FORMULATION DEVELOPMENT AND IN-VITRO CHARACTERIZATION OFLEVAMISOLE CONTROLLED RELEASE TABLETS FOR TREATMENT OF PARASITIC INFECTIONS

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ABSTRACT

The present study aims was at developing Levamisole controlled release tablets. Levamisole is anti-helminthic drug that is usually used for treatment of infections caused by parasites i.e., worms. Levamisole showed maximum absorption at wavelength 224nm in 0.1N HCL and 226nm in pH 6.8. The Drug - polymer compatibility studies conducted by FTIR provided required confirmation about their purity and indicated that there is no interaction between the drug and selected polymers. Various formulations were developed by using release rate controlling forming polymers like HPMC K100M, Eudragit RS PO and Ethyl cellulose by direct compression method. From among all the developed formulations F5 formulation controlled the drug release for longer period when compared to other formulations; So F5 was selected as the best formulation. From the research study conducted and from the release kinetics graphical profiles it was concluded and established that drug release from the optimized formulation followed Zero order release kinetics, which was specified by correlation coefficient - R^2 value that was higher for Zero order release. So the drug release mechanism is considered to follow controlled release system.

Keywords: Levamisole, HPMCK100M, Eudragit RS PO and Ethyl cellulose

Introduction

Controlled release tablets are commonly taken only once or twice daily, compared with counterpart conventional forms that may have to take three or four times daily to achieve the same therapeutic effect [1]. The benefit of administering a single dose of drug that will be released over an extended time period to maintain a near-constant or uniform blood levels of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use [2, 3]. Controlled release/ prolonged release/ modified release/ extended release or depot formulations are the general terms utilized to identify the drug delivery systems which are designed to attain or to extend the therapeutic effect and benefit by continuously and uninterruptedly releasing the medication over extended period of time period after administration of single dose [4].

The objective involved in designing a Controlled drug delivery system is to decrease the regularity and frequency of the dosing of dosage form and also to increase efficiency of the drug by its localization at site of activity, decreasing the dose required also providing uniform drug delivery [5]. So, Controlled drug release dosage forms release one or more drugs continuously in predetermined pattern and configuration for a fixed time period, either systemically or to indicated targeted organ [6,7]. Controlled release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery.

There are definite deliberations for preparation of extended drug release formulations:

- If the active ingredient have a sufficient long half-life, it could be Controlled on its own
- If the pharmacological and therapeutic activity of active ingredient is not directly and precisely related to its concentration of blood levels
- If the drug absorption is involving involves an active transport mechanism [8].
- If the active ingredient has very short half-life then it might require large quantity of drug to maintain and continue a prolonged effective dose [9].

The above factors need serious review prior to design.

Introducing matrix tablet formulations as Controlled release has produced an innovative breakthrough for the development of novel drug delivery systems in the field of Pharmaceutical technology [10]. It eliminates complex manufacturing procedures like coating/Pelletization during formulation and the drug release rate from dosage form is controlled primarily by type of polymer and its proportion used in the preparations. Hydrophilic polymeric matrix is extensively used for formulating these dosage forms [11, 12]. Matrix formulation systems are usually used for the rationale of Controlled release. It is the drug release system which will prolong and control the release of drug which is either dissolved or dispersed. A matrix is defined as well-mixed composition of one or additional drugs with a gelling agent i.e. hydrophilic polymer [13]. By this Controlled release methodology therapeutically effective and operative concentrations could be achieved in systemic circulation for an extended time periods and assist in achieving improved compliance of patients [14]. Levamisole is anti-helminthic drug which is usually used for treatment of viral and bacterial infections.

Objective of research study

The objective of study is to formulate and evaluate Levamisole Controlled release tablets using different polymers such as HPMC K100M, Eudragit RS PO, and Ethyl cellulose to control the drug release there by reducing the frequency of dosage.

MATERIALS AND METHODS

Levamisole is obtained as gift sample form Hetero drugs Ltd, Hyderabad. All the other polymers, talc and magnesium stearate was obtained from Yarrow Chem Products, Mumbai.

