3703

Table 7: Values of zero order release rate constants by vial method (S1 and NS)

Parameter	**Sterilized (S1)**	**Non-Sterilized (NS)**
pH 7.4	2.1296	2.3703

pH 6.0	2.0133	2.6681

Table 8: ANOVA for effect of pH and sterilization on in vitro release of formulation S1 and NS by Vial method

Source	Degree of freedom	Sum of sq. (S.S.)	Mean of S.S.	F-Ratio
Between rows (RSS) pH	1	0.0005590	0.0005590	0.0006820
Between columns (CSS) sterilized	1	0.2052	0.2052	0.2504
Residual	8	6.557	0.8186	

P (> 0.05) value summary: Effect of sterilization: Not significant

Effect of pH: Not significant

Table 9: Values of zero order release rate constants by R.F. method (S1 and NS)

Parameter	Sterilized (S1)	Non-Sterilized (NS)
pH 7.4	3.9854	3.6568
pH 6.0	3.9477	3.3703

Table 10: ANOVA for effect of pH and sterilization on in vitro release of formulation S1 and NS by R.F. method

Source	Degree of freedom	Sum of sq. (S.S.)	Mean of S.S.	F-Ratio
Between rows (RSS) pH	1	0.01451	0.01451	0.008891
Between columns (CSS) Sterilized	1	0.3535	0.3535	0.2166
Residual	8	13.86	1.632	

P (> 0.05) value summary: Effect of sterilization: Not significant

Effect of pH: Not significant

Table 11: Values of zero order release rate constants by vial and R.F. method (S1)

Parameter	Vial method (S1)	R.F. method (S1)
pH 7.4	2.1296	3.9854
pH 6.0	2.0133	3.9477

Table 12: ANOVA for effect of pH and sterilization on in vitro release of formulation S1.

Source	Degree of freedom	Sum of sq. (S.S.)	Mean of S.S.	F-Ratio
Between rows (RSS) pH	1	1.756	1.756	6.975
Between columns (CSS) Sterilized	1	0.3888	0.3888	1.545
Residual	8	2.0143	0.2517	

P (>0.01 to 0.05) value summary: Effect of Method: * Significant

Effect of pH: Not significant

Thus, the release rate constants of sterilized formulation obtained by two different methods are significantly different (Inference no. 1)

Table 13: Values of zero order release rate constants by Vial and R.F. method (Formulation NS)

Parameter	Vial method (NS)	R.F. method (NS)
pH 7.4	2.3703	3.6568
pH 6.0	2.6681	3.3703

Table 14: ANOVA for effect of pH and sterilization on in vitro release of formulation NS.

Source	Degree of freedom	Sum of sq. (S.S.)	Mean of S.S.	F-Ratio
Between rows (RSS) pH	1	7.092	7.092	6.618
Between columns (CSS) Sterilized	1	0.007849	0.007849	0.007324
Residual	8	8.573	1.072	

P (>0.01 to 0.05) value summary: Effect of Method: * Significant

Effect of pH: Not significant

Thus the release rate constants of non sterilized formulation obtained by two different methods are significantly different (Inference no. 2)

Table 15: Values of zero order release rate constants by Vial and R.F. method for marketed Formulation (M) at (7.4 and 6.0)

Parameter	pH 7.4	pH 6.0
Vial method (M)	2.1035	2.2008
R.F. method (M)	2.0239	2.0291

Table 16: ANOVA for effect of method on in vitro release of marketed formulation (M)

Source	Degree of freedom	Sum of sq. (S.S.)	Mean of S.S.	F-Ratio
Between rows (RSS) pH	1	0.0002627	0.0002627	1.239
Between columns (CSS) Sterilized	1	0.01579	0.01579	7.445
Residual	1	0.002121	0.002121	

