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Original Article

Formulation and In-Vitro Evaluation of Matrix Type Sustained Release Tablets of Paliperidone

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Abstract

Paliperidone is a well know dopamine antagonist of the atypical antipsychotic class. In present study Paliperidone was formulated as matrix type sustained release tablets using natural and synthetic polymers separately or in combination. The aim of sustained release formulation is to reduce the frequency of dosing. Tablets were prepared by direct compression method. The optimized formulations contain Paliperidone as active ingredient and hydroxy propyl methyl cellulose, ethyl cellulose, kollidone SR, polyethylene oxide, sodium alginate are used as polymers. The evaluation parameters include the thickness, weight variation test, drug content, hardness, friability and in vitro release studies. The prepared formulations are F1-F9 and among the formulation F2 follows non-Fickian Transport, with Zero order, Higuchi mechanism and F3, F5 and F8 following first order. Based on the results of *in-vitro* studies it was concluded that the natural and synthetic polymers can be used as an efficient matrix former to provide sustained release of Paliperidone. The release of Paliperidone was prolonged for 20 hrs, indicating the usefulness of the formulations for once daily dosage forms. Thus the reducing frequency of dosing increases patient compliance.

Keywords: Keywords: Paliperidone, Kollidone SR, Xanthan gum Hydroxypropyl methylcellulose (HPMC K100).

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1. Introduction

Extended release (ER) dosage forms are designed in such a manner as to allow the enclosed drug available over an extended period of time after its administration. Various terms including sustained release, prolonged release and controlled release are also employed to distinguish such a modified drug delivery systems [1]. The modified drug delivery systems (MDDSs) including extended release, evolved over a period of time. They are particularly designed to exert control on drug release to further enhance drug's efficacy, safety and compliance. The MDDSs can also enhance the value of the company's current products, allowing it to charge a premium for the extra benefits. Foundations of MDDSs were laid in 1952, with the introduction of the first sustained-release capsule of Dexedrine. The MDDSs have been classified on the basis of their sophistication and mechanism of drug release [2,3] [Table 1]. The term matrix indicates a three dimensional network composed of drug(s), polymer(s) and other excipients. Because of simplicity, ease in manufacturing, scale-up and process validation; stability and low costs, matrix preparation has become a popular approach [4]. Drugs are usually embedded in hydrophilic or hydrophobic matrices to exert control on their release [5].

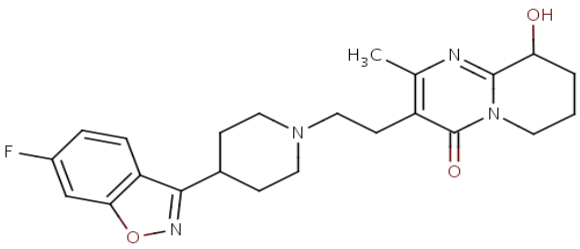
Now-a-days, controlled-release product development has become much easier than before because of availability of advanced technology for matrix fabrication. These advancements have made it feasible to design delivery of a wide variety of drugs (with different physical, chemical and biological characteristics) as desired. All this has resulted in a large number of patents and commercial products [6] available in the market.

Classification	**Description/Mechanism of drug release**
Rate-preprogrammed DDSs	Polymer membrane permeation Polymer matrix diffusion Microreservoir partition
Physical-activatedDDSs	Osmotic pressure activated Hydrodynamic pressure activated Hydration activated Vapor pressure activated Mechanically activated Magnetically activated Ultrasound activated Electrically activated
Chemically activated DDSs	pH activated Ion activated Hydrolysis activated
Biochemically activated DDSs	Enzyme activated Biochemical activated
Site targeted DDSs	Passive targeting Active targeting

Oral drug delivery has become the major segment of the total drug delivery market. It is growing day by day because of being a favorite route for drug administration. Now-a-days, hydrophilic matrices are receiving preference in formulation of extended release oral products [7].

Paliperidone is a dopamine antagonist of the atypical antipsychotic class of medications and is an active metabolite of the older antipsychotic risperidone (paliperidone is 9-hydroxy risperidone). Paliperidone has antagonist effect at α1 and α2 adrenergic receptors and at H1 histamine receptors. It does not bind to muscarinic acetylcholine receptors. In addition it binds with dopamine and serotonin receptors [8].

Structure:



Presently Paliperidone is available as INVEGA Extended-Release Tablets in 1.5mg, 3mg, 6mg and 9mg strengths. INVEGA utilizes OROS osmotic drug release technology [9]. Paliperidone (as Invega) was approved by the FDA for the treatment of schizophrenia in 2006. It is marketed for the treatment of schizophrenia and schizoaffective disorder. Paliperidone was approved by the FDA for the treatment of schizoaffective disorder in 2009. It may also be used off-label for other conditions.

However, there are reports of sustained release tablets for the selected of drugs have been found, but they use osmotic drug-release technology, core and coating technology etc. hence the present study was selected [10].

The objective of the study is to design and evaluate palperidone oral extended release tablets using polymers such as hydroxy propyl methyl cellulose, ethyl cellulose, kollidon SR, polyethylene oxide, sodium alginate [11,12,13].

