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Original Research Article

FORMULATION AND EVALUATION OF PROPRANOLOL HCl EXTENDED RELEASE PELLETS

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ABSTRACT

The present study performed by Formulation and Evaluation of Extended Release Pellets of Propranolol HCl which is an anti-hypertensive drug. Pellets were formulated with various materials like ethyl cellulose 7cps, HPMC E-5, HPMC phthalate 55 as rate controlling polymers, Diethyl phthalate as plasticizer, povidone K-30 as binder and Acetone, Isopropyl alcohol as solvents. The pellets were prepared by both Pan coating and fluid bed coating technology. The variant proportion of the polymers ethyl cellulose 7cps, HPMC E-5 and HPMC pthalate 55 showed significant difference in the release rates. The drug release rate decreased as the concentration of ethyl cellulose is increased.

Key words: Propranolol HCl, Extended release pellets, antihypertensive, fluid bed coating.

INTRODUCTION

Propranolol HCl ($C_{16}H_{21}NO_2$.HCl) is an anti hypertensive drug, which is a synthetic non-selective beta-adrenergic receptor blocking agent. It has high aqueous solubility almost completely absorbed after oral administration. However, its bioavailability is very limited (30%) due to the hepatic first-pass effect. Its elimination half-life is also relatively short (about 2–6 h) hence frequent administration of drug is required. Therefore, it was chosen as a model drug for preparation of the once-daily extended-release dosage form. The purpose of this work is to develop a novel extended release pellets with a by using different rate controlling polymers. Extended release formulation is an important program for new drug research and development to meet several unmet clinical needs[1]. There are several reasons for attractiveness of these dosage forms viz. provides increase bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak trough concentration and side effects and possibly improves the specific distribution of the drug[2]. Multiple unit dosage forms (MUDFs) are formulated as granules, pellets, or mini tablets. The concept of this multiple unit dosage forms answers many formulating problems and is a common strategy to control the release of drug as showing the reproducible release profiles when compared to SUDFs. These MUDFs, can either be filled in to hard capsules or compacted in to bigger tablets or can be dispensed in a dose pouches or packets[3,4]. Pelletization can be defined as an agglomeration (size-enlargement) process that converts fine powders or particles of bulk drugs and excipients into small, free-flowing more or less spherical units called pellets[5]. Pelletization is often referred to as a size-enlargement process that involves the manufacture of agglomerates with a relatively narrow size range usually with mean size from 0.5 to 2.0 mm, named “pellets”. Compaction and Drug layering are the most widely used Pelletization techniques in the pharmaceutical industry. Of the compaction techniques used, extrusion and spheronization is the most popular method [6,7]. There are other few Pelletization methods such as Melt pelletization, Globulation, Balling and Compression are also used in the development of pharmaceutical pellets although in a limited scale[8]. Thus, being a consumer-friendly alternative, over the single unit dosage forms many of the pharmaceutical companies are switching their product franchise to improve the technology[9,10]. This technology option can also provide a good platform for patent non-infringing product development.

MATERIALS AND METHODS

Materials

Propronolol Hcl was obtained as a gift sample from Pellets Pharma Ltd., Hyderabad, India. Ethyl cellulose 7cps,

HPMC E-5, HPMC pthalate 55, Diethyl phthalate and Povidone K-30 was obtained as a gift sample from Pellets Pharma Ltd. All other ingredients, reagents and solvents were of analytical grade.

Methods

Drug loading (Pan Coating)

Step1: Weigh appropriate quantities of all the ingredients required for drug loading.

Step2: Take Povidone, IPA into tank, switch on homogenizer and mix for 10mins.

Step3: Load Milled Drug on to sugar spheres while spraying povidone solution in pancoater.

Step4: Unload the Drug loaded pellets from the pan & dry at specified temp for about 3 hrs (55 – 65℃).

Step5: Load Milled sucrose onto dried pellets while spraying povidone solution & dry at specified temp for about 3 hrs (55 – 65℃)

Polymer loading (Fluid Bed Coating)

Step1: Load HPMC E-5 polymer solution under fluidization of the pellets with peristaltic pump till completion of the solution and maintain the fluidization for 10 min.

