FORMULATION AND IN VITRO EVALUATION OF EXTENDED RELEASE MATRIX TABLETS OF LEVOSULPIRIDE BY USING NATURAL POLYMERS

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RESEARCH ARTICLE

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DOI: https://doi.org/10.22270/ijdra.v5i2.200

ABSTRACT

The aim of the present study was to develop sustained release formulation of Levosulpiride to maintain constant therapeutic levels of the drug for over 12 hrs. By using various Natural polymers like Fenugreek, Almond gum and Tamarind gum were employed as polymers. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F8) showed better and desired drug release pattern i.e., 99.81% in 12hours. It contains the Fenugreek 1:1.5 ratio as sustained release material. It followed zero order kinetics.

Keywords: Levosulpiride, Extended release system, Natural Polymers.

INTRODUCTION

Extended release formulations make the drug available over extended time period after oral administration. The extended release product will optimize therapeutic effect and safety of a drug at the same time improving the patient convenience and compliance. By incorporating the dose for 24 hrs into one tablet/capsule from which the drug is released slowly. (1) This formulation helps to avoid the side effects associated with low and high concentrations. The ideal drug delivery system should show a constant zero-order release rate and maintain the constant plasma concentrations.

Advantages (2-7)

Extended release products having many advantages.

- The extended release formulations may maintain therapeutic concentrations over prolonged periods.
- The use of extended release formulations avoids the high blood concentration.
- Extended release formulations have the potential to improve the patient compliance.
- Reduce the toxicity by slowing drug absorption.
- Increase the stability by protecting the drug from hydrolysis or other degradative changes in gastrointestinal tract.
- Minimize the local and systemic side effects.
- Improvement in treatment efficacy.
- Minimize drug accumulation with chronic dosing.
- Usage of less total drug.
- Improvement the bioavailability of some drugs.
- Improvement of the ability to provide special effects.

Drug properties, which are suitable for extended release formulation (8-10)

Physiochemical Properties of the drug

- Aqueous solubility: (>0.1mg/ml)
- Partition co-efficient: (1000:1 octanol: water system)
- Drug stability *in vivo*: (High enough, so drug remain stable during release from system)
- Protein binding: (Drug with high protein binding will not required release modification)
- Drug pKa & ionization at physiological pH:

(pKa for acidic API= 3.0 - 7.5, pKa for Basic API = 7.0 - 11.0)
- Mechanisms and sites of absorption: (Mechanism of absorption should not be active type and absorption window should not be narrow)
- Molecular size and diffusivity: (Molecule size should be small (100-400 D so it can be easily diffused through polymer matrix)
- Dose size: (<300mg)

Biological Properties of Drug.

- Distribution: (A.P.I. with large volume of distribution is not suitable).
- Metabolism: (A.P.I. should be metabolized with intermediate speed).
- Half-life of drug: (2 - 8 hrs).
- Margin of safety: (High enough so dose dumping does not cause any serious side effect).
- Plasma concentration response relationship: (A.P.I. having linear relationship is better candidate).

Design and fabrication of extended release system

Monolithic as oral extended release drug delivery system

Monolithic ER formulations are defined as single unit formulations from which the drug release is controlled over certain period of time. According to the mechanism of drug release, monolithic extended release formulations are classified to:

A) Diffusion controlled extended release formulations

The release of the drug is controlled predominantly by its diffusion through a water insoluble polymeric layer. Drug dissolution also contributes to the release of the drug but to a lesser extent.

Reservoir system (11-15)

Extended release formulations where film coating constitutes the main factor in controlling drug release. The first application involved the use of pan-coating process to apply various mixtures of fats and waxes to drug-loaded pellets. Since then, a variety of coating materials and coating machines have been developed and modified.e.g. Hardened gelatin, Methyl or ethyl cellulose, Polyhydroxymethacrylate, Methacrylate ester copolymers, Various waxes. Ethyl cellulose and methacrylate ester copolymers are the most commonly used systems in the pharmaceutical industry.

Matrix system

Extended release formulations in which the drug is uniformly distributed through the release controlling element. Two major types of materials are used in the pharmaceutical industry to control the drug release from matrix devices; insoluble plastics and fatty compounds.

E.g.; Insoluble plastics:

Methylacrylatemethyl methacrylate copolymers, polyvinyl chloride, Polyethylene. Fatty compounds: Carnuba wax and Glyceryl tristearate.

PURPOSE OF THE STUDY

The Oral route of administration still continues to be the most preferred route due to its manifold advantages including ease of ingestion, pain avoidance, versatility , and most importantly patient compliance. The most popular dosage forms being tablets and capsules.

When conventional dosage forms are taken on schedule and more than once daily, leads to fluctuations in plasma drug concentration and doses may be missed. To overcome this, Extended/sustained release formulations have been designed. These have advantages such as reduced blood level fluctuations; reduction in dosing frequency, enhanced patient convenience and compliance, reduction in adverse side effects and reduction in overall health care costs.

This system is commonly used to manufacturing of prolonged release dosage forms because it makes such manufacturing easy. In the last two decades, Extended/sustained release dosage forms have made significant progress in terms of clinical efficacy and patient compliance. Preparation of drug embedded matrix tablets that involves the direct compression of a blend of drug, retarding material and additives is one

of the least complicated approaches for delivering drug in a temporal pattern into the systemic circulation. The matrix system is only used for manufacturing sustained release dosage forms because it makes such manufacturing easy.

Aim

The Aim of the present work is to formulate and evaluate the Levosulpiride Extended release tablets using natural polymers such as Tamarind gum, Almond gum, and Fenugreek.

Objective

The objective of this present study is to reduce the dosing frequency of Levosulpiride So prepared Extended release dosage form for prolong its duration of action, and reduced side effects.

PLAN OF WORK

- Literature Review
- Selection of drug and polymers
- Construction of standard graph
- Drug and Excipients compatibility studies
- Formulation and development of Sustained release tablets of Levosulpiride using natural polymers.
- Evaluation parameters
- Pre compression parameters
    - Angle of repose
    - Bulk density
    - Tapped density
    - Powder flow Properties
- Post compression parameters
    - Thickness
    - Hardness
    - Friability
    - Uniformity of weight
    - Drug content
    - *In vitro* dissolution studies
- Optimization of Sustained release formulations.
- Applied release kinetics to optimized formulation.