2. Material and Method

Paliperidone was procured as a gift sample from Pharma Train, Kukatpally, Andhra Pradesh; HPMC K100M, Ethyl cellulose, PEO, Xanthangum, Sodium alginate Lactose and Magnesium stearate were also provided by Pharma Train .The other chemicals used were purchased from Merck chemicals. All other chemicals used in our work were of analytical grade.

Extended release tablets were prepared by direct compression method. All ingredients were weighed and passed through 40# sieve, blended except lubricant. These above granules were lubricated with Magnesium stearate, which was previous, passed through 60# Sieve. The lubricated granules were for compressed 100 mg tablet using 6mm die and punches, with hardness between 5-6 kg/cm^2

In total, nine formulations containing different combination of polymers were prepared. The first formulation (F1) is a combination of ethyl cellulose and HPMCK100M and from the second formulation, one of the above mentioned

polymer is kept constant and the other is replaced by Kollidon SReSR, Xanthangum, PEO or Sodium alginate. The combinations are clearly depicted in the Table 2. [14]

Evaluation of Granules

Angle of repose

The angle of repose of granules was determined by the funnel method. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

Tan θ = h/r

Where h and r are the height and radius of the powder cone respectively.

Bulk Density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined and calculated by using the following formulas.

LBD=weight of the powder/volume of the packing

TBD=weight of the powder/tapped volume of the packing

Compressibility index:

The compressibility index of the granules was determined by Carr's compressibility index.

Carr's index (%) = [TBD-LBD] /TBD X 100

Evaluation of the compressed tablets

Paliperidone tablets were evaluated for post compression parameters like hardness, weight variation, friability, drug content uniformity etc. The data was presented in (Table 4).

Average weight

Weight variation was studied by taking 20 tablets of each formulation, they were weighed on an electronic balance (Shimadzu, AUX 220, Japan), and the test was carried according to the Indian Pharmacopoeia

Hardness and Friability

The hardness and friability were determined using the Monsanto hardness tester (Cadmach, Ahmedabad, India) and the friability testing apparatus (Campbell Electronics, Mumbai, India.), respectively [14].

Determination of drug content

The drug content was carried out by weighing 10 tablets from each batch and calculated the average weight. Then the tablets were triturated to get a fine powder. From the resulting triturate, powder was weighed accurately which was equivalent to 5 mg Paliperidone and dissolved in 100 ml volumetric flask containing 50 ml of 0.1N HCL and volume was made to 100 ml with solvent. The volumetric flask was shaken using sonicator for 1 hr and after suitable dilution with 0.1N HCL, the drug content was determined using UV-Visible Spectrophotometer at 238 nm.

***In- Vitro* dissolution studies of paliperidone extended released tablets**

The dissolution test for Paliperidone control release tablets was done by using 0.1N HCL for 2hrs after which the dissolution medium was changed to 4.5pH acetate buffer for 2hrs and finally to 6.8 phosphate buffer period using USP type II (paddle) Dissolution Testing Apparatus (Electrolab) 900ml of the medium was used as dissolution medium agitated at 50 RPM, at temperature of $37^{O}\pm 0.5^{O}C$. 5 ml samples were withdrawn from 1-20 hrs. An equal volume of fresh medium was immediately replaced to maintain the dissolution volume.

The amount of Paliperidone dissolved was determined by taking reading of absorbance at the wavelength of maximum absorbance

of about 237 nm of filtered portion of samples withdrawn. Dissolution studies were performed two times for each tablet formulation and the mean values were taken.

Kinetic Modeling of Drug Release Profiles

The rate and mechanism of release of Paliperidone from the prepared extended release tablets were analyzed by fitting the dissolution data into the zero-order equation,

$$Q = k_0 t$$

Where Q is the amount of drug released at time t, and k0 is the zero order release rate constant [15,16]. The dissolution data was fitted to the first order equation:

$$\ln (100–Q) = \ln 100 – k_1 t$$

Where k_1 is the first order release rate constant.

The dissolution data was fitted to the Higuchi's equation:

$$Q = k_2 t1/2$$

Where k_2 is the diffusion rate constant. The dissolution data was also fitted to the well known equation (Korsmeyer equation), which is often used to describe the drug release behaviour from polymeric systems

$$Mt/ M = k3tn \quad (5.13)$$

$$\log (Mt/ M\infty) = \log k3 + n \log t$$

Where Mt is the amount of drug released at time t, $M\infty$ is the amount of drug release after infinite time, k is a release rate constant incorporating structural and geometric characteristics of the tablet and n is the diffusional exponent indicative of the mechanism of drug release.

For a matrix tablet, when 'n' takes the value of (In case of cylindrical shape), 0.45 - Fickian diffusion-controlled drug release.

The data was presented in (Table 5), the mechanism of drug release was shown in (Fig 1-5).

3. Results and discussion

The granules were evaluated for angle of repose and compressibility (Table3)

The angle of repose values obtained for the formulations are in between 27.96 - 30.01respectively.This indicates good flow property of the powder blends.

The compressibility index values for the formulations are in between14.18-22.4(Carr's index). This indicates the powder blends are good for direct compression.

It was observed from (Table 4) that the prepared tablets were evaluated for Weight variation, Hardness, Friability, Thickness, drug content.