P (>0.01 to 0.05) value summary: Effect of Method: Not Significant

Effect of pH: Not significant

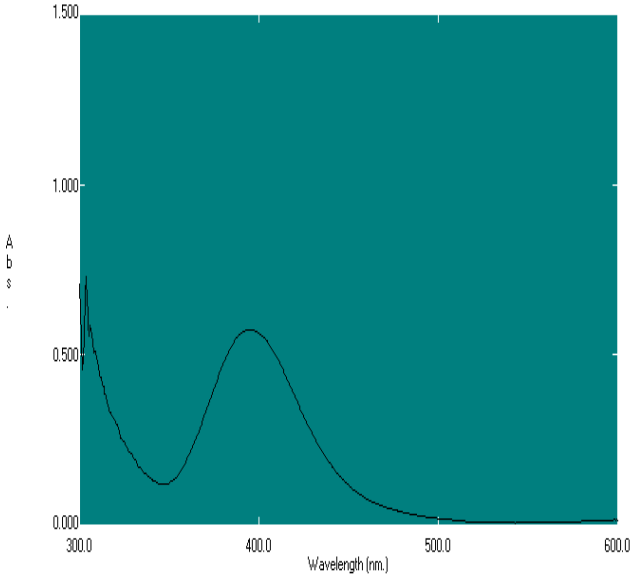

Figure 1: UV Spectrum of Disulfiram

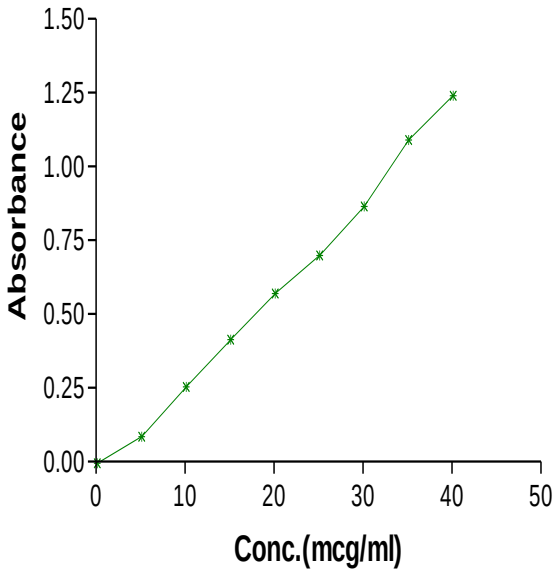

Figure 2: Beer - Lambert's plot of Disulfiram in 0.1%w/v cupric chloride solution

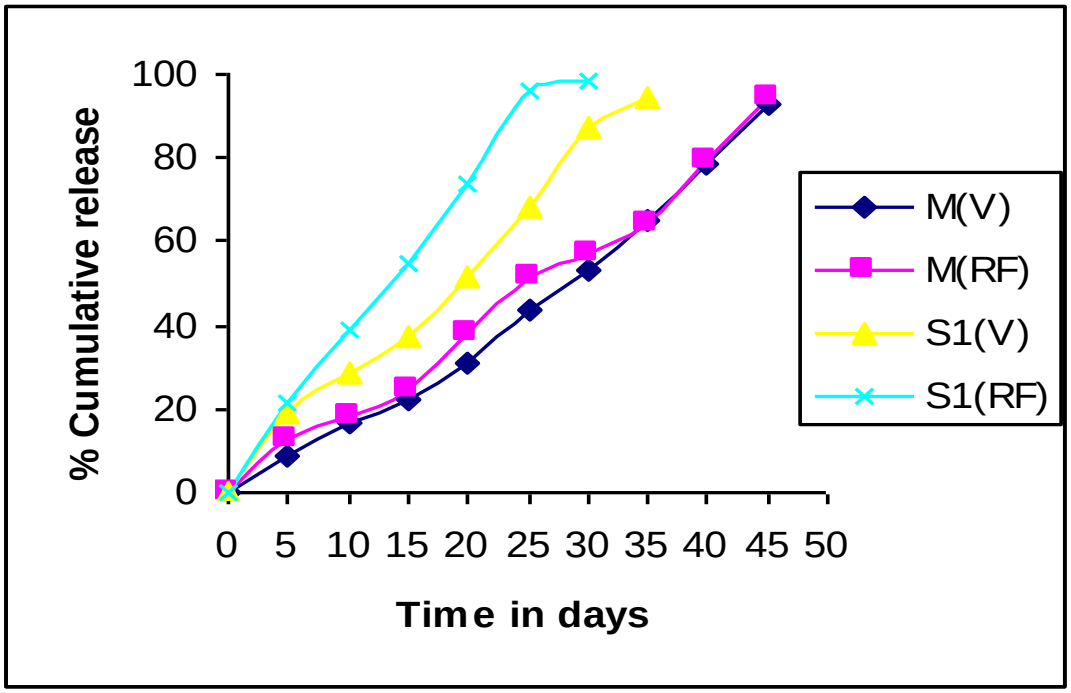

Figure 3: Zero order kinetic and percent cumulative release (Mean + SEM) of drug formulation M & S1 by R.F. & Vial Method at pH 7.4