METHODOLOGY

Analytical method development:

Determination of absorption maxima

100mg of Levosulpiride pure drug was dissolved in 15ml of Methanol and make up to 100ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with100ml by using 0.1 N HCL (stock solution-2 i.e 100µg/ml). Scan the 100µg/ml using Double beam UV/VIS spectrophotometer in the range of 200 – 400 nm.

Preparation calibration curve

100mg of Levosulpiride pure drug was dissolved in 15ml of Methanol and volume make up to 100ml with 0.1N HCL (stock solution-1). 10ml of above solution was taken and make up with100ml by using 0.1 N HCl (stock solution-2 i.e 100µg/ml). From this take 2, 4, 6, 8 and 10 ml of solution and make up to 10ml with 0.1N HCl to obtain 20, 40, 60, 80 and 100 µg/ml of Levosulpiride per ml of solution. The absorbance of the above dilutions was measured at 282nm by using UV-Spectrophotometer 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. The above procedure was repeated by using pH 6.8 phosphate buffer solutions.

Drug – Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy

Drug excipient interaction studies are significant for the successful formulation of every dosage form. Fourier Transform Infrared (FTIR) Spectroscopy studies were used for the assessment of physicochemical compatibility and interactions, which helps in the prediction of interaction between drug and other excipients. In the current study 1:1 ratio was used for preparation of physical mixtures used for analyzing of compatibility studies. FT-IR studies were carried out with a Bruker, ATR FTIR facility using direct sample technique.

Formulation development of Sustained release Tablets

All the formulations were prepared by Wet granulation method. The compositions of

different formulations are given in Table. The tablets were prepared as per the procedure given below and aim is to extended release of Levosulpiride.

Procedure

- Levosulpiride and all other ingredients except Mg stearate and talc were individually passed through sieve no ≠ 40.
- Levosulpiride, MCC, mix thoroughly than add the solution contain gum/polymer mix properly up to 15 min.
- Dry the above mixture at 65-70^{o}C by using dryer.
- After completion of drying the mixture is passed through sieve no ≠ 22.
- The powder mixture was lubricated with Mg stearate and Talc.
- Finally go for compression.

Table 1: Formulation of Sustained release tablets

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Levosulpiride	50	50	50	50	50	50	50	50	50
Tamarind gum	50	75	100	-	-	-	-	-	-
Almond gum	-	-	-	50	75	100	-	-	-
Fenugreek	-	-	-	-	-	-	50	75	100
MCC 102	95	70	45	95	70	45	95	70	45
Mg.stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Aerosil	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total Wt	200	200	200	200	200	200	200	200	200

Evaluation Parameters

Pre Compression parameters

Bulk density (D_B)

Bulk density is the ratio between a given mass of the powder and its bulk volume.

Bulk density = Mass of Powder / Bulk volume of the powder

Bulk density (D_B) = W /V_0

Procedure: An accurately weighed quantity of granules (w) (which was previously passed through sieve No: 40) was carefully transferred into 250 ml measuring cylinder and measure the bulk volume.

Tapped Density (D_T)

Tapped density is the ratio between a given mass of powder (or) granules and the constant (or) fixed volume of powder or granules after tapping.

Tapped density = mass of the powder/ tapped volume

Procedure: An accurately weighed quantity of granules (w) (which was previously passed through sieve No: 40) was carefully transferred into 250 ml measuring cylinder and the cylinder was tapped on a wooden surface from the height of 2.5 cm at two second intervals. The tapping was continued until no further change in volume (until a constant volume) was obtained (V_f). The tapped density was calculated by using the formula

Tapped density (D_T)=W/V_f

Hausner's ratio

Hausner's ratio is an indirect index of ease of powder flow and was calculated by the formula,

Hausner'sratio = D_T/D_B

Where, D_T is the tapped density

D_B is the bulk density

Compressibility index

Compressibility index (CI) was determined by measuring the initial volume (V_o) and final volume (V_f) after hundred tapping's of a sample in a measuring cylinder. It indicates the powder flow properties and expressed in terms of percentage and given in table no. 14 and calculated by using the formula

% Compressibility index = V_o - V/V_o x 100

Angle of repose

Angle of repose was measured by fixed funnel method. It determines flow property of the powder. It is defined as maximum angle formed between the surface of the pile of powder and the horizontal plane.

The powder was allowed to flow through the funnel fixed to a stand at definite height (h). By measuring the height and radius of the heap of powder formed (r), angle of repose was calculated by using formula given below and the calculated values obtained was shown in table no. 14

$$\theta = \tan^{-1} (h / r)$$

Where, θ is the angle of repose

h is the height in cm

r is the radius in cm

Flow property

Table 2: The flow property of powder blend

Flow property	Angle of repose	Compressibility index (%)	Hausner's ratio
Excellent	25-30	<10	1.00-1.11
Good	31-35	11-15	1.12-1.18
Fair	36-40	16-20	1.19-1.25
Passable	41-45	21-25	1.26-1.34
Poor	46-55	26-31	1.35-1.45
Very poor	56-65	32-37	1.46-1.59
Very very poor	>66	>38	>1.60

Post Compression parameters

Weight variation test

Twenty tablets were randomly selected and weighed, to estimate the average weight and that were compared with individual tablet weight. The percentage weight variation was calculated as per Indian Pharmacopoeial Specification. Tablets with an average weight 250 mg so the % deviation was ±5 %.

Table 3: IP standards of uniformity of weight

S. No.	Average weight of tablet	% of deviation
1	≤ 80 mg	10
2	> 80 mg to <250 mg	7.5
3	≥ 250 mg	5

Friability test

Twenty tablets were weighed and subjected to drum of friability test apparatus. The drum rotated at a speed of 25 rpm. The friabilator was operated for 4 minutes and reweighed the tablets. % loss(F) was calculated by the following formula.

F =100 (W0-W)/W0

Where W0 = Initial weight, W = Final weight

Hardness test

The hardness of tablets was measured by using Monsanto hardness tester. The results were complies with IP specification.

Thickness test

The rule of physical dimension of the tablets such as sizes and thickness is necessary for consumer acceptance and maintain tablet uniformity. The dimensional specifications were measured by using screw gauge. The thickness of the tablet is mostly related to the tablet

hardness can be used as initial control parameter.

