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Development and *In-Vitro* Evaluation of Resperidone Delayed Release Tablets

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A B S T R A C T
The aim of the present study was to develop Delayed release formulation of Resperidone to maintain constant therapeutic levels of the drug for over 10 hrs. Various natural polymers such as Guar gum, Xanthan gum and Chitosan were employed as polymers. Resperidone dose was fixed as 10 mg. Total weight of the tablet was considered as 100 mg. Polymers were used in the concentration of 20 and 40 mg concentration. 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 (F3) showed better and desired drug release pattern i.e., 97.65 % in 10 hours. It followed zero order release kinetics mechanism.

Keywords: Resperidone, Guar gum, Chitosan, Xanthan gum and Delayed release tablets.

A R T I C L E I N F O

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1. Introduction

Drug Delivery System: The treatment of acute diseases or chronic illness has been achieved by delivery of drugs through different drug delivery systems such as tablets, injectables, suspensions, creams, ointments, liquids and aerosols. Another role of the delivery systems is to allow the safe application of the drug. This includes that the drug in the formulation must be chemically, physically and microbiologically stable. Side-effects of the drug and drug interactions should be avoided or minimized by the use of suitable drug delivery systems. The delivery systems also need to improve the patient's compliance with the pharmacotherapy by the development of convenient applications. Finally, the delivery system needs to be reliable and its formulation needs to be technically feasible. This means the pharmaceutical quality of the delivery systems needs to be assured, drug release from the system needs to be reproducible and the influence of the body on drug release should be minimized. The ultimate goal of any drug delivery system is to provide a therapeutic amount of drug in the proper site in the body to achieve promptly and then to maintain the desired drug concentration.

Oral drug delivery:

This is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost effective manufacturing process. For the past decades, there has been enhanced demand for patient complaint dosage forms. As a result the demand for the technologies has been increased 3 fold annually. Since the development cost of new chemical entity is very high, the pharmaceutical companies are focusing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize the side effects. Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects. In addition, the oral medication is generally considered as the first avenue investigated in the discovery and development of new drug entities, pharmaceutical formulations, mainly because of patient acceptance and convenience in administration. Oral route of drug administration have wide acceptance up to 50-60% of total dosage forms. Solid dosage forms are popular because of ease of administration, accurate dosage, self-medication, pain avoidance and most importantly patient compliance. The most popular solid dosage forms are tablets and capsules. But the important drawback of these dosage forms is the difficulty to swallow.

Conventional Drug Therapy

Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional drug delivery is effective, but some drugs which posses narrow therapeutic window and which cause irritation to gastric mucosa require modified drug delivery system to achieve desired therapeutic effect. These delivery systems have a number of advantages over traditional systems such as improved efficiency, reduced toxicity and improved patient convenience. The main goal of modified drug delivery systems is to improve the effectiveness of drug therapies. Conventional dosage forms are rapidly absorbed, with the ascending and descending portions of the concentrations versus time curve reflecting primarily the rate of absorption and elimination, respectively. Because of the rapid rate of absorption from conventional dosage forms, drugs are usually administered more than once daily, with the frequency being dependent on biological half life (t½) and duration of pharmacological effect. The time of dosing may also be effected by therapeutic index of a drug.

Disadvantages of Conventional Drug Delivery Systems

- In conventional oral drug delivery systems, there is little or no control over the release of the drug and effective concentration at the target site.
- The dosing pattern in conventional dosage forms results in constantly changing, unpredictable and often sub-therapeutic plasma concentrations, leading to marked side effects in some cases.
- Conventional drug delivery system is not suitable for the drugs which cause irritation to the gastric mucosa.
- The rate and extent of absorption of drug from conventional formulations may vary greatly, depending on the factors such as physicochemical properties of the drug, presence of excipients, various physiological factors such as the presence or absence of food, pH of the gastrointestinal tract, gastrointestinal motility and so on.