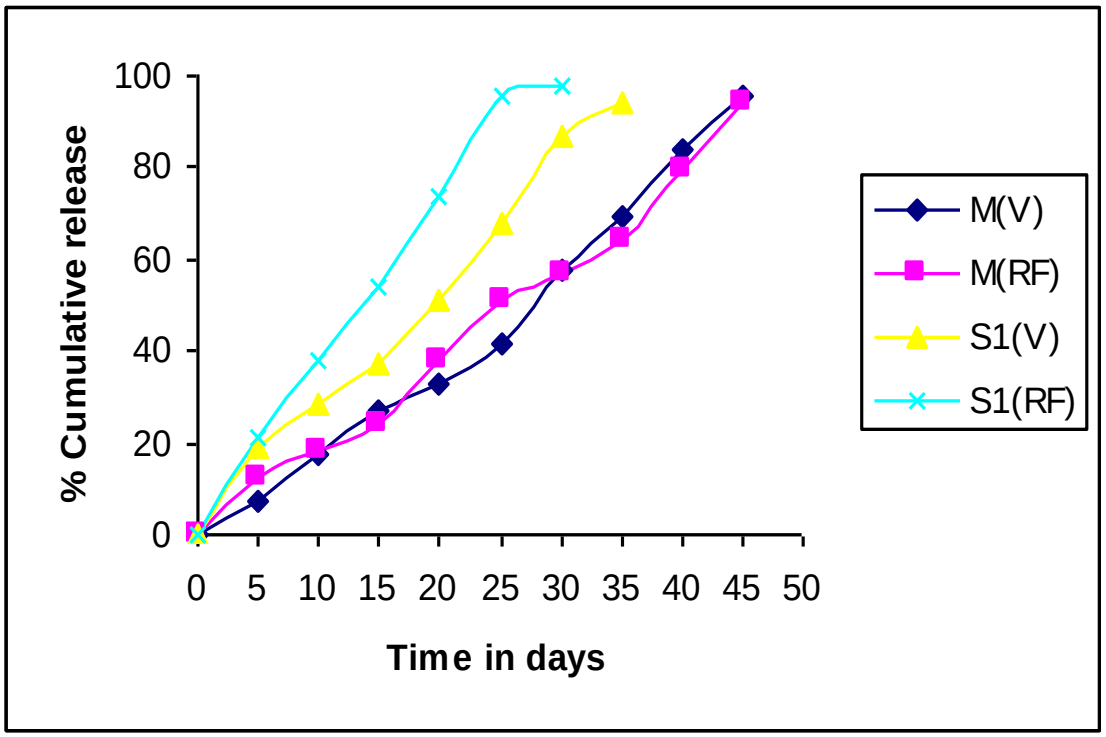

Figure 4: Zero order kinetic and percent cumulative release (Mean + SEM) of drug formulation M & S1 by R.F. & Vial Method at pH 6.0