Drug content

The amount of drug in tablet was important for to monitor from tablet to tablet, and batch to batch is to evaluate for efficacy of tablets. For this test, take ten tablets from each batch were weighed and powdered. Weighed equivalent to the average weight of the tablet powder and transferred into a 100 ml volumetric flask and dissolved in a suitable quantity of media. The solution was made up to the mark and mixed well. Then filter the solution. A portion of the filtrate sample was analyzed by UV spectrophotometer.

Table 4: *In vitro* drug release studies

Apparatus: USP-II, Paddle Method
Dissolution Medium: 0.1 N HCl , pH 6.8 Phophate buffer
RPM: 50
Sampling intervals (hrs):1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12.
Temperature 37°c $\pm$ 0.5°c

Procedure

900 ml of 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The media 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. Then 0.1 N HCl was replaced with pH 6.8 phosphate buffer and process was continued upto 12 hrs at 50 rpm. At specific time intervals, withdrawn 5 ml of sample and again 5ml media was added to maintain the sink condition. Withdrawn samples were analyzed at 282nm wavelength of drug using UV-spectrophotometer.

Application of Release Rate Kinetics to Dissolution Data

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics

To study the zero–order release kinetics the release rate data ar e fitted to the following equation.

$$\mathbf{F = K_o\, t}$$

Where, 'F' is the drug release at time't', and 'K_o' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation

$$\mathbf{Log\ (100\text{-}F) = kt}$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$\mathbf{F = k\ t1/2}$$

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model:

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$\mathbf{M_t/\ M_\infty = K\ t^n}$$

Where, M_t/ M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for supercase II transport, n > 1. In this model, a plot of log (M_t/ M_∞) versus log (time) is linear.

RESULTS AND DISCUSSION

The present work was designed to developing

solid dispersion Extended tablets of Levosulpiride using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Analytical Method

Standard graph of Levosulpiride in 0.1N HCl

The scanning of the 100µg/ml solution of Levosulpiride in the ultraviolet range (200-400nm) against 0.1 N HCl the maximum peak observed at λ_{max} as 282 nm. The standard concentrations of Levosulpiride (20-100 µg/ml) was prepared in 0.1N HCl showed good linearity with R^2 value of 0.999, which suggests that it obeys the Beer-Lamberts law.

Table 5: Standard curve of Levosulpiride in 0.1N HCl

Concentration (µg/ ml)	Absorbance
0	0
20	0.172
40	0.331
60	0.478
80	0.631
100	0.804

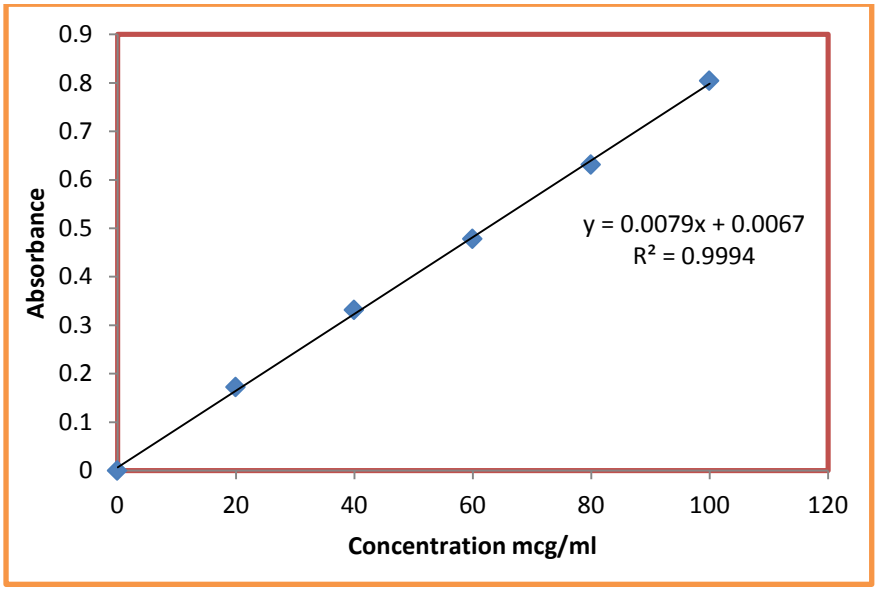

Figure 1: Calibration curve of Levosulpiride in 0.1 N HCl at 282 nm

Standard Curve of Levosulpiride in Phosphate buffer pH 6.8

The scanning of the 100µg/ml solution of Levosulpiride in the ultraviolet range (200-400nm) against 6.8 pH phosphate the maximum peak observed at the λ_{max} as 282 nm. The standard concentrations of Levosulpiride (20-100µg/ml) prepared in 6.8 pH phosphate buffer showed good linearity with R^2 value of 0.999, which suggests that it obeys the Beer-Lamberts law