Step2: Load HPMC P55 polymer solution and maintain the fluidization for 10 min.

Step3: Load Ethyl cellulose 7cps polymer solution and maintain the fluidization for 10 min.

EVALUATION PARAMETERS

The prepared pellets were evaluated for Loss on drying, Drug content, Bulk density, Friability, Scanning Electron microscopy, Percentage yield and In vitro dissolution studies.

Loss on Drying:

Determination on 1g by drying in an oven at 100-105°C for 5min. Weigh the empty bottle (W_1). Put the sample in the bottle, replace the cover and accurately weigh the bottle with content (W_2) by gentle side- wise shaking, distribute the sample as evenly as practicable to a depth of about 5mm.Place the loaded bottle in the drying chamber. Dry the sample at the specified temperature in desicator before weighing[11]. Weigh the bottle(W_3). The difference in successive weighing should be less than 0.3%. Loss on drying is calculated by the formula.

$$\% LOD = \frac{W2 - W3}{W2 - W1} \times 100$$

Friability:

Roche friabilator was used to determine the friability of the pellets. It is expressed in percentage (%). Initially 5gm of pellets were weighed and transferred into the friabilator. It was operated at 25 rpm for 4 minutes[12]. The pellets were weighed again after 4 minutes the % friability was then calculated by using the formula.

% Friability= initial weight - final weight/ Initial weight*100

Percentage yield:

All the formulations of Propranolol HCl pellets prepared by pan coating and fluid bed coating were evaluated for percentage yield. The actual percentage yields of pellets were calculated by using the following formula.

Percentage yield of pellets =_Practical yield of pellets / Theoretical yield of pellets x 100

Bulk Denisity:

A quantity of 5 gm of pellets weighed and transferred to a measuring cylinder and observed the volume occupied by the sample. The initial volume was noted. Bulk density was calculated using the formula.

Bulk Density = Mass/ Volume

Drug Content Uniformity:

Take 3g of pellets into a mortor and grind finely. Transfer sample powder equivalent to 100mg weighed quantity of Propranolol Hydrochloride WS in 100ml volumetric flask. Add 25ml of water, sonicate and makeup to the volume. Filter, transfer 2ml of filtrate to 50ml volumetric flask and dilute with water. Check the absorbance at 320 nm.

Sieve analysis:

Take about 25g of sample into top [Lowest sieve number] sieve. Close the sieve nest with top lid. Place the sieve nest in an Electromagnetic sieve shaker and fix the nest by using knobs, adjust the amplitude to 10 and run the sieve shaking for 5 minutes[13,14]. Take out each sieve and transfer the contents to the tarred container and weigh on electrical balance. Calculate retention % on each sieve.

In Vitro Dissolution Studies:

In-vitro drug release studies were carried out using USP XXIV dissolution apparatus type I, with 900ml of dissolution medium maintained at 37±0.5°C for 24hrs, at 100 rpm,(pH 1.2) 0.1N HCL buffer for 1.5 hour and 6.8 phophate buffer for remaining hours as dissolution medium. Sample was withdrawn at pre determined time intervals replacing with an equal quantity of drug free dissolution fluid. The samples withdrawn were filtered through 0.45µ membrane filter, and concentration of drug in each sample was analyzed by UV spectrophotometer at 320 nm and cumulative percent drug release was calculated. The study was performed in triplicate.