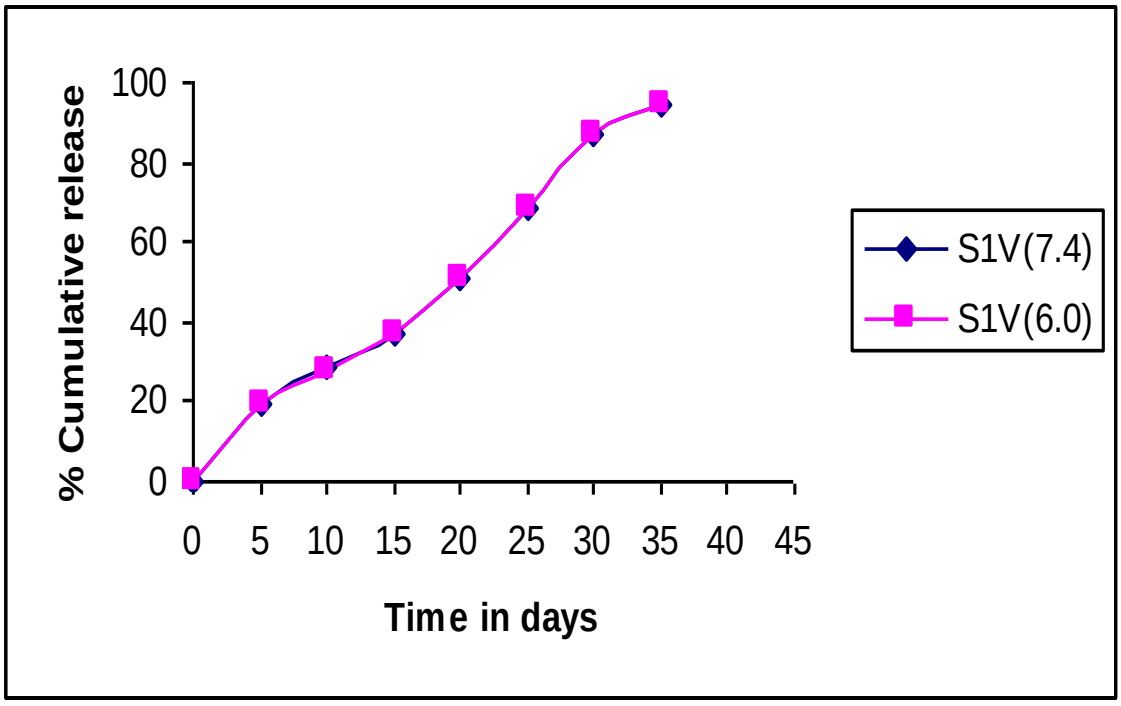

Figure 5: Percent cumulative release (Mean + SEM) of drug formulation S1 by Vial Method at pH 7.4 & 6.0 for optimization of effect of pH on release by vial method

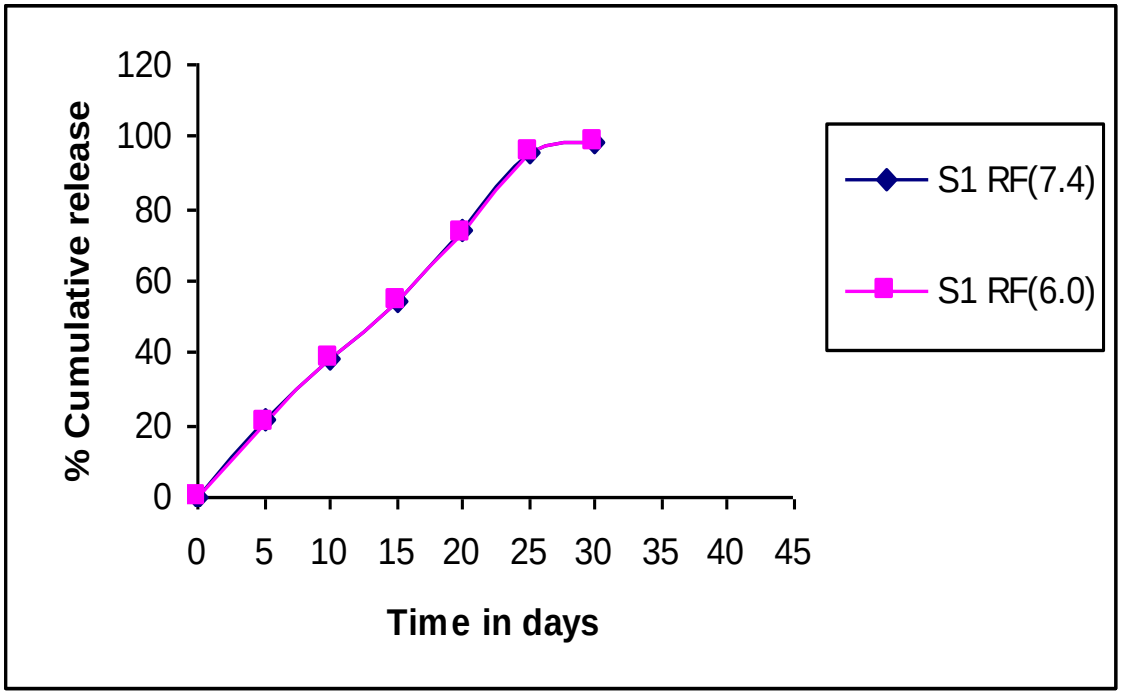

Figure 6: Percent cumulative release (Mean + SEM) of drug formulation S1 by R.F. Method at pH 7.4 & 6.0 for optimization of effect of pH on release by R.F. method