Thickness was found to be in the range of 2.5 to 3.0 mm. Hardness of the tablets was in the range of 5.2 ± 0.2 to 5.6 ± 0.2 kg/cm^2 which was sufficient for the handling of tablets throughout the shelf life. Percentage % friability was between 0.38 – 0.69 % and complies with pharmacopoeial limit of less than 1%. Average weight is between 96.03 – 99.01 mg which is a pharmacopoeial limit. Drug content of Paliperidone found to be in the range of 97.56 ±0.78 to 100.83 ±0.78%, was within the limits as per I.P and ICH guidelines

From the results obtained (Table 2) it was observed that F1 formulation is a combination of HPMC K100M and ethyl cellulose in 1:2 ratio (approx.). It is known that concentrations of 15–35% w/w of hydroxypropyl cellulose may be used to produce tablets with an extended drug release and Ethyl cellulose is practically

insoluble in water, but the combination showed 100% release at end of 10thhr.

Formulation F2 is a combination of HPMC K100M and kollidon SR in 1:2 ratio (approx). Kollidon SR is suitable for manufacturing of pH-independent sustained – release matrix tablets by direct compression and concentrations of 15–35% w/w of hydroxypropyl cellulose may be used to produce tablets with an extended drug release. This combination has worked well and shown sustained release for 20 hrs

Formulation F3 is a combination of HPMC K100M and xanthum gum in 1:2 ratio (approx). Xanthan gum has also been used to prepare sustained-release matrix tablet and produce directly compressed matrices that display a high degree of swelling due to water uptake, and a small amount of erosion due to polymer relaxation. This combination has shown sustained release for 20 hrs.

Formulation F4 is a combination of HPMC K100M and PEO in 1:2 ratio (approx).Both being hydrophilic matrix did not really work well together even after having variation in viscosities. 100% drug release is seen at end of 12thhr.

Formulation F5 is a combination of HPMC K100M and Sodium alginate in 1:2 ratio (approx). Sodium alginate has also been used in the preparation of sustained-release oral formulations since it can delay the dissolution of a drug from tablets, capsules, and aqueous suspensions.
This combination has worked well and has shown sustained release for 20 hrs.

Formulation F6 and F7 are combination of ethyl cellulose with kollidone SR and xanthum gum respectively showing 76% and 88% release at end of 20thhr.

Formulation F8 is a combination PEO and ethyl cellulose in 1:2 ratio (approx).PEO acts as hydrophilic matrix whereas ethyl cellulose being insoluble in water adds a hydrophobic nature to the combination and shows the sustained release for 20 hrs.

Formulation F9 is a combination if ethyl cellulose and sodium alginate in 2:1 ratio (approx) it shows 88% release at end of 20th hr.

From the Table 5 it was found that the release of drug from F2,F3,F5,F8 gave the better release than other formulations. So when the HPMC K100M was used as polymer along with Kollidone SR, Xanthan gum and PEO the drug release was extended and 102.1%,100% and 98 % respectively. When ethylcellulose is combined with PEO it is also showed extended action and the drug release was 78% after 20 hours.

In order to understand the complex mechanism of drug release from the F2, F3,F5 and F8 extended release tablets the % in vitro drug release was fitted into Korsmeyer-peppas (fig 4) model and the diffusional exponent value (n) was interpreted for mechanism of drug release. The release exponent value (n), thus obtained were 0.788, 0.572, 0.50, 0.643. Therefore, we can conclude that it F2 follows non- Fickian Transport, with Zero order, Higuchi mechanism.

When we compare the r^2 value for zero order and first order graphs (fig no.1,2) for F2, F3,F5, F8 and from the graph (fig no.3)it was observed that the Higuchi plot r^2 values for F2 is 0.99 , for F3, F5 values are 0.97 and for F8 it is 0.95.From this we can conclude that formulations F2 is following zero order and F3,F5 and F8 following first order.

Table 2: Formulation Of Paliperidone sustained release tablets using hpmc polymer k100m grade, ethylcellulose, sodium alginate, kollidone sr, xanthum gum, Pe K100m

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
	mg	mg	mg	mg	mg	mg	mg	mg	mg
Paliperidone	6	6	6	6	6	6	6	6	6
Ethyl cellulose	60	_	_	_	_	60	60	60	60
HPMC K100 M	28	28	28	28	28	_	_	_	_
Magnesium Stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Lactose	5	5	5	5	5	5	5	5	5
Aerosil	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Kollidone SR	_	60	_	_	_	28	_	_	_
Xanthan gum	_	_	60	_	_	_	28	_	_
PEO	_	_	_	60	_	_	_	28	_
Sodium alginate	_	_	_	_	60	_	_	_	28
Total weight	100	100	100	100	100	100	100	100	100

Table 3: Precompression parameters of Paliperidone formultions

Formulation Code	Angle of Repose(θ) Degrees ±S.D	Bulk Density (g/cc)±S.D	Tapped Density(g/cc)±SD	Hausner's Ratio±S.D	Carr's Index(%)±S.D
F1	29.17±0.18	0.448±0.016	0.538±0.026	1.20±0.23	16.72±0.18
F2	28.9±0.12	0.46±0.02	0.56±0.0212	1.21±0.24	17.85±0.12