DRUG RELEASE KINETICS:

Zero order release rate kinetics:

To study the zero order release kinetics the release rate data are fitted to the following equation

$$F=K_0t$$

Here, F is the fraction of drug release
K_0 is the rate constant
T is the release time

First order model:

This model has also been used to describe absorption and/elimination of drug, the release of the drug which followed first order kinetic can be expressed by the equation

$$\text{Log } C = \log c_0 - kt/2.303$$

Where, C_o is the initial concentration of drug

K is the first order rate constant

t = is the time

Higuchi release model:

To study the higuchi release kinetics, the release rate data was fitted to the following equation

$$F = K_H.t^{1/2}$$

Where, F is the amount of the drug release

Kh is the release time

t is the release time

Korsmeyer and peppas model:

The release rate date were fitted to the following eqution,

$$Mt/M8 = K_M.t^n$$

Where, Mt/M8 is the fraction of drug release

K_M is the release constant

t is the release time

RESULTS

Table.1.Optimization of drug loading stage (per each capsule)

S.no	Ingredients	Trial-1	Trial-2	Trial-3
1.	Propranolol HCl	140	140	140
2.	Non pariel seeds (20#25)	70	80	80
3.	Povidone k30 (2% & 3%)	6	9	--
4.	Povidone k90 (2%)	--	--	6
5.	Sugar powder	40	40	40
6.	HPMC e5	2	2	2
7.	Povidone s630	2	2	2
8.	Isopropyl alcohol	Q.S	Q.S	Q.S
9.	Water	Q.S	Q.S	Q.S

*** Quantities were taken in milligrams**

Table.2. Polymer loading stage for optimized (trial II) pellets

Ingredients (mg)	F-1	F-2	F-3	F-4	F-5	F-6	F-7
HPMC P55	1.5	2	3	3.5	4	4.5	5
Ethyl cellulose(7cps)	1.5	1.5	2	2	3	3	4.5
Cetyl alcohol	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Diethyl pthalate	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Talc	0.9	0.9	0.9	0.9	0.9	0.9	0.9
IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Acetone	q.s	q.s	q.s	q.s	q.s	q.s	q.s

*** Quantities were taken in milligrams**

Table.3. Physical parameters of pellets

Formulations	Bulk density	Tapped density	Carr's index	Hausners ratio	Angle of repose
F-1	0.80±0.02	0.85±0.06	5.88±1.23	1.06±0.04	26.54±0.02
F-2	0.75±0.04	0.80±0.02	6.25±0.98	1.06±0.02	26.84±0.06
F-3	0.75±0.01	0.81±0.05	7.40±1.12	1.08±0.05	25.98±0.05
F-4	0.80±0.03	0.86±0.04	6.97±1.24	1.07±0.08	26.38±0.08
F-5	0.81±0.06	0.87±0.06	6.89±1.61	1.07±0.06	26.10±0.01
F-6	0.77±0.02	0.83±0.03	7.22±0.92	1.07±0.02	27.12±0.05
F-7	0.76±0.03	0.81±0.04	6.17±0.86	1.14±0.05	26.78±0.02

Table.4.Evaluation of pellets

Formulations	LOD	Particle size	Friability	Percentage yield	Assay
F-1	2 ±0.2	1072 ± 20	0.53 ±0.06	94	98.2 ± 0.3
F-2	1.8 ±0.1	1073 ± 25	0.52 ±0.01	95	97.6 ± 0.6
F-3	2.1 ±0.4	1066 ± 16	0.43 ±0.03	92	99.5 ± 0.4
F-4	1.9 ±1.1	1061 ± 24	0.47 ±0.06	94	101.9 ± 0.2
F-5	2.2±0.5	1085± 34	0.45 ±0.09	92	98.2 ± 0.5
F-6	1.9 ±0.1	1081± 24	0.49 ±0.12	96	99.8 ± 0.4
F-7	1.8 ±0.9	1075± 27	0.55 ±0.06	95	97.7 ± 0.4

Table.5.*In Vitro* Dissolution Data

S.no	Time (hr)	F-1	F-2	F-3	F-4	F-5	F-6	F-7
1.	1.5	45±1.7	39.7±1.8	22.9±1.7	21.7±2.1	20.9±2.3	20.1±1.6	18.2±1.7
2.	4	78.9±2.1	65.7±2	61.5±2.5	52.7±1.9	41.2±2.4	35.5±1.9	28.5±2.1
3.	8	97.3±2.4	89.2±2.6	82.6±2.4	75.6±2.4	55.6±1.5	48.2±1.5	37.6±1.8
4.	14	--	95.7±2.1	98.8±2.2	81.4±2.1	79.5±1.9	68±2.2	51.7±2.4
5.	24	--	--	--	90.6±2.6	93.6±2.1	98.9±2.6	78.6±2.5