FTIR study

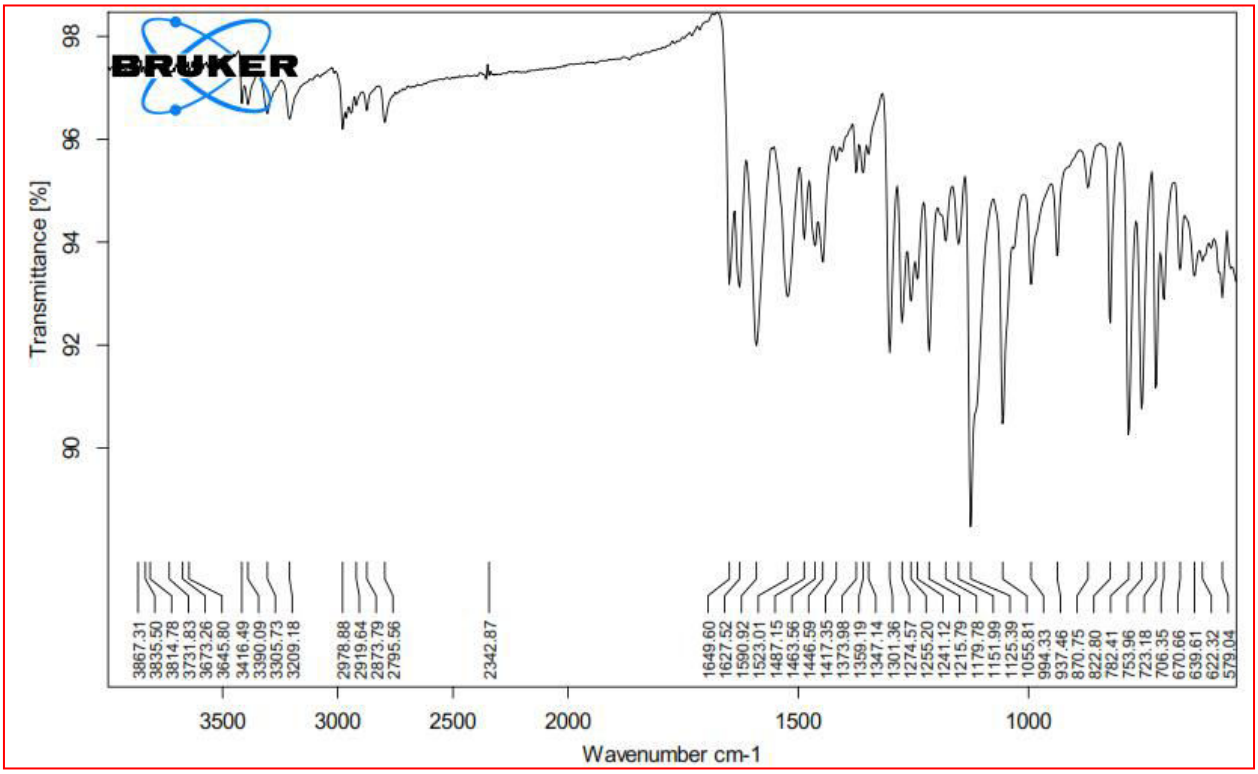

Figure 2: FTIR graph of pure drug

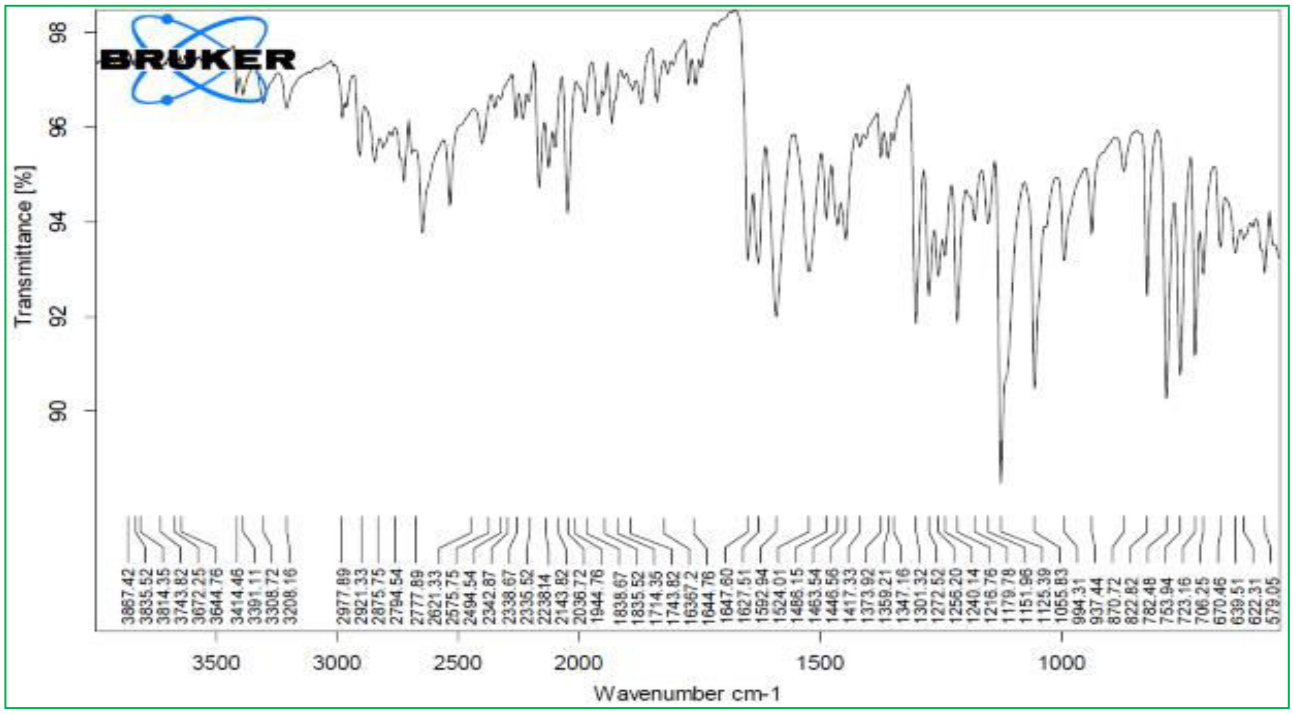

Figure 3: FTIR graph of optimized formulation

From the FTIR data it was evident that the drug and excipients doses not have any interactions. Hence they were compatible.

EVALUATION PARAMETERS

Pre-compression parameters

Table 6: Pre-compression parameters of powder blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25.41 ±0.65	0.52 ±0.091	0.59 ±0.064	14.33 ±0.21	1.19 ±0.022
F2	26.08 ± 0.51	0.55 ± 0.011	0.62 ± 0.06	11.29 ± 0.35	1.12 ± 0.023
F3	24.15 ± 0.58	0.49 ± 0.01	0.56 ± 0.08	12.5 ± 0.21	1.14 ± 0.012
F4	27.61 ± 0.63	0.53 ± 0.09	0.61 ± 0.071	13.1 ± 0.15	1.15 ± 0.021
F5	25.46 ± 0.57	0.55 ± 0.08	0.62 ± 0.011	11.29 ± 0.57	1.12 ± 0.015
F6	27.26 ± 0.56	0.52 ± 0.055	0.59 ± 0.08	11.86 ± 0.57	1.13 ± 0.026
F7	28.38 ± 0.56	0.47 ± 0.08	0.54 ± 0.01	12.96 ± 0.42	1.14 ± 0.031
F8	26.43 ±0.62	0.55± 0.08	0.64 ± 0.022	10.21 ± 0.12	1.12 ± 0.056
F9	25.25 ±0.52	0.43 ±0.022	0.61 ±0.033	11.20 ±0.03	1.10 ±0.06

Tablet powder blend was subjected to various pre-compression parameters. The angle of repose values was showed from 25 to 30; it indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.43±0.03 to 0.55 ± 0.08 (gm/cm3) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.54 ± 0.01to 0.64 ± 0.022showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging from 10.21 ± 0.12to 14.33 ±0.21which showed that the powder has good flow properties. All the formulations were showed the hausner ratio ranging from 0 to 1.19 indicating the powder has good flow properties.