F3	30.01±0.14	0.46±0.01	0.58±0.02	1.23±0.19	20.69±0.14
F4	28.18±0.12	0.445±0.03	0.565±0.02	1.22±0.16	21.2±0.12
F5	28.69±0.13	0.45±0.01	0.55±0.023	1.22±0.19	18.18±0.13
F6	28.41±0.13	0.45±0.01	0.58±0.025	1.24±0.18	22.4±0.13
F7	28.53±0.16	0.455±0.02	0.567±0.026	1.24±0.18	19.75±0.16
F8	27.96±0.15	0.464±0.012	0.53±0.027	1.14±0.18	17.4± 0.15
F9	29.17±0.13	0.472±0.011	0.55±0.028	1.16±0.23	14.18±0.13

Table 4: Results of post compression parameters of compressed tablets

Formulation Code	Average weight (mg) (n=20)	Hardness (kg/cm) (n=3)	Thickness (mm) (n=3)	Friability (n=20)	Drug Content (%)
F1	96 ± 0.3	5.3 ± 0.3	2.5 ± 0.05	0.56	99.03 ± 0.31
F2	99 ± 0.01	5.0 ± 0.2	2.4 ± 0.07	0.49	99.86 ± 0.70
F3	98 ± 0.04	5.4 ± 0.2	2.5 ± 0.011	0.63	99.27 ± 0.66
F4	97 ± 0.12	5.2 ± 0.3	2.6 ± 0.10	0.54	100.61 ± 0.73
F5	99 ± 0.01	5.3 ± 0.4	2.5 ± 0.08	0.56	98.83 ± 0.41
F6	96 ± 0.13	5.6 ± 0.2	2.5 ± 0.07	0.38	100.83 ± 0.78
F7	97 ± 0.07	5.5 ± 0.3	2.4 ± 0.13	0.54	97.35± 0.42
F8	99 ± 0.01	5.2 ± 0.2	2.6 ± 0.09	0.69	98.94 ± 0.05

F9	98 ± 0.01	5.4 ± 0.3	2.5 ± 0.06	0.53	97.56 ± 0.78

*(±S.D) (S.D= Standard deviation)

Table 5: Cumulative % drug release of Paliperidone tablet

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	43 ± 1.27	15 ± 1.15	18.4 ± 1.46	20.6 ± 1.37	25.9 ± 1.52	12.8 ± 1.58	16 ± 1.64	16 ± 1.81	16 ± 1.52
2	44.6 ± 0.74	30 ± 1.25	35.3 ± 1.36	37.8 ± 1.42	38.1 ± 1.26	20 ± 1.72	32 ± 1.75	28 ± 1.61	26 ± 1.52
3	53.9 ± 0.91	39 ± 1.42	39.5 ± 0.25	51.04 ± 1.13	44 ± 1.26	22.4 ± 1.14	35 ± 1.36	38 ± 1.42	33 ± 1.28
4	62.1 ± 1.33	43 ± 1.23	40.8 ± 1.54	53 ± 1.12	56 ± 1.64	27 ± 1.69	44 ± 1.46	46 ± 1.84	39 ± 1.62
6	82 ± 1.25	52 ± 1.53	52 ± 1.69	62 ± 1.54	63 ± 1.21	34 ± 1.38	50 ± 1.53	54 ± 1.27	48 ± 1.64
8	89 ± 1.33	61 ± 1.24	68 ± 1.14	76 ± 1.18	69 ± 1.36	44.4 ± 1.69	59 ± 1.52	60 ± 1.42	65 ± 1.24
10	98 ± 1.29	68 ± 0.62	70 ± 0.41	86 ± 1.72	80 ± 0.67	57.6 ± 0.37	68 ± 0.61	62 ± 028	70 ± 1.13
12	99	77 ± 1.28	72 ± 1.84	98 ± 0.21	83 ± 1.34	61 ± 0.94	71 ± 1.73	64 ± 1.68	75 ± 1.42
16	99	85 ± 1.24	83 ± 1.67	100	87 ± 1.59	66 ± 1.75	77 ± 1.86	77 ± 1.69	80 ± 1.83
20	100	102.1	100	101	98	76	88	78	88

Table 6: R^2 values of Paliperidone formulations

Formulation code	R^2 value				n value
	Zero order	First order	Higuchi plot	Pepas plot	
F2	0.96	0.88	0.99	0.96	0.788
F3	0.94	0.95	0.97	0.95	0.572
F5	0.91	0.99	0.97	0.988	0.50

F8	0.90	0.99	0.95	0.97	0.643

Figure 1: Zero order plot for optimized formulation

Figure 1.a: Zero order graph of optimized formulation (F1 to F4)