Preformulation studies and formulation development of Levamisole tablets

Preparation of the calibration curve in 0.1 N Hcl and pH 6.8 phosphate buffer

100mg of Levamisole pure drug was dissolved in 100ml Methanol it is considered as stock solution which is 1mg/ml solution, 10ml from the above solution was taken and then made up to 100ml using 0.1 N HCL, it is considered as 100µg/ml solution. From this 100µg/ml solution, 10ml was taken and the volume was made up to 100 ml with 0.1 N HCL which is considered as 10µg/ml. The above solution was subsequently diluted with 0.1N HCL to obtain series of dilutions Containing 5,10,15,20 and 25 µg/ml of Levamisole per ml of solution. The absorbance

of the above dilutions was measured at 224 nm using UV-Spectrophotometer [15] taking 0.1N HCL as blank. Then a graph was plotted by taking Concentration on X-Axis and Absorbance on Y-Axis which gives a straight line Linearity of standard curve was assessed from the square of correlation coefficient (R^2) which determined by least-square linear regression analysis [16]. The above procedure was repeated by using pH 6.8 phosphate buffer solutions and absorbance was measured at 226 nm. Calibration Graphs of Levamisole in 0.1 N Hcl i.e., in Simulated Gastric fluid (pH 1.2) and in pH 6.8 phosphate buffers were determined at 224 nm and 226nm respectively.

FTIR studies

FTIR studies and DSC evaluation studies for pure drug and drug excipient mixture were conducted to understand and analyse the drug excipient compatibility. The compatibility between the drug and other excipients can be evaluated using FTIR peak matching method.

Formulation development of Levamisole Tablets

All the formulations were prepared by using the technique of direct compression [17]. The compositions of different formulations are presented in Table 1.The tablets were prepared as per the procedure given below with the aim to prolong and control the release of Levamisole. The total weight of the tablet was considered as 120mg.

- All the ingredients were weighed according to the requirement
- Then Levamisole and all other ingredients were individually passed through sieve no ≠ 60.
- All the ingredients were mixed thoroughly by triturating up to 15 minutes until uniform mixture is obtained.
- The powder mixture was then lubricated with talc and magnesium stearate.
- The powder blend was compressed into tablets by using direct compression method [18, 19].

Table 1: Formulation composition for Levamisole tablets

Composition	F1	F2	F3	F4	F5	F6	F7	F8	F9
Levamisole	10	10	10	10	10	10	10	10	10
HPMCK100M	10	20	30	-	-	-	-	-	-
Eudragit RS PO	-	-	-	10	20	30	-	-	-
Ethyl cellulose	-	-	-	-	-	-	10	20	30
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	5	5	5	5	5	5	5	5	5
MCC	90	80	70	90	80	70	90	80	70
Total weight	120	120	120	120	120	120	120	120	120

(All the quantities are in mg)

Evaluation of pre - compression parameters for powder blend

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends [20]. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends were tested as per Pharmacopoeia which includes the following.

- Angle of repose
- Bulk density
- Tapped density
- Compressibility index
- Haussner's ratio

Evaluation of post compression parameters for prepared Tablets

The tablets formulated were studied for their physicochemical properties like weight variation, hardness, thickness, friability, drug content and in-vitro drug release studies.

Weight variation

The weight variation was performed by taking twenty tablets followed by determining their

individual weights on a digital weighing balance. Then the average weight of all the 20 tablets was determined [21-23]. Then the individual tablet weight was compared with the average weight to determine the percentage weight variation.

The percent weight variation deviations were calculated using below formula.

$$\% \text{ Deviation} = (\text{Individual weight} - \text{Average weight} / \text{Average weight}) \times 100$$

Hardness

Hardness of a tablet is described as force applied across diameter of tablet to produce breakage of the tablet [24]. For each formulation, hardness of the three tablets was calculated utilizing Monsanto hardness tester and average hardness is calculated and presented in the pre-compression table.

Thickness

The Tablet thickness is one of the important characteristic in reproducing the appearance. The thickness was determined utilizing a Vernier caliper [25, 26]. Ten tablets from each formulation were used and the average values were calculated which are presented in the pre-compression table.

Friability

It is considered as a measure of the mechanical strength of formulated tablets. Roche friabilator is usually used to determine friability of tablets [27, 28].

In the determination of friability Roche friabilator is used by using the following procedure. The tablets weighed before were placed in friabilator. The tablets were under rotation at 25 rpm for duration of 4 minutes with total 100 rotations [29-31]. After completion of test, the tablets were re weighed, the loss in weight of tablet is considered as the measure of friability and it is expressed in the percentage as follows

$$\% \text{ Friability} = [(W1-W2) / W1] \times 100$$

Where, W1 = Initial weight of the tablets

W2 = Weight of the tablets after friability testing

Determination of drug content

The prepared tablets were tested for drug content. The procedure involves powdering ten tablets and the quantities of powder equivalent to one tablet weight of the drug were precisely weighed, then transferred into 100 ml volumetric flask which contains 50 ml water [32]and it was allowed to stand for few minutes to ensure and confirm complete solubility of drug]33]. Then the mixture was made up to the required volume with media, followed by suitably diluting the solution then the absorption was determined using UV –Visible spectrophotometer [34]. The concentration of the drug was calculated from calibration curve [35, 36].