2. Materials and methods

Materials: Resperidone, Guar gum, Chitosan, Gum karaya, Magnesium stearate, Micro crystalline cellulose, Talc

Methodology

Analytical method development:

Determination of absorption maxima: A solution containing the concentration 10 µg/ ml drug was prepared in 0.1N HCl and pH 6.8 Phosphate buffer UV spectrums was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

Preparation calibration curve:

100 mg of Resperidone pure drug was dissolved in 100 ml of 0.1 N HCl (stock solution)10 ml of solution was taken and make up with 100 ml of 0.1 N HCl (100 µg/ml).from this 10 ml was taken and make up with 100 ml of 0.1 N HCl (10 µg/ml). The above solution was subsequently diluted with 0.1N HCl to obtain series of dilutions Containing 5,10,15,20,25,30,35 and 40 µg/ml of Resperidone per ml of solution. The absorbance of the above dilutions was measured at 278 nm 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.

Pre-formulation parameters: The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. 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 tested as per Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured.

Bulk density:

Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size distribution, particle shape and the tendency of particles to adhere together. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting.

Tapped density:

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit.

Measures of powder compressibility:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities. In theory, the less compressible a material the more flow able it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed.

Formulation development of Tablets:

All the formulations were prepared by direct compression. The compositions of different formulations are given. The tablets were prepared as per the procedure given below and aim is to prolong the release of Resperidone. Total weight of the tablet was considered as 100 mg.

Procedure:

1) Resperidone and all other ingredients were individually passed through sieve no ≠ 60.
2) All the ingredients were mixed thoroughly by triturating up to 15 min.
3) The powder mixture was lubricated with talc.
4) The tablets were prepared by using direct compression method.

Evaluation of post compression parameters for prepared Tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test:

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage. The mean and deviation were determined.

Hardness:

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness:

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

Friability:

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations).

Determination of drug content:

Tablets were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of Meloxicam were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV–Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

***In vitro* drug release studies**

Dissolution parameters:

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

As the preparation was for floating drug release given through oral route of administration, different receptors fluids are used for evaluation the dissolution profile.

Procedure:

900 ml of 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c $\pm$ 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 2 hours and then the medium 0.1 N HCl was removed and pH 6.8 phosphate buffer was added process was continued from up to 12 hrs at 50 rpm. At definite time intervals of 5 ml of the receptors fluid was withdrawn, filtered and again 5 ml receptor fluid was replaced. Suitable dilutions were done with receptor fluid and analyzed by spectrophotometrically at 278 nm 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 are fitted to the following equation.

$$F = K_o t$$

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

$$Log (100-F) = kt$$

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.

$$F = k\ t1/2$$

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.

$$M_t/ M_\infty = K\ t^n$$

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.

Hixson-Crowell release model:

$$(100-Q_t)^{1/3} = 100^{1/3} – K_{HC}.t$$

Where, k is the Hixson-Crowell rate constant.

Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets).

3. Result and Discussion

The present study was aimed to developing extended release tablets of Resperidone using various polymers. All the formulations were evaluated for physicochemical properties and *in-vitro* drug release studies.

Analytical Method

Graphs of Resperidone were taken in Simulated Gastric fluid (pH 1.2) and in p H 6.8 phosphate buffer at 278 nm and 274 nm respectively.

Table 2: Observations for graph of Resperidone in 0.1N HCl (278 nm)

Conc [µg/ml]	Abs
5	0.104
10	0.205
15	0.302
20	0.411
25	0.503
30	0.608
35	0.710
40	0.808