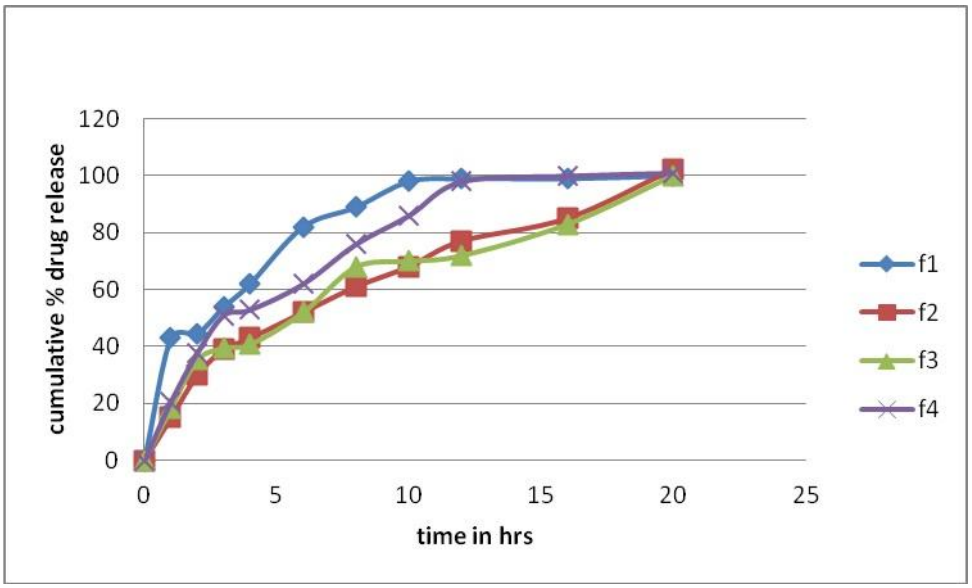


Figure 1.b: Zero order graph of optimized formulation (F5 to F9)