In Vitro Drug Release Studies

Dissolution studies

900ml 0f 0.1 HCL was placed in vessel and the USP apparatus –II (Paddle Method) was assembled [37- 39]. The medium was allowed to equilibrate to temp of 37°c $\pm$ 0.5°c. Tablet was placed in the vessel and apparatus was operated for 2 hours and then the media 0.1 N HCL was removed and pH 6.8 phosphate buffer was added [40], process was continued up to 12 hours at 50 rpm. At definite time intervals 5ml samples were withdrawn and analyzed.

RESULTS AND DISCUSSION

Calibration graphs of Levamisole were taken in Simulated Gastric fluid (pH 1.2) 0.1 N Hcl, the observations are presented in table 2 and in pH 6.8 phosphate buffer the observations are presented in table 3 at a absorption maxima of 224 nm and 226nm respectively.

The calibration graphs in in Simulated Gastric fluid (pH 1.2) 0.1 N Hcl are presented in Figure 1 and graph in pH 6.8 phosphate buffer are presented in Figure 2

Table 2: Observations for Levamisole in 0.1N HCl (224 nm)

Concentration [µg/mL]	Absorbance
0	0
5	0.156
10	0.313
15	0.477
20	0.613
25	0.754

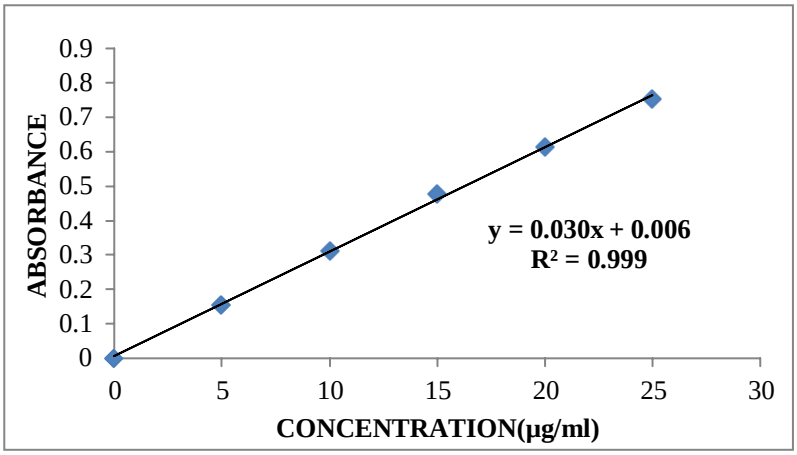

Figure 1: Standard graph of Levamisole in 0.1N HCl (224 nm)

Table 3: Observations for Levamisole in pH 6.8 phosphate buffer (226 nm)

Concentration [µg/ml]	Absorbance
0	0
5	0.112
10	0.246
15	0.388
20	0.534
25	0.659

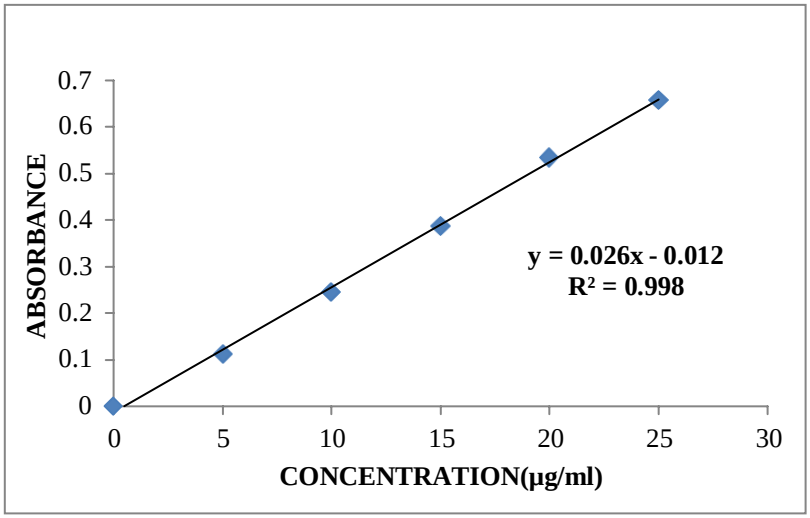

Figure 2: Standard graph of Levamisole pH 6.8 phosphate buffer (226nm)

FTIR studies

From the FTIR study data it was evident that the drug and excipients does not have any interactions. Hence they were compatible, the FTIR spectrum of pure drug is presented in figure 3, the spectrum for drug and excipient physical mixture is presented in figure 4. The DSC studies also infer there are no sign of interaction between drug and excipients, DSC for pure drug is presented in figure 5, the figure 6 represents DSC of drug and excipient physical mixture. There was no appearance or disappearance of peaks in the drug-excipient mixture, which confirmed the absence of any chemical interaction in between drug, excipients.