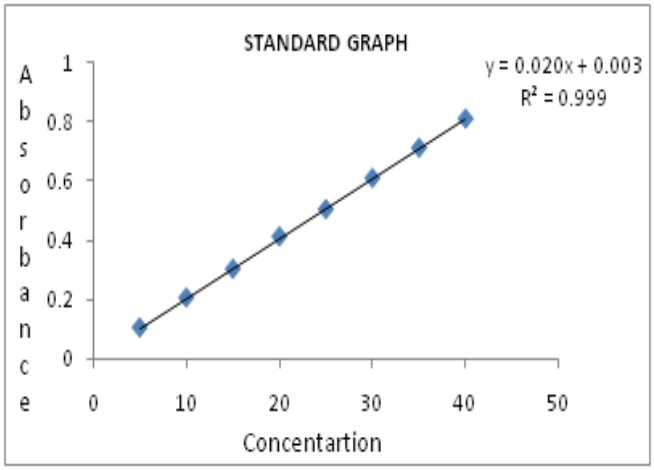

Figure 1: Standard graph of Resperidone in 0.1N HCl

Table 3: Observations for graph of Resperidone in p H 6.8 phosphate buffer (274 nm)

Conc [µg/l]	Abs
5	0.098
10	0.195
15	0.298
20	0.392
25	0.490
30	0.595
35	0.690
40	0.776

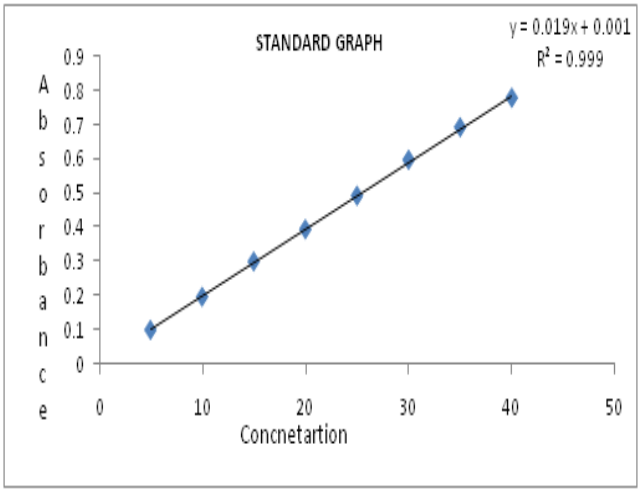

Figure 2: Standard graph of Resperidone p H 6.8 phosphate buffer (274nm)

Preformulation parameters of powder blend

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values 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±0.07 to 0.58±0.06 (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 0.57 to 0.69 showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 16 to 18 which shows that the powder has good flow properties. All the formulations has shown the hausner ratio ranging between 0 to 1.2 indicating the powder has good flow properties.

Quality Control Parameters For tablets:

Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet.

***In-vitro* quality control parameters for tablets**

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

***In-Vitro* Drug Release Studies**

Table 6: Dissolution Data of Resperidone Tablet Formulation (F1-F3)

Time (hr)	Cumulative percent drug dissolved (n=3±sd)		
	F1	F2	F3
0.5	25.52	20.13	16.44
1	46.74	39.46	26.78
2	76.55	55.32	34.67
3	98.47	75.36	42.43
4		87.38	55.46
5		99.44	67.41
6			85.42
7			90.56
8			92.34
9			94.13
10			97.65

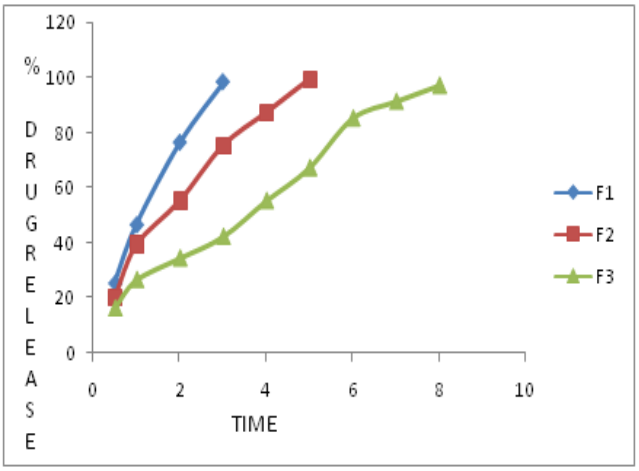

Figure 3: Dissolution profile of Resperidone (F1, F2, F3 formulations)