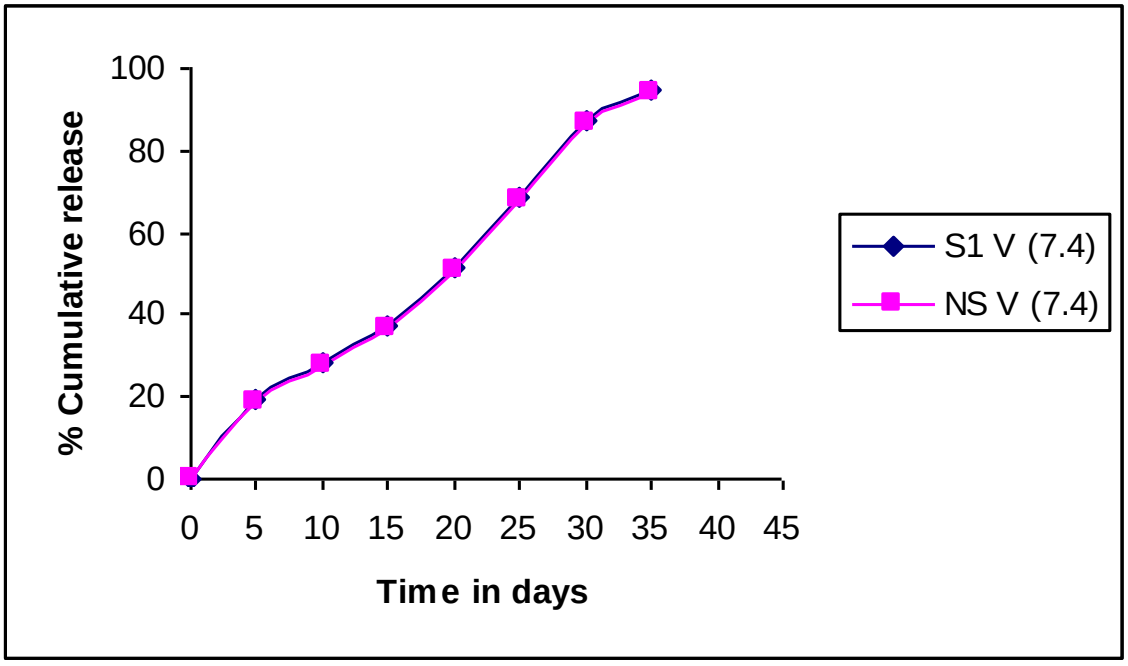

Figure 7: Percent cumulative release (Mean + SEM) of drug formulation S1 & NS by Vial Method at pH 7.4 for optimization effect of sterilization on release by vial method at pH 7.4