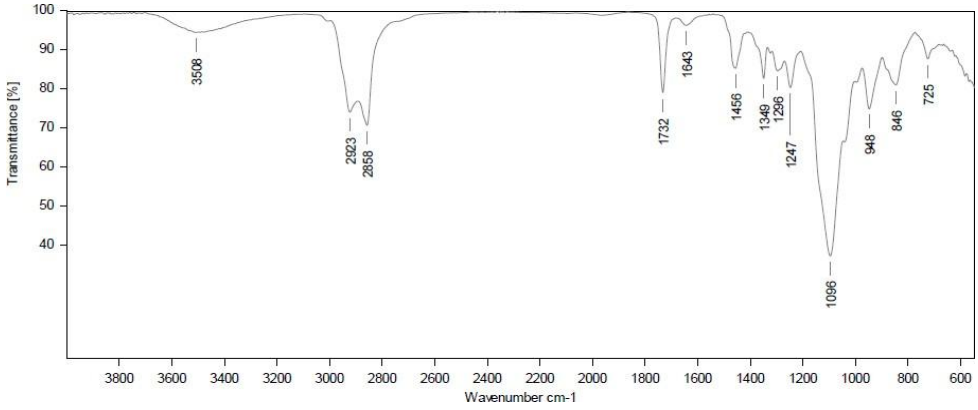

Figure 3: FT-IR Spectrum of Levamisole pure drug

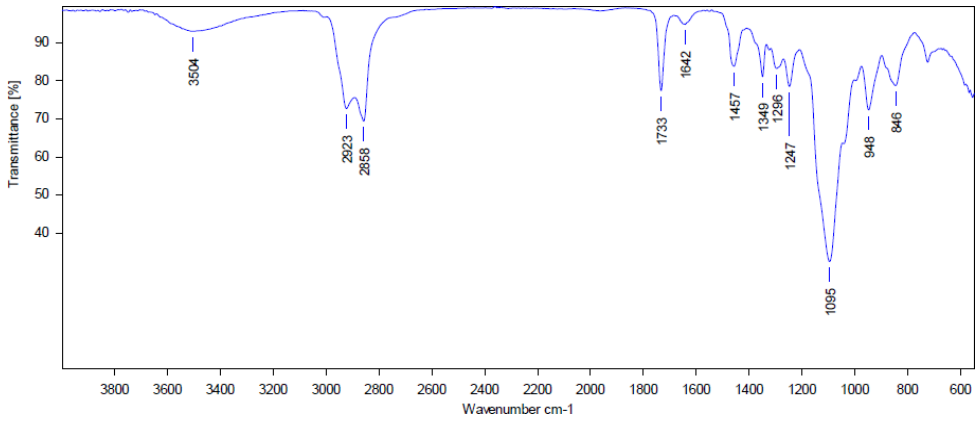

Figure 4: FT-IR spectrum of physical mixture of drug and excipients

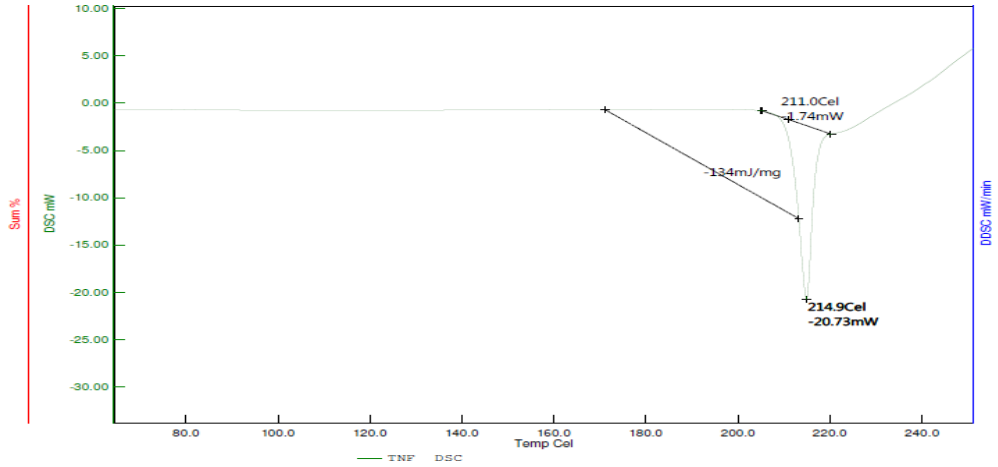

Figure 5: DSC of Levamisole pure drug

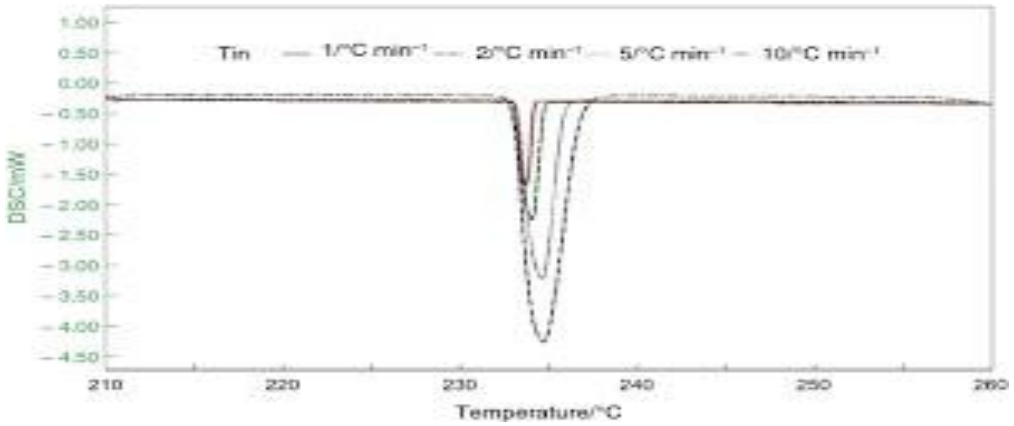

Figure 6: DSC of physical mixture of drug and excipients

From the FTIR study data it was evident that the drug and excipients does not have any interactions. Hence they were compatible. The DSC studies also infer there are no signs of interaction between drug and excipients. There was no appearance or disappearance of peaks in the drug-excipient mixture, which confirmed the absence of any chemical interaction in between drug, excipients.

Evaluation studies

Pre-compression parameters

Tablet powder blend was evaluated and observed for various pre-compression parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was observed to be in range of 0.31 ±0.015 to 0.333 ±0.006 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was observed to be in range of 0.42 ±0.02 to 0.413 ±0.01. The compressibility index of all the formulations was observed to be in range between 15.08 ±1.38 to 19.84 ±2.75. The pre-compression parameters were evaluated and represented in table 4.