Post Compression Parameters For tablets

Table 7: Post Compression Parameters of Tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	201.3 ±0.11	5.1±0.03	0.52±0.03	3.4±0.05	100.2 ± 0.17
F2	199.6 ± 0.55	4.8 ± 0.02	0.561±0.03	3.2 ±0.02	98.3 ± 0.22
F3	203.5 ± 0.98	4.2±0.09	0.48±0.08	3.6 ±0.09	98.3 ± 0.20
F4	200.4±1.61	4.6±0.01	0.45±0.02	3.7±0.04	101.2 ± 0.18
F5	202.5 ± 0.73	4.8±0.04	0.55±0.07	3.3 ±0.05	102.1 ± 012
F6	203.2 ± 1.35	4.4±0.01	0.45±0.02	3.6±0.06	99.2 ± 0.15
F7	199.5 ± 0.95	4.6±0.07	0.51±0.04	3.6±0.04	102.3 ± 0.28
F8	202.26 ± 0.81	4.7±0.01	0.55±0.02	3.4 ±0.05	102.1 ± 0.21
F9	201.36 ± 1.17	4.4±0.04	0.58±0.04	3.2±0.08	97.2 ± 0.19

Weight variation and thickness

All the formulations were evaluated for uniformity of weight using electronic weighing balance and the results are shown in table 9.5. The average tablet weight of all the formulations was found to be between 199.5 ± 0.95 to 203.2 ± 1.35**.** The maximum allowed percentage weight variation for tablets weighing >250 mg is 5% and no formulations are not exceeding this limit. Thus all the formulations were found to comply with the standards given in I.P. And thickness of all the formulations was also complying with the standards that were found to be between 3.2 ±0.02 to 3.7±0.04.

Hardness and friability

All the formulations were evaluated for their hardness, using monsanto hardness tester and the results are shown in table 9.5. The average hardness for all the formulations was found to be between (4.2±0.09 **to** 5.1±0.03) Kg/cm^2 which was found to be acceptable.

Friability was determined to estimate the ability of the tablets to withstand the abrasion during packing, handling and transporting. All the formulations were evaluated for their percentage friability using Roche friabilator and the results were shown in table 9.5. The average percentage friability for all the formulations was between 0.45±0.02 and 0.58±0.04, which was found to be within the limit.

Drug content: All the formulations were evaluated for drug content according to the procedure described in methodology section and the results were shown in table 9.5. The drug content values for all the formulations were found to be in the range of (97.2 ± 0.19 **to** 102.3 ± 0.28)**.** According to IP standards the tablets must contain not less than 95% and not more than 105% of the stated amount of the drug. Thus, all the FDT formulations comply with the standards given in IP.

***In Vitro* Drug Release Studies (16-20)**

The formulations prepared with different polymers by direct compression method. The tablets dissolution study was carried out in paddle dissolution apparatus using 0.1N HCl for 2 hours and 6.8 pH phosphate buffers for remaining hours as a dissolution medium.

Table 8: Dissolution Data of Levosulpiride Tablets Prepared with Natural Polymer

Tamarind gum

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED		
	F1	F2	F3
0	0	0	0
1	28.06	25.51	22.18
2	36.10	34.03	31.03
3	49.54	43.68	39.58
4	55.65	51.79	48.55
5	67.44	59.04	54.23
6	78.86	68.19	63.14
7	84.33	76.37	69.11
8	91.65	84.8	76.85
9	99.39	96.6	84.25
10		99.86	93.14
11			100.2
12			

The % drug release of formulations (F1 to F3) containing Tamarind gum depends on the concentration of polymer. The concentration of Tamarind gum contains F1 and F2 was unable to retard the drug release up to desired time. When the concentration of polymer contain 100mg was able to retard the drug up to 11 hours. In F3 formulation 1:2 ratio (drug: polymer) concentration was used, showed maximum % drug release up to 11 hours i.e., 100.2%.

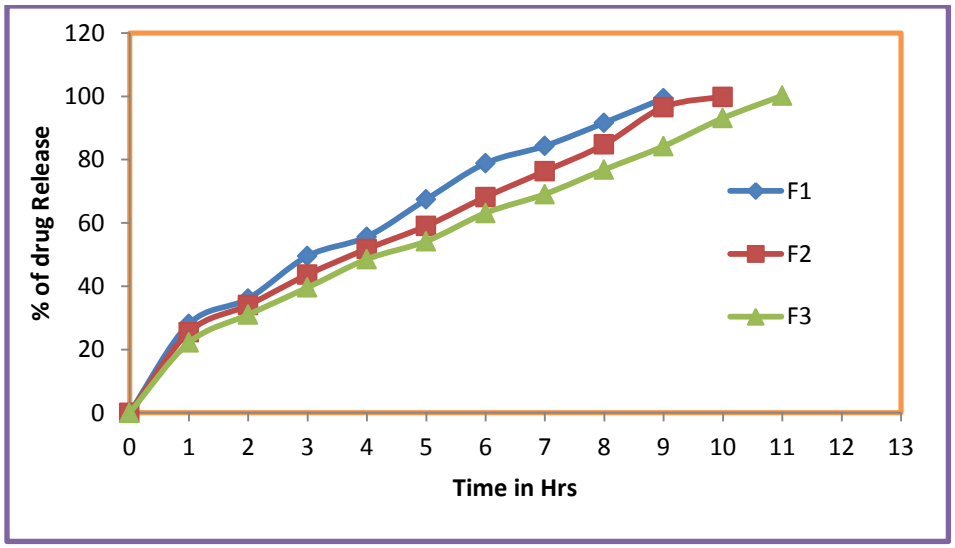

Figure 4: Dissolution study of Levosulpiride Extended tablets (F1 to F3)

Table 9: Dissolution Data of Levosulpiride Tablets Prepared With Natural Polymer Almond gum

TIME (hr)	Cumulative percent drug released		
	F4	F5	F6
0	0	0	0
1	36.33	32.66	29.36
2	48.74	45.68	37.38
3	56.95	51.33	47.63
4	64.66	59.75	53.86
5	78.54	68.55	62.33
6	84.75	76.91	71.57
7	93.86	86.11	80.01
8	99.75	94.21	87.91
9		99.2	92.3
10			97.2
11			99.3
12			