Table 7: Dissolution Data of Resperidone Tablet Formulation (F4-F6)

TIME (hr)	Cumulative percent drug dissolved (n=3±sd)		
	F4	F5	F6
0.5	17.25	16.42	14.62
1	38.26	25.73	19.86
2	54.16	36.63	22.35
3	72.01	45.04	31.45
4	88.26	58.25	39.80
5	97.10	65.33	45.25
6		76.41	58.24
7		84.84	66.73
8		97.80	71.34
9			75.52
10			82.17

Table 8: Dissolution Data of Resperidone Tablet Formulation (F7-F9)

Time (hr)	Cumulative percent drug dissolved (n=3±sd)		
	F7	F8	F9
0.5	10.4	9.4	8.5
1	16.5	15.6	14.5
2	28.6	21.4	18.4
3	39.5	36.7	23.4
4	48.5	42.4	28.2
5	59.4	49.6	34.8
6	69.2	55.3	40.2
7	74.5	60.3	44.8
8	82.3	72.8	50.4
9	98.78	83.52	63.34
10		88.65	69.27
11		96.56	74.86
12			79.97

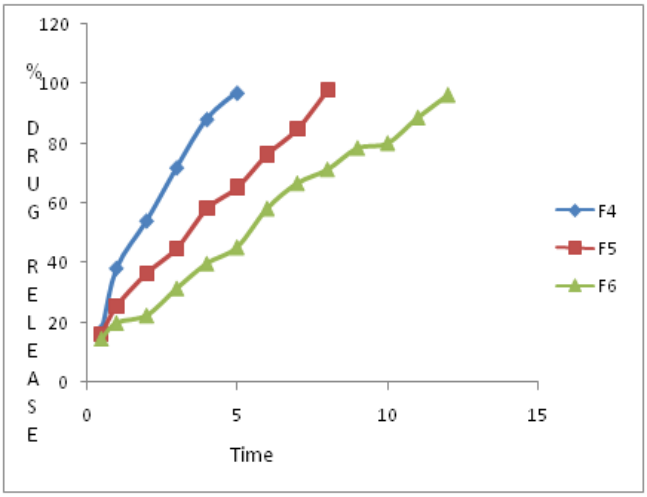

Figure 4: Dissolution profile of Resperidone (F4, F5, F6 formulations)

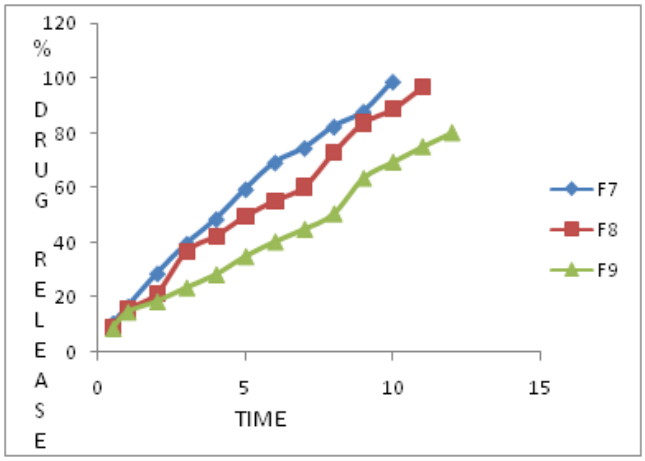

Figure 5: Dissolution profile of Resperidone (F7, F8, F9 formulations)