Table 4: Pre-compression parameters of the powder blend

Code of Formulation	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio
F1	28.37 ±0.16	0.34 ±0.011	0.42 ±0.02	19.84 ±2.75	1.09±0.17
F2	29.58 ±0.44	0.337 ±0.01	0.413 ±0.01	17.73 ±1.14	1.11±0.21
F3	24.78 ±1.15	0.333 ±0.006	0.407 ±0.011	18.01 ±0.89	1.08±0.19
F4	27.16 ±1.39	0.30 ±0.011	0.357 ±0.006	15.87 ±1.39	1.11±0.17
F5	29.24 ±0.76	0.30 ±0.011	0.353 ±0.021	15.08 ±1.38	1.09±0.12
F6	29.53 ±0.50	0.31 ±0.015	0.367 ±0.006	15.44 ±1.35	1.10±0.19
F7	28.95 ±0.50	0.31 ±0.021	0.37 ±0.01	16.18 ±2.26	1.08±0.21
F8	28.88 ±0.62	0.343 ±0.011	0.42 ±0.011	18.25 ±2.75	1.09±0.18
F9	28.46 ±0.51	0.333 ±0.006	0.403 ±0.006	18.53 ±1.78	1.10±0.19

All values are presented as Mean ±S.D

Post-compression parameters

The prepared tablet formulations were also evaluated for various post compression parameters which includes weight variation, hardness, and friability, thickness, and the drug release studies in 0.1 N Hcl for 2 hours followed by pH 6.8 Phosphate buffer up to 12 hours. The post-compression parameters evaluated were presented in table 5.