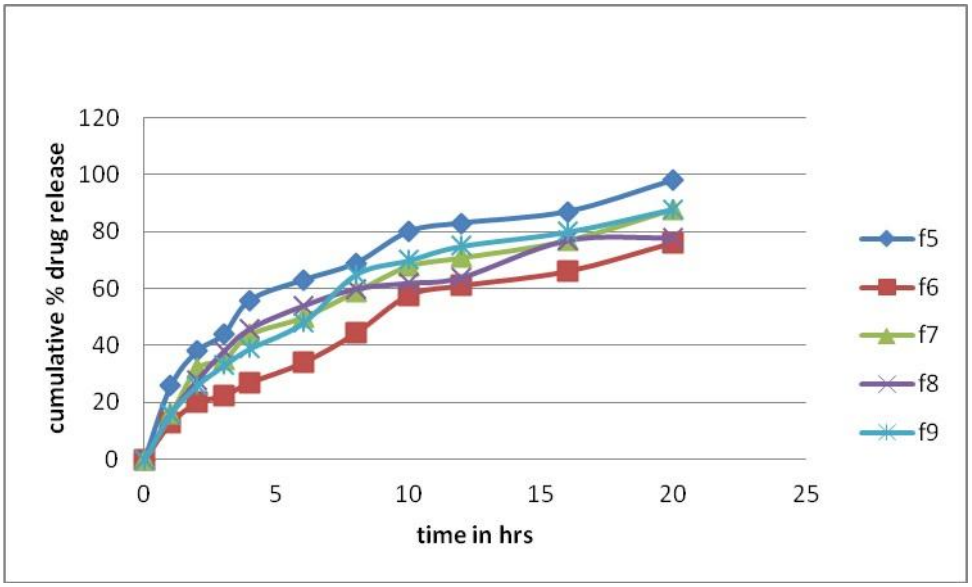


Figure 2: First order plot for optimized formulation

Figure 2a: First order plot for F1 to F2

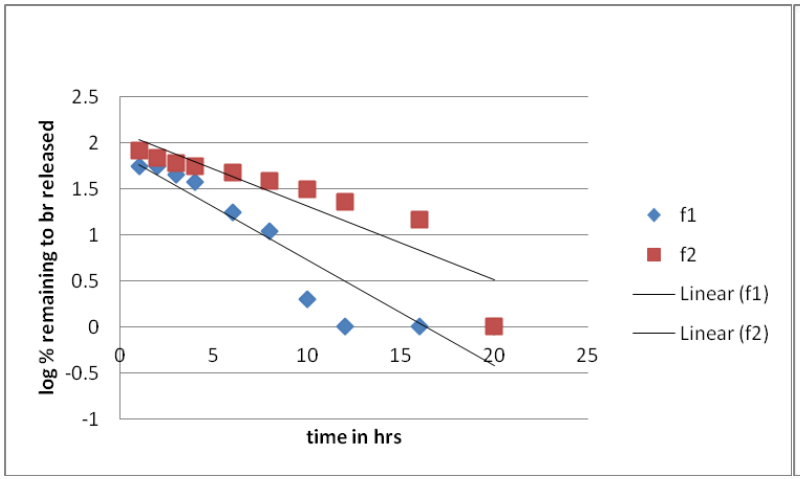


Figure 2 b: First order plot for F3 to F5

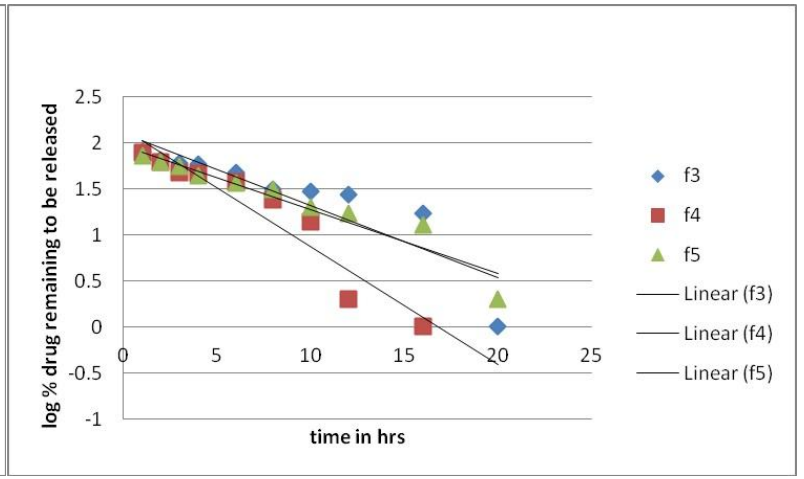


Figure 2 c: First order plot for F6 to F7

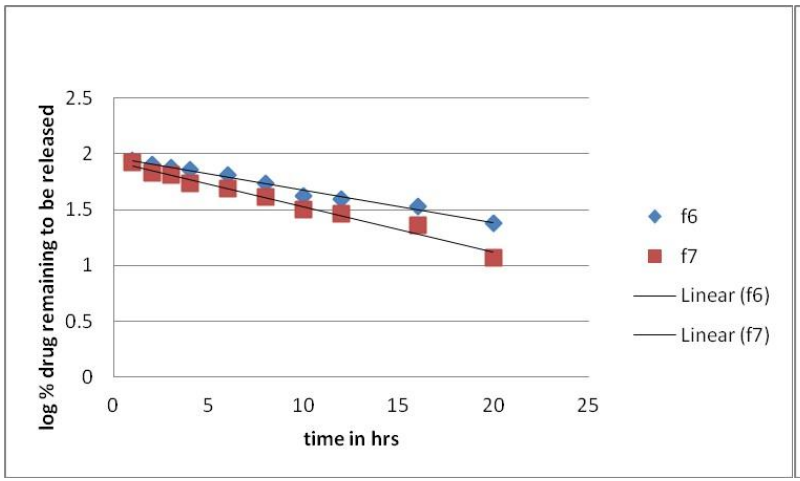


Figure 2 d: First order plot for F8 to F9

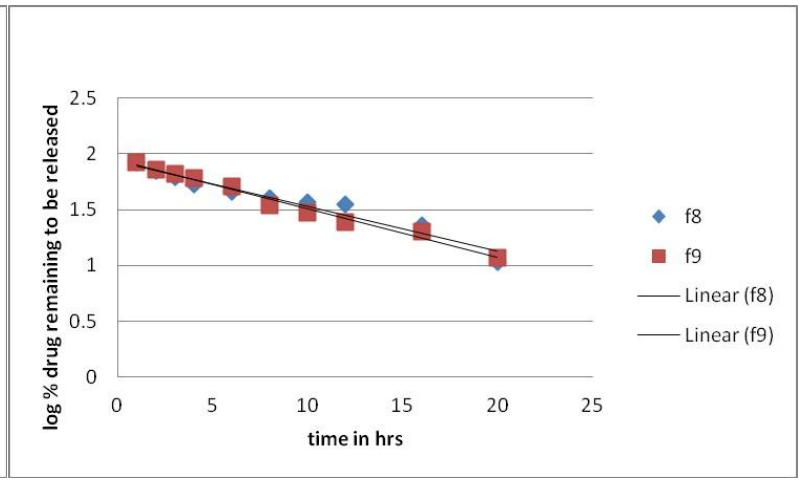


Figure 3: Higuchi plot for optimized formulation

Figure 3 a: Higuchi plot for F2

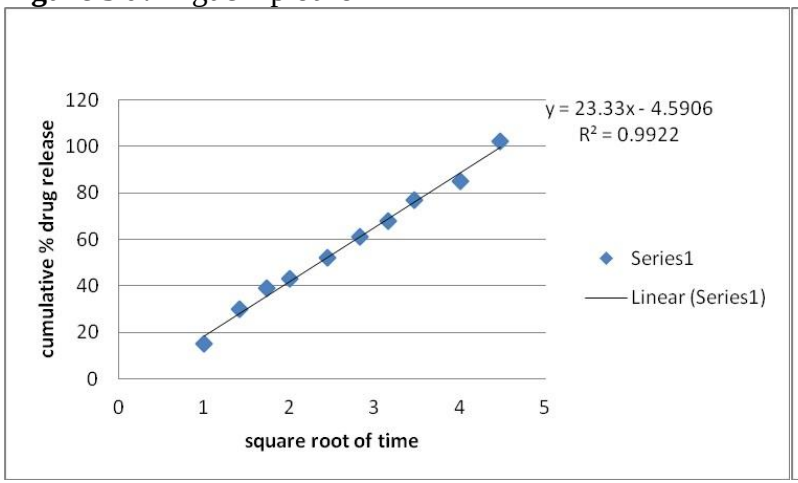


Figure 3 b: Higuchi plot for F3

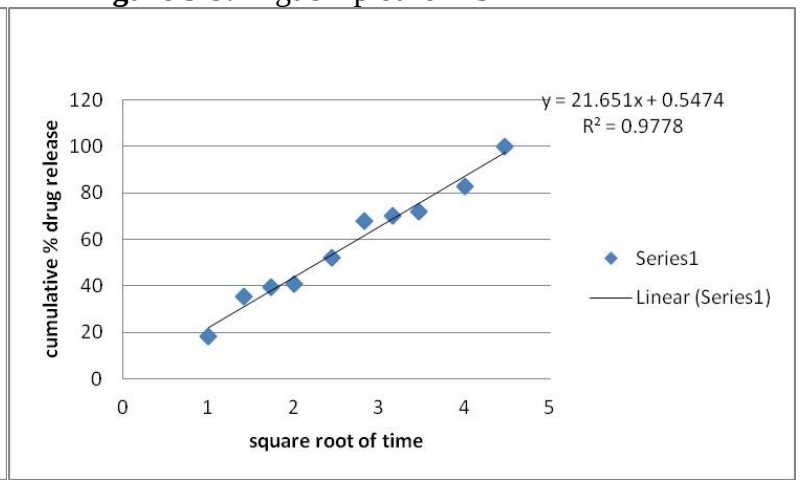


Figure 3 c: Higuchi plot for F5

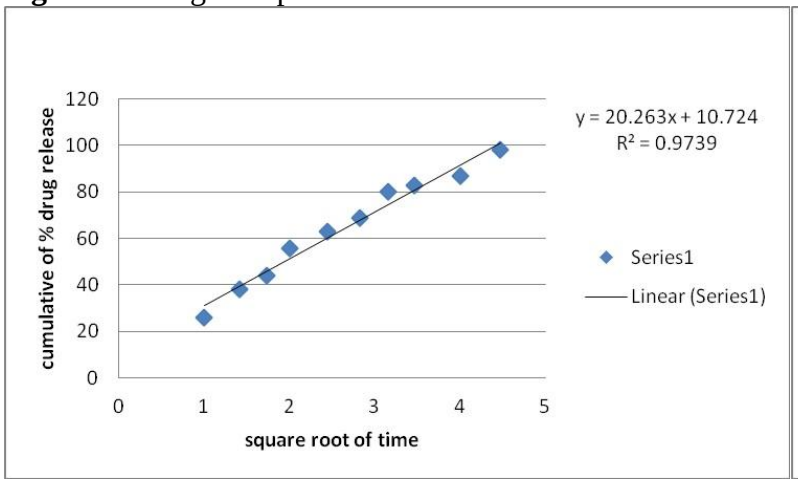