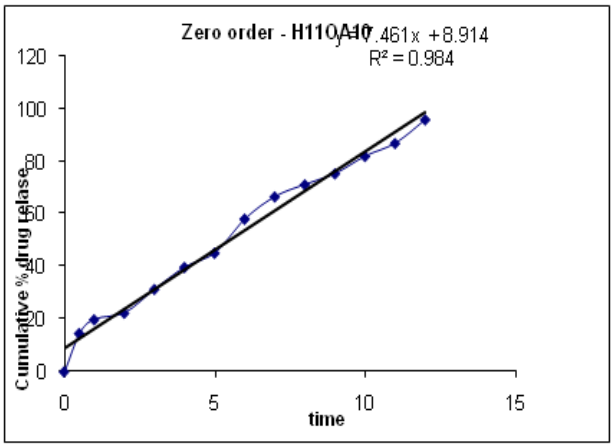

Figure 6: Zero order release kinetics graph

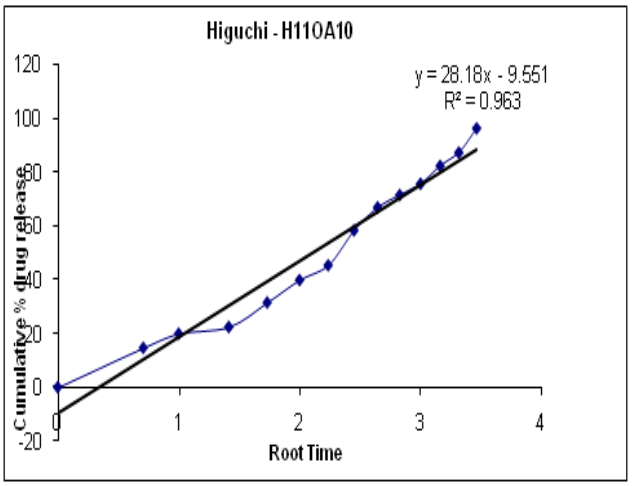

Figure 7: Higuchi release kinetics graph

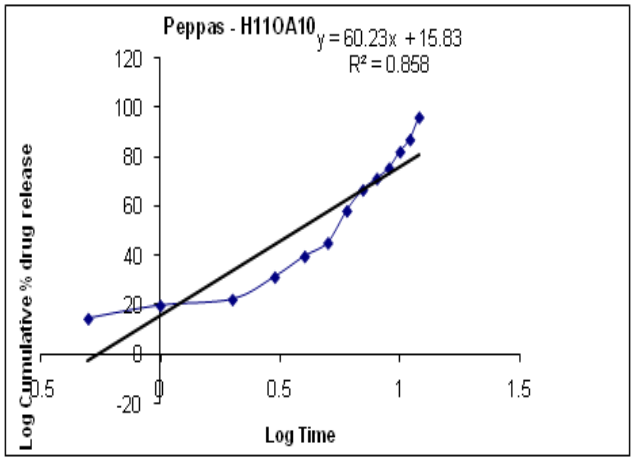

Figure 8: Karsmayer Peppas graph

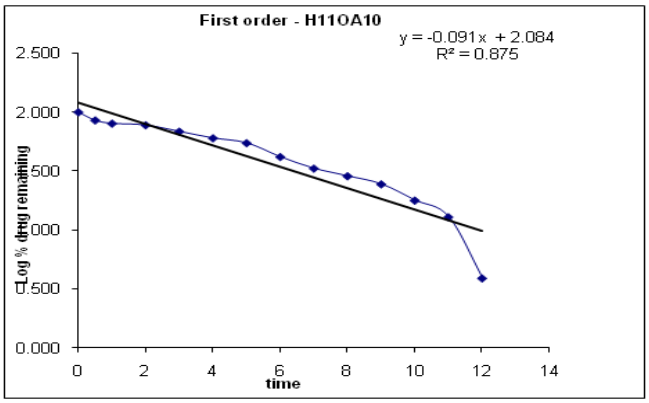

Figure 9: First order release kinetics graph

From the above graphs it was evident that the formulation F3 was followed Zero order release kinetics. From the dissolution data it was evident that the formulations prepared with Guar gum as polymer were unable to retard the drug release up to desired time period i.e., 10 hours. Whereas the formulations prepared with xanthan gum retarded the drug release in the concentration of 20 mg showed required release pattern i.e., retarded the drug release up to 10 hours and showed maximum of 97.65% in 10 hours with good retardation. The formulations prepared with Chitosan showed more retardation even after 10 hours they were not shown total drug release. Hence they were not considered.