Table 5: Post compression parameters for tablets

Formulation codes	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	118.58±0.45	2.54±0.30	0.36±0.16	1.12±0.01	99.12±0.32
F2	119.76±0.54	2.43±0.42	0.31±0.16	1.15±0.05	98.44±0.33
F3	117.31±0.32	2.51±0.33	0.28±0.16	1.36±0.09	99.36±0.45
F4	119.11±0.43	2.49±0.51	0.33±0.16	1.23±0.03	97.72±0.52
F5	120.22±0.17	2.42±0.49	0.25±0.16	1.11±0.02	99.84±0.17

F6	121.33±0.45	2.55±0.21	0.29±0.16	1.19±0.04	98.57±0.16
F7	119.48±0.36	2.63±0.37	0.32±0.16	1.24±0.05	97.33±0.27
F8	123.65±0.39	2.47±0.26	0.39±0.16	1.33±0.04	99.17±0.38
F9	118.04±0.33	2.58±0.31	0.34±0.16	1.28±0.03	99.23±0.23

All values are presented as Mean ±S.D

All the parameters such as weight variation, friability, hardness, thickness and drug content were found within the limits.

In - Vitro Drug Release Studies

The drug release studies which were conducted and release of the drug from formulation containing HPMCK 100M are represented in table.6/figure 7. Drug release studies were conducted and the release of drug from formulations containing Eudragit RS PO is represented in table.7/ figure 8. The release of drug form formulation containing Ethyl cellulose is represented in table.8/ figure 9.

Table 6: Dissolution Data of Levamisole Tablets Prepared With HPMC K100M

Time (hours)	F1	F2	F3
0	**0**	**0**	**0**
0.5	5.11	8.14	10.57
1	12.05	14.67	16.81
2	18.71	21.44	23.23
3	26.36	29.31	33.62
4	32.67	35.42	37.04
5	41.33	46.64	48.38
6	49.56	52.17	55.14
7	58.45	59.72	63.25
8	65.78	67.49	69.72
9	72.43	74.23	76.36

10	78.54	81.92	83.45
11	83.73	85.09	87.03
12	86.83	89.22	92.61

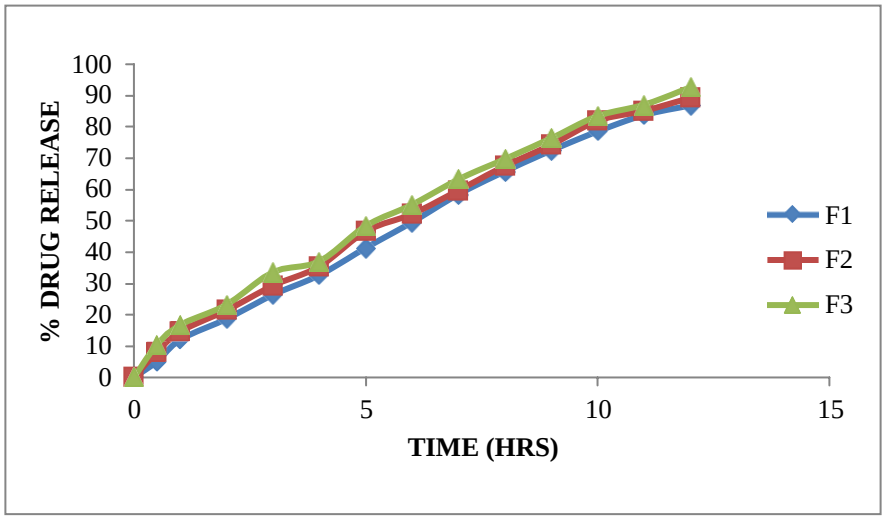

Figure 7: Dissolution profile of Levamisole (F1, F2, and F3 formulations).

Table 7: Dissolution Data of Levamisole Tablets Prepared With Eudragit RS PO

Time (hours)	F4	F5	F6
0	0	0	0
0.5	13.08	15.19	17.27
1	19.77	22.11	21.38
2	26.14	28.64	25.45
3	38.48	43.22	39.62
4	42.11	46.78	44.73
5	49.06	53.07	51.28
6	57.15	61.31	59.17
7	65.66	69.55	67.83

8	72.34	77.47	75.54
9	78.81	82.36	79.49
10	85.25	88.24	86.37
11	91.44	94.82	92.91
12	95.39	99.89	97.79