Figure 3 d: Higuchi plot for F8

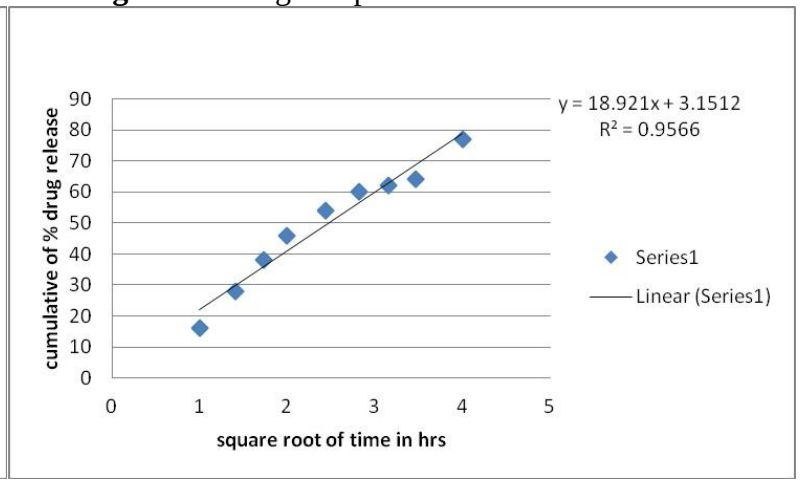


Figure 4: Korsmeyer-peppas graph of optimized formulation

Figure 4 a: Korsmeyer - peppas graph for **F2**

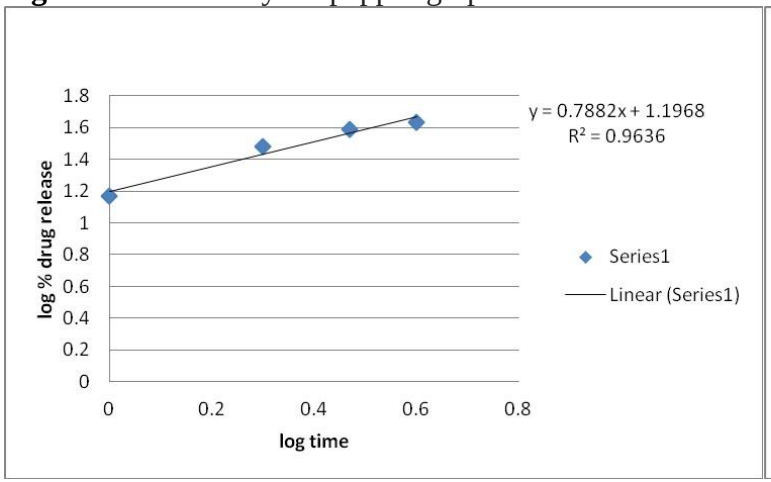


Figure 4 b: : Korsmeyer - peppas graph for F3

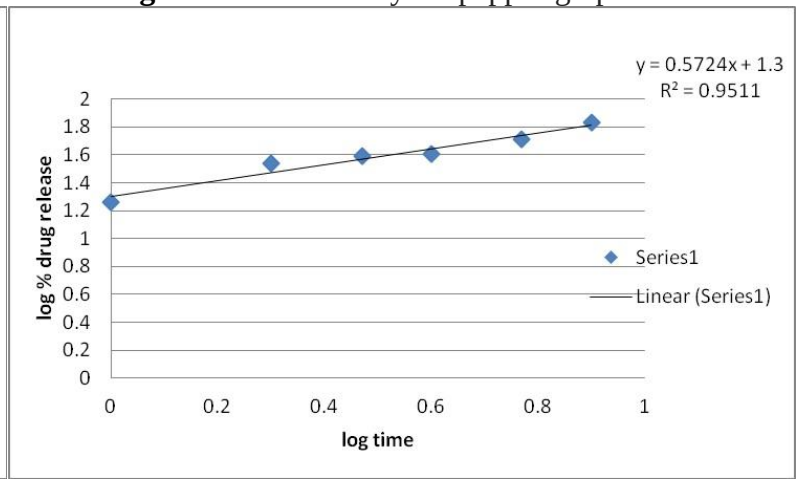


Figure 4 c : Korsmeyer-Peppas Graph for F5

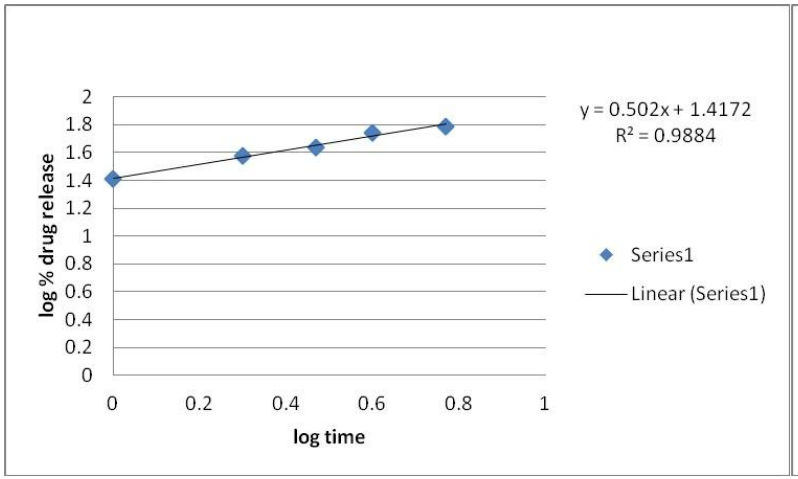
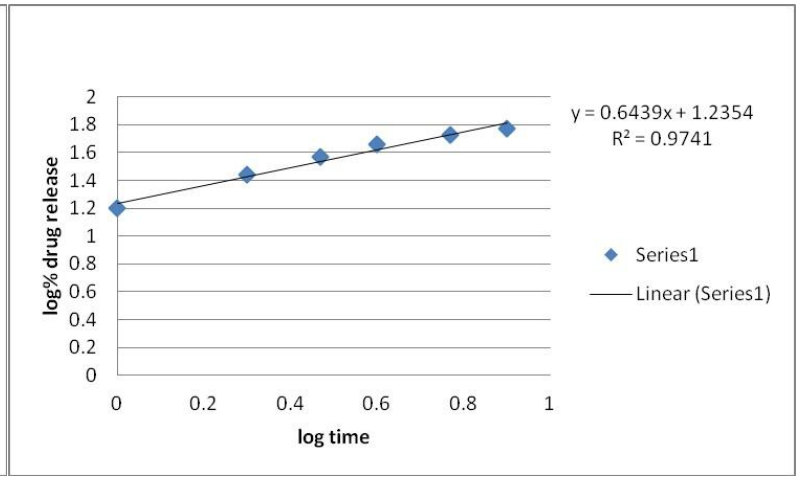


Figure 4 d: Korsmeyer - Peppas Graph for F8



Conclusion

The results of this investigation enabled us to fabricate extended release matix tablets containing Paliperidone. It is also demonstrated that the release of Paliperidone from directly compressed matrix tablets can be modified by changing the type and amount of polymer in the matrix tablets.

These 100 mg tablet containing 6 mg Paliperidone could be given to the patient once a day. The aim of the study was to study the effect of various hydrophilic and hydrophobic polymers on *in-vitro* release rate from sustained release tablets of Paliperidone. Different types of matrix forming polymers like and Ethyl cellulose were studied. The polymer Kollidone SR (F2), Xanthan gum (F3) and sodium alginate (F5) in combination with HPMC K100M and Sodium alginate with PEO (F8) were successful to achieve the sustained drug release for 20 hours.

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