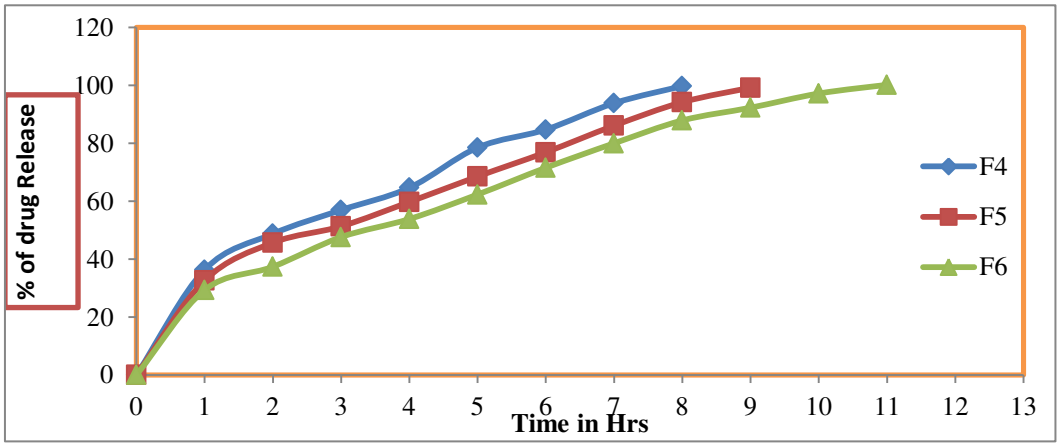

Figure 5: Dissolution study of Levosulpiride tablets (F4 to F6)

The % drug release of F4 to F6 formulations depends on ratio of polymer in the solution. The concentration of Almond gum was unable to retard the drug release up to desired time. When the concentration of polymer increased in F6 drug polymer ratio is 1:2 showed maximum % drug release i.e 99.3% at 11 hours.

Table 10: Dissolution Data of Levosulpiride by using Natural Polymer

Fenugreek Mucilage

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASED		
	F7	F8	F9
0	0	0	0
1	27.61	22.63	19.36
2	34.55	29.32	24.31
3	42.51	36.31	31.96
4	49.62	42.22	42.84
5	55.35	51.32	49.24
6	64.85	59.95	57.84
7	71.16	68.81	62.75
8	80.60	75.23	68.91
9	87.33	79.58	72.13
10	92.36	86.22	78.74
11	99.8	92.33	84.11
12		99.81	92.26

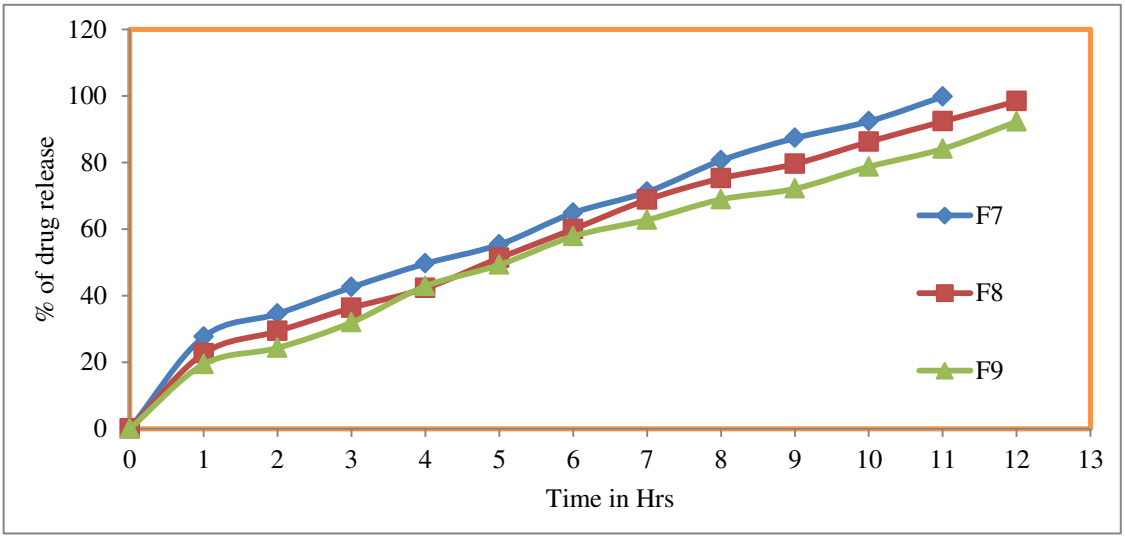

Figure 6: Dissolution study of Levosulpiride by using Natural Polymer

Fenugreek Mucilage

The % drug release of F6 to F9 formulations depends on polymer ratio Fenugreek Mucilage. The concentration of Natural Fenugreek Mucilage 1:1 was unable to retard the drug release up to desired time. In F7 formulations, Fenugreek Mucilage contain 1:1.5 ratio showed maximum % drug release i.e 99.81% at 12 hours. When the Fenugreek Mucilage 1:2 ratio was more retardation, maximum drug release was showed after 12 hours.

Hence based on dissolution data of 9 formulations, F8 formulation showed better release up to 12 hours. So F8 formulation is optimised formulation.

Application of Release Rate Kinetics to Dissolution Data (21-26)

Data of *in vitro* release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of Levosulpiride release from extended tablets. The data was fitted into various kinetic models such as zero, first order kinetics; higuchi and korsmeyer peppas mechanisms and the results were shown in below table

Table 11: Release kinetics data for optimized formulation (F8)

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	% Drug Remaining
0	**0**	0			2.000		100
22.63	**1**	1.000	1.355	0.000	1.889	22.630	77.37
29.32	**2**	1.414	1.467	0.301	1.849	14.660	70.68
36.31	**3**	1.732	1.560	0.477	1.804	12.103	63.69
42.22	**4**	2.000	1.626	0.602	1.762	10.555	57.78
51.32	**5**	2.236	1.710	0.699	1.687	10.264	48.68
59.95	**6**	2.449	1.778	0.778	1.603	9.992	40.05
68.81	**7**	2.646	1.838	0.845	1.494	9.830	31.19
75.23	**8**	2.828	1.876	0.903	1.394	9.404	24.77
79.58	**9**	3.000	1.901	0.954	1.310	8.842	20.42
86.22	**10**	3.162	1.936	1.000	1.139	8.622	13.78
92.33	**11**	3.317	1.965	1.041	0.885	8.394	7.67
99.81	**12**	3.464	1.993	1.079	0.201	8.201	1.59