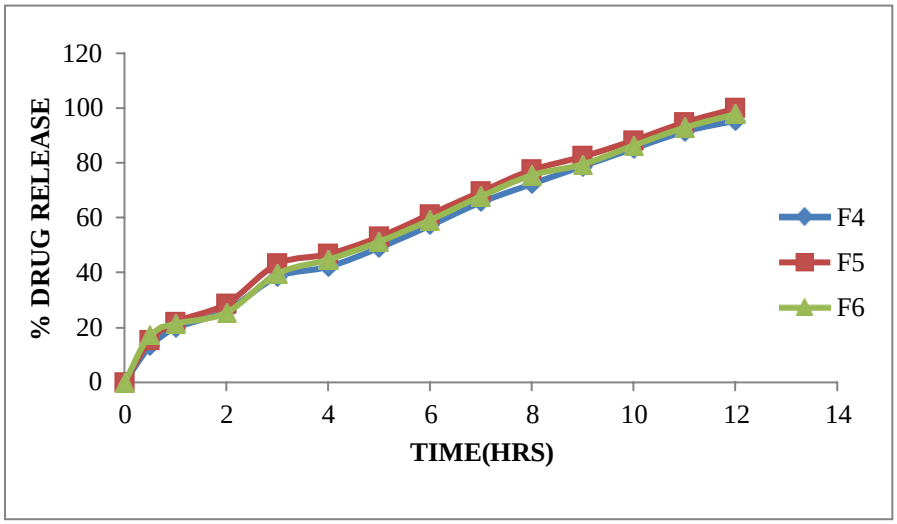

Figure 8: Dissolution profile of Levamisole (F4, F5, and F6formulations)

Table 8: Dissolution Data of Levamisole Tablets Prepared with Ethyl cellulose

Time (hours)	**F7**	**F8**	**F9**
0	0	0	**0**
0.5	16.25	14.91	8.17
1	18.49	16.73	12.37
2	24.11	22.04	19.28
3	35.29	31.73	27.66
4	41.56	39.69	35.43

5	47.83	44.74	41.16
6	58.73	56.89	53.82
7	64.15	61.88	57.41
8	73.26	69.64	64.06
9	78.33	75.37	71.75
10	84.41	82.69	76.23
11	89.64	85.76	82.68
12	94.59	91.09	89.49

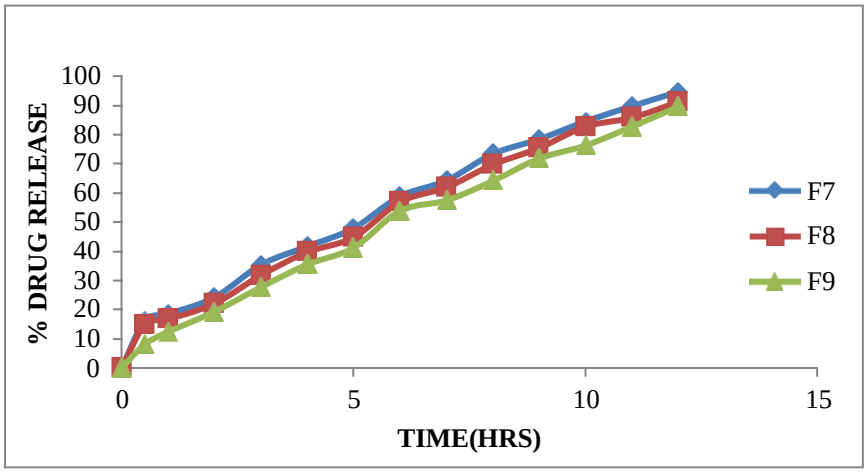

Figure 9: Dissolution profile of Levamisole (F7, F8 and F9 formulations)

From the dissolution data it was evident that the formulations prepared with HPMCK100M as polymer were able to retard the drug release up to desired time period i.e., 12 hours. The formulations prepared with Ethyl cellulose were able retarded the drug release, while the formulations manufactured using Eudragit RS PO retarded the release of drug at the concentration of 20mg levels which is indicated in F5 Formulation that presented essential drug release pattern i.e., it retarded drug release up to time period of 12 hours and displayed maximum of 99.89 % in 12 hours with good retardation. From the above results it was evident that the formulation F5 is best formulation with desired drug release pattern extended up to 12 hours.

Application of Release Rate Kinetics to Dissolution Data:

To analyse the mechanism of the drug release rate kinetics of the dosage form, the obtained data of the optimized formulation was fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model and the graphs are represented in figure 10/11/12/13, respectively. From the graphs it was evident that the optimized formulation F5 follows Zero order release kinetics.