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.

Table 1: Formulation composition for tablets

Formulation No.	Resperidone	Guar gum	Xanthan gum	Chitosan	Mag. Stearate	Talc	MCC pH 102	Total wt of tablet
F1	10	20			5	5	QS	200
F2	10	40			5	5	QS	200
F3	10		20		5	5	QS	200
F4	10		40		5	5	QS	200
F5	10			20	5	5	QS	200

F6	10			40	5	5	QS	200
F7	10	20	20		5	5	QS	200
F8	10		20	20	5	5	QS	200
F9	10	20		20	5	5	QS	200

Table 4: Pre-formulation parameters of Core blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25.11	0.49±0.04	0.54±0.04	16.21±0.06	0.86±0.06
F2	25.67	0.52±0.09	0.52±0.04	16.87±0.05	0.98±0.05
F3	25.54	0.50±0.05	0.58±0.05	17.11±0.01	0.64±0.03
F4	25.43	0.51±0.06	0.54±0.07	17.67±0.08	1.12±0.04
F5	25.34	0.52±0.03	0.57±0.03	16.92±0.04	1.2±0.08
F6	24.22	0.53±0.04	0.56±0.06	17.65±0.09	1.06±0.09
F7	25.18	0.54±0.06	0.59±0.04	16.43±0.05	0.76±0.03
F8	24.22	0.58±0.04	0.67±0.02	17.97±0.02	1.15±0.09
F9	25.05	0.55±0.08	0.5 2±0.03	17.54±0.09	1.17±0.02

Table 5: *In-vitro* quality control parameters for tablets

Formulation codes	Weight variation(mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	101.5	4.5	0.50	6.8	99.76
F2	105.4	4.5	0.51	6.9	99.45
F3	98.6	4.4	0.51	4.9	99.34
F4	100.6	4.5	0.55	6.9	99.87
F5	99.4	4.4	0.56	6.7	99.14
F6	100.7	4.5	0.45	6.5	98.56
F7	102.3	4.1	0.51	6.4	98.42
F8	101.2	4.3	0.49	6.7	99.65
F9	98.3	4.5	0.55	6.6	99.12

Table 9: Release kinetics data for optimised formulation

Time (T)	Cumulative (%) Release Q	Log (%) Release	Log (%) Remain	Release Rate (Cumulative % Release / t)	1/CUM% Release	Peppas log Q/100	% Drug Remaining
0	0		2.000				100
0.5	14.62	1.165	1.931	29.240	0.0684	-0.835	85.38
1	19.86	1.298	1.904	19.860	0.0504	-0.702	80.14
2	22.35	1.349	1.890	11.175	0.0447	-0.651	77.65
3	31.45	1.498	1.836	10.483	0.0318	-0.502	68.55
4	39.8	1.600	1.780	9.950	0.0251	-0.400	60.2
5	45.25	1.656	1.738	9.050	0.0221	-0.344	54.75
6	58.24	1.765	1.621	9.707	0.0172	-0.235	41.76
7	66.73	1.824	1.522	9.533	0.0150	-0.176	33.27
8	71.34	1.853	1.457	8.918	0.0140	-0.147	28.66
9	75.52	1.878	1.389	8.391	0.0132	-0.122	24.48
10	82.17	1.915	1.251	8.217	0.0122	-0.085	17.83

4. Conclusion

The aim of the present study was to develop Delayed release formulation of Resperidone to maintain constant therapeutic levels of the drug for over 10 hrs. Various natural polymers such as Guar gum xanthan gum and Chitosan were employed as polymers. Resperidone dose was fixed as 10 mg. Total weight of the tablet was considered as 100 mg. Polymers were used in the concentration of 20 and 40 mg concentration. 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 (F3) showed better and desired drug release pattern i.e.,97.65 % in 10 hours. It followed zero order release kinetics mechanism.

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