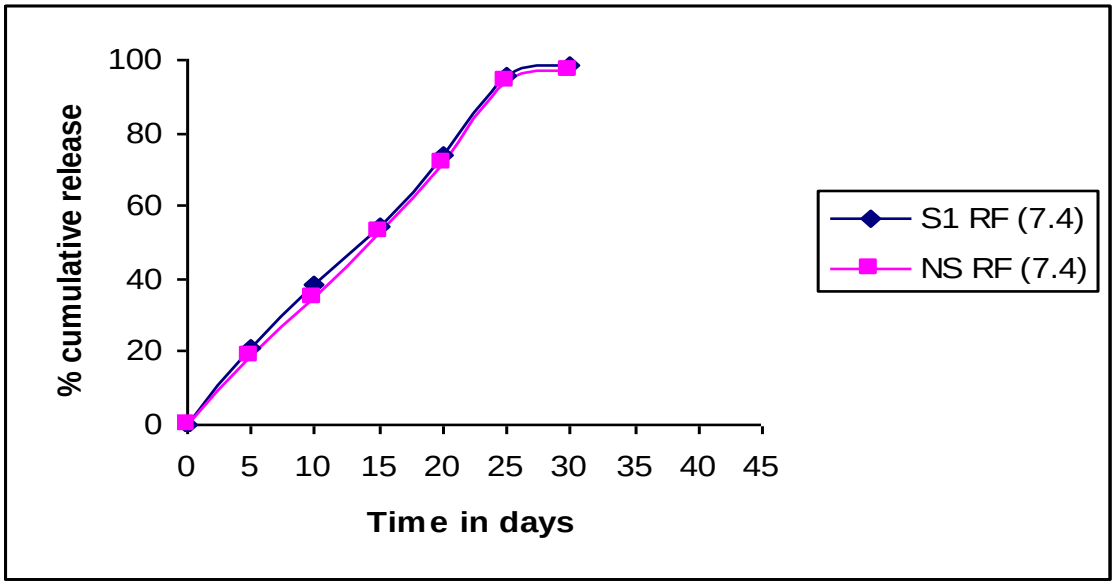

Figure 8: Percent cumulative release (Mean + SEM) of drug formulation S1 & NS by R.F. Method at pH 7.4 for optimization effect of sterilization on release by R.F. method at pH 7.4

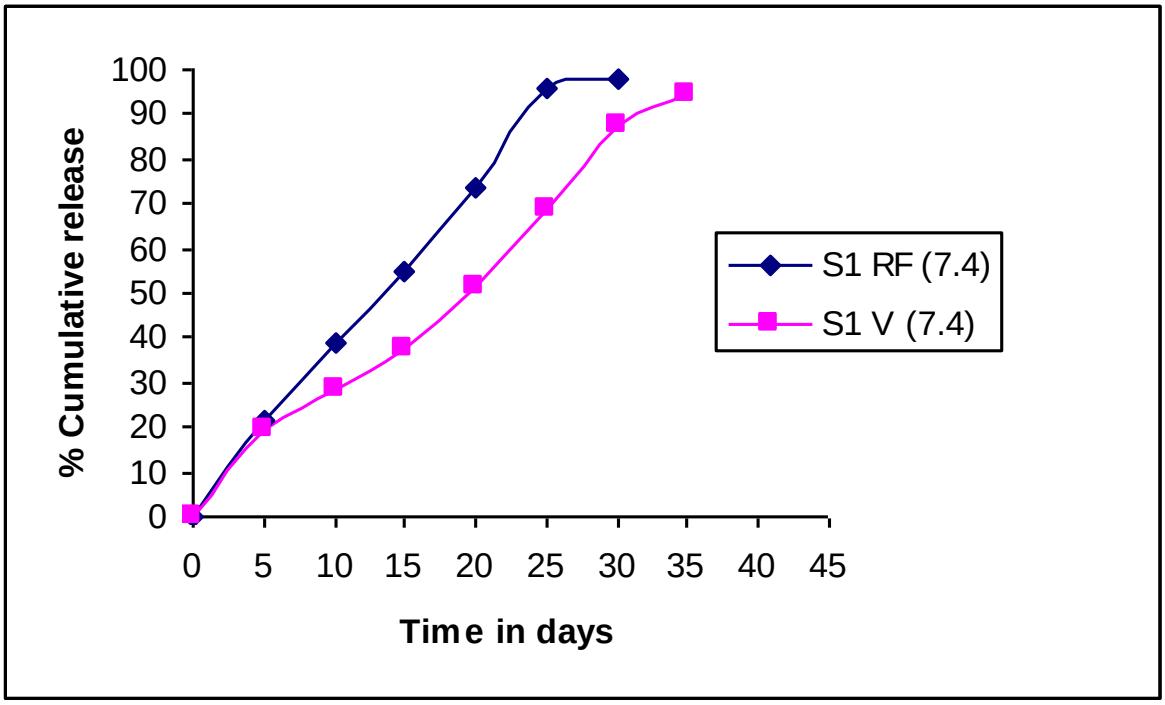

Figure 9: Percent cumulative release (Mean + SEM) of drug formulation S1 by Vial & R.F. Method at pH 7.4 for optimization effect of method at pH 7.4