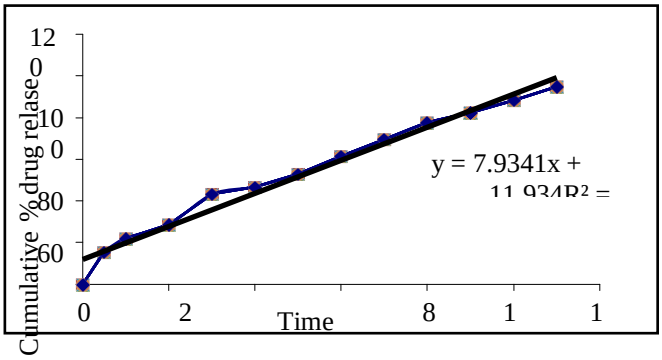

Figure 10: Zero order release kinetics graph

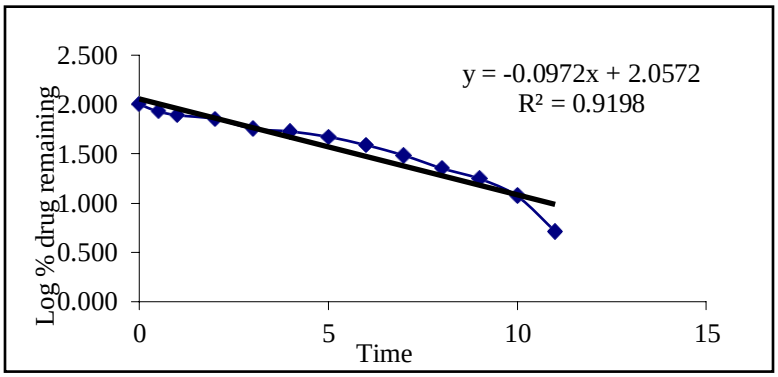

Figure 11: First order release kinetics

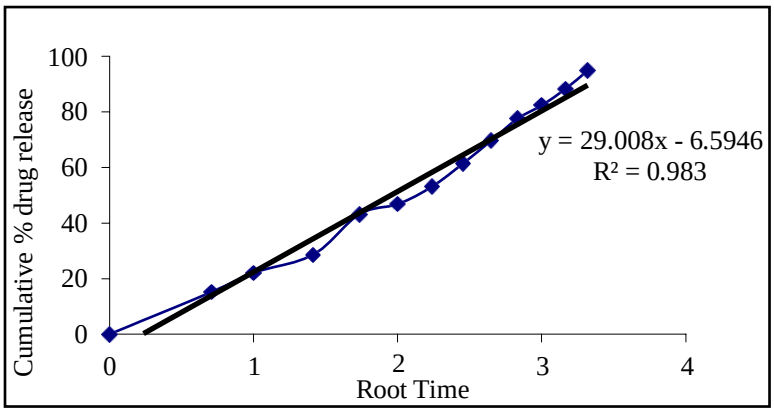

Figure 12: Higuchi release kinetics

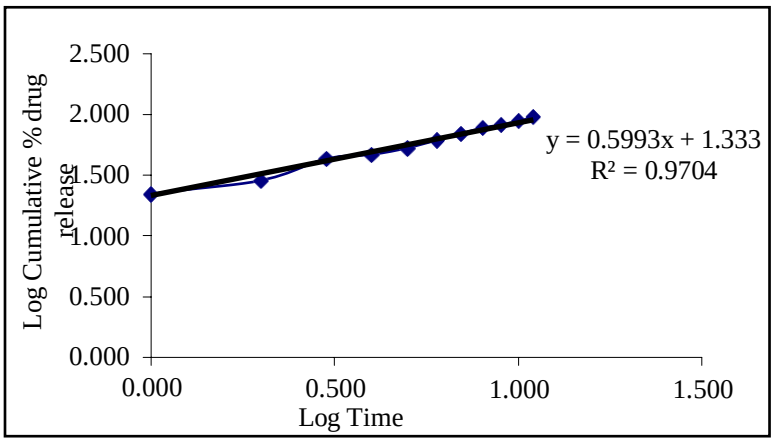

Figure 13: Korsmeyer- Peppas

CONCLUSION

Levamisole is an Anti-helminthic drug used for treatment of conditions like Parasitic Infections. Therefore the present investigation was concerned with formulating controlled release Levamisole tablets which helps in prolonging the duration of action after the oral administration. Various formulations were developed by using drug release rate retarding and controlling polymers like HPMC K100M, Eudragit RS PO and Ethyl cellulose by direct compression method. Thus we conclude that among all the developed formulations F5 formulation controlled the drug release for longer period of time for 12hrs, when compared to other formulation prepared with different polymers, So F5 was selected as a best formulation and the drug release kinetics of F5 exhibited zero order release which indicates the objective of present study to be fulfilled and agreeable in formulating Levamisole controlled release tablets.

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