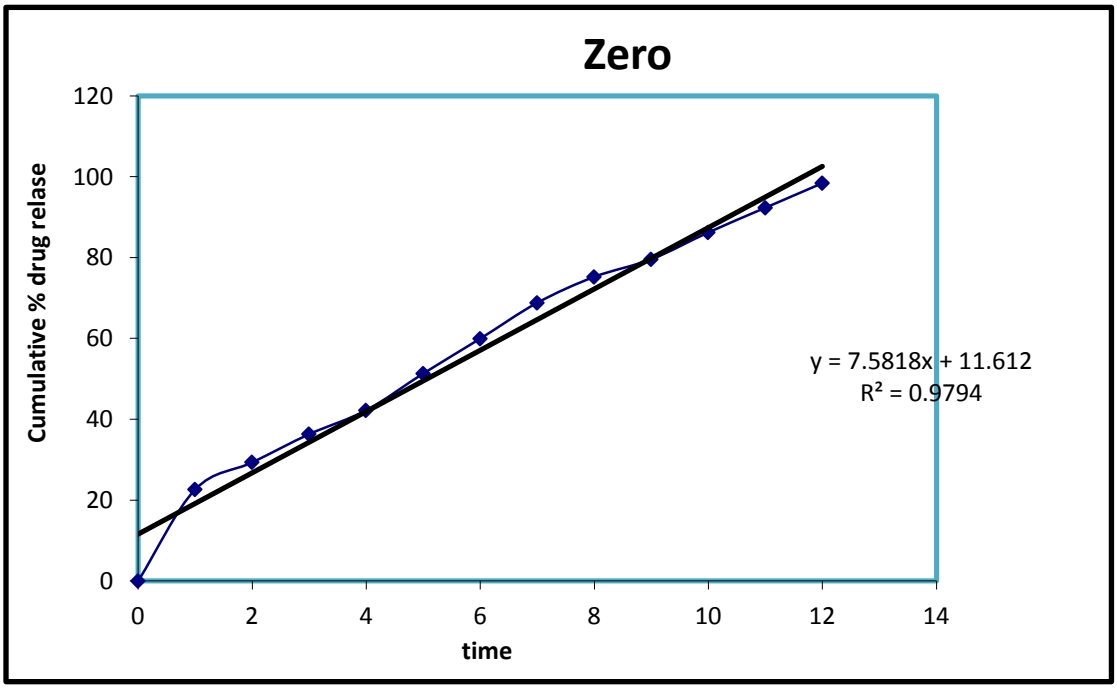

Figure 7: Graph of zero order kinetics

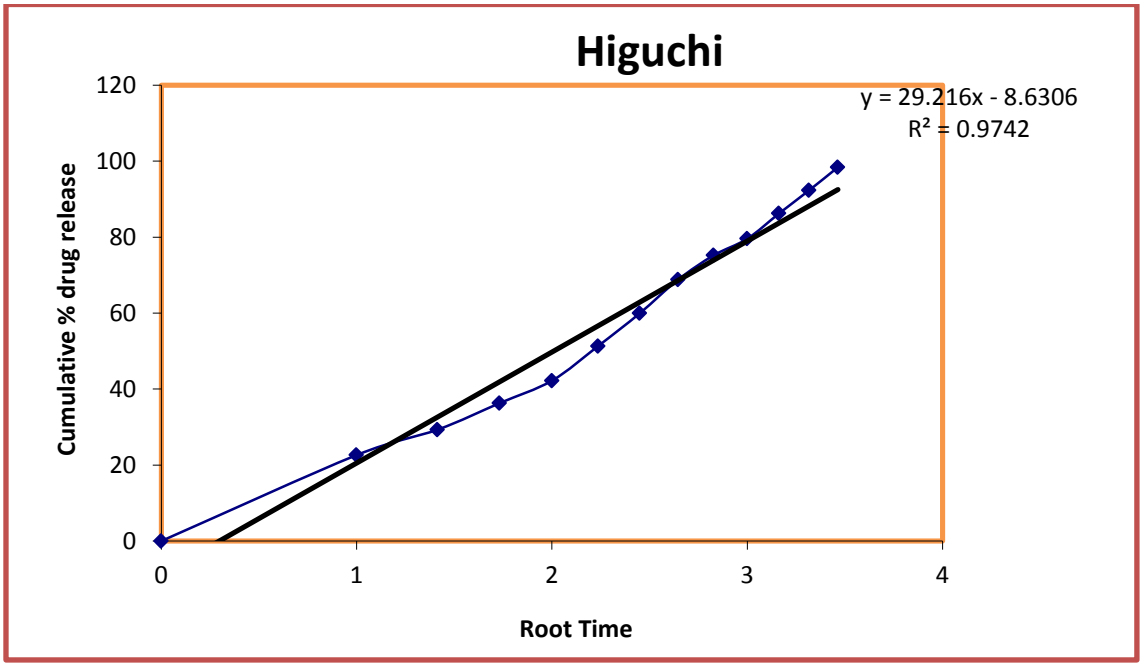

Figure 8: Graph of higuchi release kinetics

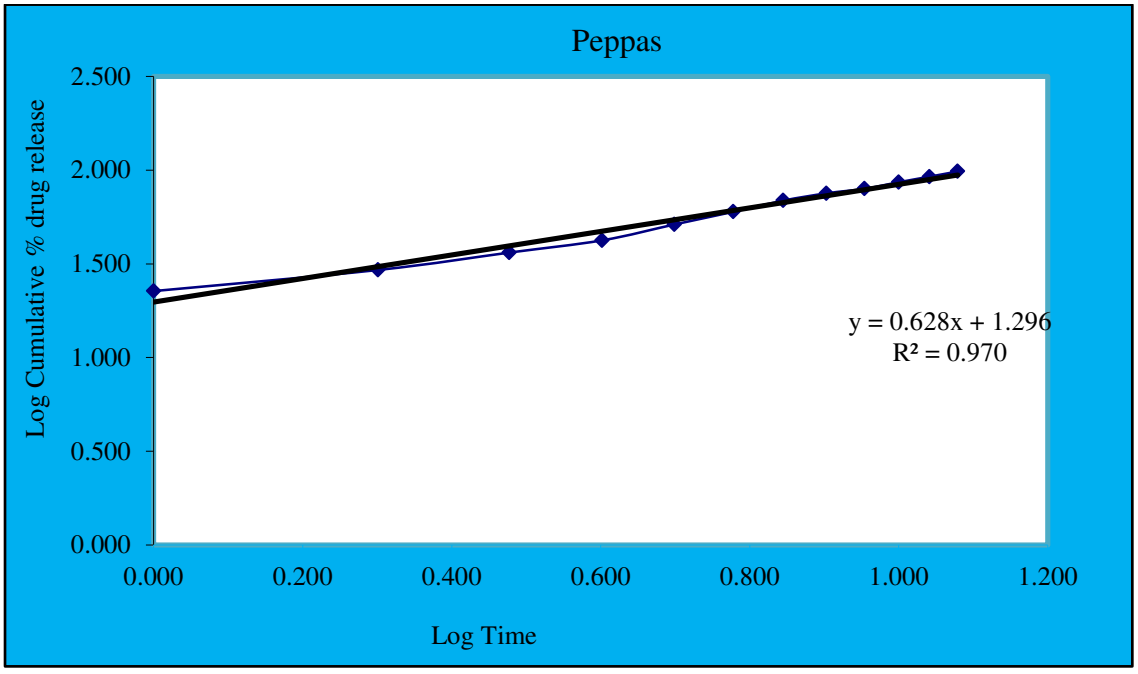

Figure 9: Graph of peppas release kinetics

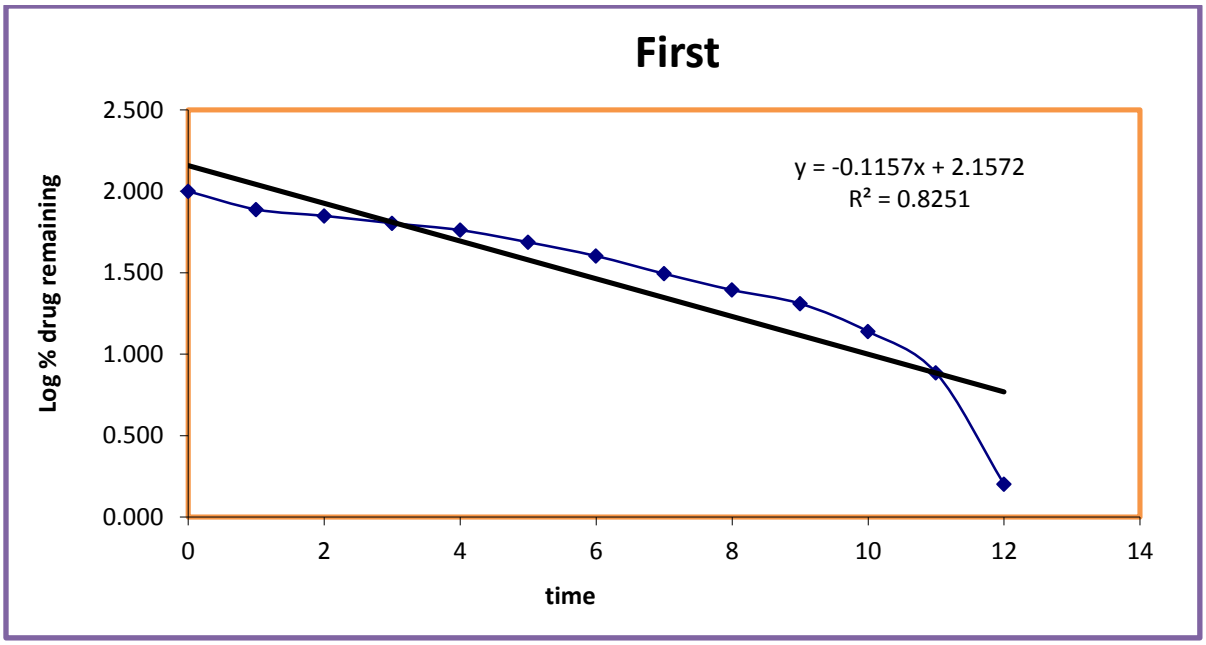

Figure 10: Graph of first order release kinetics

SUMMARY

Development of extended release tablets is one of the alternative routes of administration to prolonged sustained release of drug. Extended release tablets of Levosulpiride were prepared by wet granulation method using various Natural polymers like Fenugreek, Almond gum and Tamarind gum. Among these natural polymers Fenugreek mucilage shows good release compare to Almond gum and Tamarind gum. The optimized formulation F8 contains (1:1.5) drug and Polymer showed maximum % drug release i.e 99.81% at 12 hours.

The formulated extended release tablets were evaluated for different parameters such as drug excipient compatibility studies, weight variation, thickness, hardness, content uniformity and *In vitro* drug release. *In vitro* drug release studies performed in pH 1.2 and phosphate buffer pH 6.8 for 12 hrs in standard dissolution apparatus. The data was subjected to zero order, first order, Zero and First diffusion models.

The following conclusions could be drawn from the results of various experiments

FTIR studies concluded that there was no interaction between drug and Excipients. The physico-chemical properties of all the formulations prepared with various Natural polymers like Fenugreek, Almond gum and Tamarind gum were shown to be within limits. Properties and from the results, it was concluded that the *in vitro* drug release of the optimized formulations is suitable for Extended/sustained drug delivery system.

CONCLUSION

The present study concludes that extended drug delivery of Levosulpiride can be a good way to prolong duration of action of drug by reducing the dosing frequency of Levosulpiride Present study concludes that extended drug delivery system should be a suitable method for Levosulpiride administration. The optimised formulation was found to be F8 formulation contain drug and Natural polymer Fenugreek (1:1.5) which shows the good release within the specified limits.

ACKNOWLEDGEMENT

I take this opportunity to express my deep sense of gratitude to all teaching and non-teaching staff of St. Johns college of pharmaceutical sciences, yerakota, yemmiganur , Kurnool (Dist) , Andhra Pradesh India for his encouragement, guidance and inspiration to write this article and also thankful to Sura Lab, Hyderaad, Telangana for providing necessary facilities for research work.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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