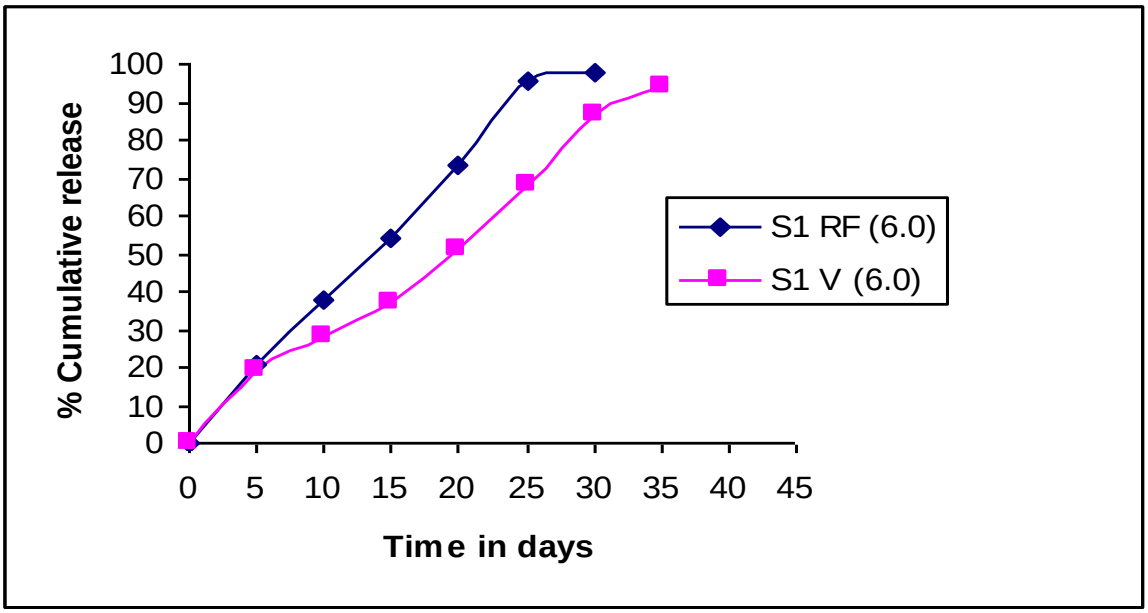

Figure 10: Percent cumulative release (Mean + SEM) of drug formulation S1 by Vial & R.F. Method at pH 6.0 for optimization effect of method at pH 6.0

This means that the release rate of the disulfiram implant is not affected even if the pH values change from 6.0 to 7.4. The effect of two different in vitro release methods on the release profile of sterilized formulation (S1) at zero-order release rate constant data obtained from the study of in vitro release by vial and R.F. method at both pH (7.4 and 6.0) (Table 11) was subjected to two-way ANOVA (Table 12). The effect of two different in vitro release methods on the release profile of Non sterilized formulation (NS) at zero-order release rate constant data of formulation NS obtained from the study of in vitro release by vial and R.F. method at both pH (7.4 and 6.0) (Table 13) was subjected to two-way ANOVA (Table 14 and Figure 5-8). The effect of two different in vitro release methods on the release profile of Marketed formulation (M) at both pH (6.0 and 7.4) at zero-order release rate constant data of marketed formulation (M) obtained from the study of in vitro release by vial and R.F. method at both pH (7.4 & 6.0) (Table 15 and Figure 9-10) was subjected to two ways ANOVA (Table 16). From the above inferences (inferences no 1,2 and 3) it can be concluded that, "the formulations S1 and NS give significantly different zero order release constants when evaluated by two different methods i.e., rotary flask and vial methods but marketed formulation (M) doesn't give significantly different zero order release constants when evaluated by these two different methods". This is clear indication that though the marketed formulation (M) gives best-fit line for zero order kinetics, similar to formulation S1 & NS, marketed formulation (M) has got release pattern different from that of S1 and NS. The two methods used in the present investigation differ in two parameters: volume of dissolution medium and agitation speed. Hence as observed from there was more release of drug of the same formulation (in case of formulation S1 and NS) by rotary flask method. The higher drug release could be attributed to the agitation used in the Rotary Flask method and more amount of dissolution medium. In the Rotary Flask Method as the hydrodynamics are increased, there is decrease in diffusional distance and, hence, an increase in dissolution rate. In case of marketed formulation there is no increase in release rate because of use of rotary flask methods. This indicates that most probably hydrodynamics of diffusion doesn't play an important role in the release of marketed formulation.

Summary and conclusion:

The drug Disulfiram can be directly compressed to prepare implantable pellets. The drug containing implants can be effectively sterilized by terminal gamma ray sterilization. The results of sterilization and pH of administration site does not affect the release characteristics of implants. The graphical representation of release kinetic mechanism from all the formulation was found to be zero order. Both the methods of in vitro dissolution testing are found significantly different for formulations prepared in laboratory but not for marketed formulation, indicating the different mechanism of release of marketed formulation.

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