Table.6. Machine parameters for pan coater

Process Controls	Specifications
Pan speed	20-25 rpm
Inlet air temperature	45°c
Nozzle diameter	1mm
Atomizing air pressure	2.5 kg/cm^2
Spray rate	20-30 gm/min

Table.7. Machine parameters for Fluid Bed Coater

Process Controls	Specifications
Batch size	500 G
Inlet air temperature	40°c
Outlet air temperature	35°c
Product temperature	35°c
Chamber humidity	60% RH
Air flow	2000-4500 cfm
Nozzle aperture	1.2 mm
No of spray guns	1
Spray direction	Bottom spray
Spray pressure	2.5 kg/cm^2

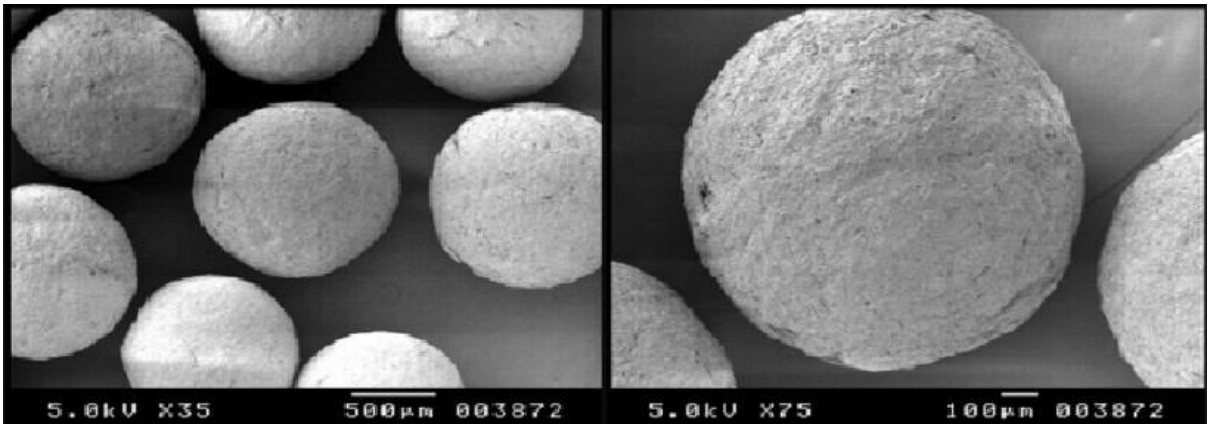

Fig.1.SEM image of pellets

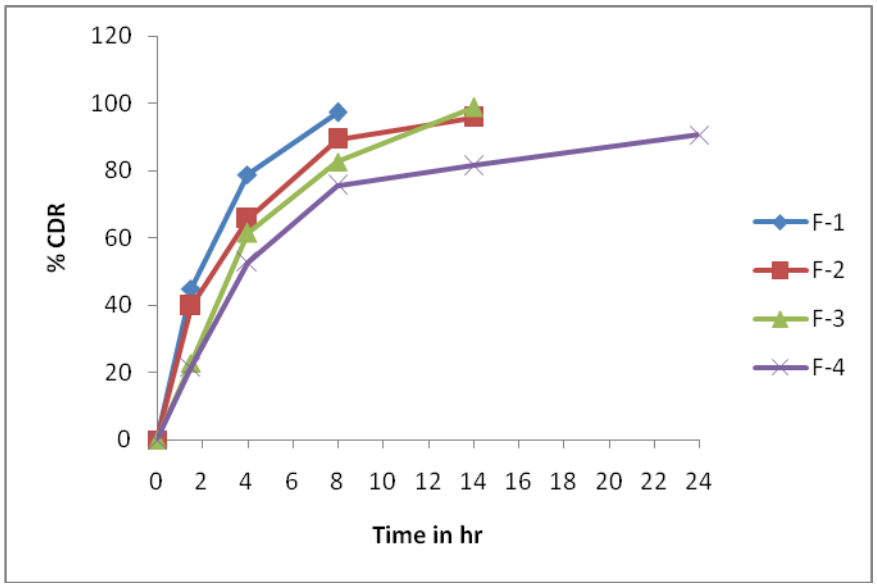

Fig.2. *In Vitro* Dissolution Profile For Batches F1 – F4

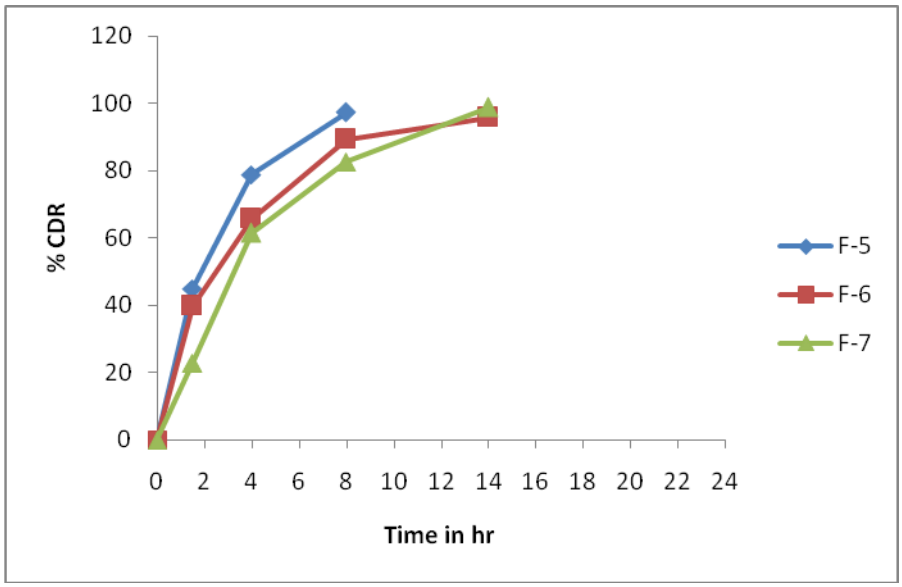

Fig.3. *In Vitro* Dissolution Profile For Batches F5 – F7

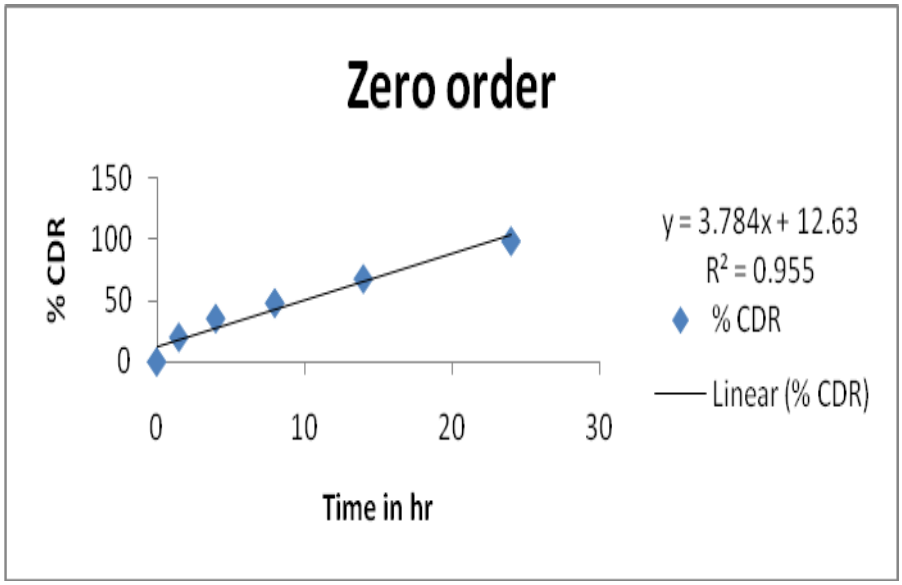

Fig.3. Graphical representation of Zero order kinetic studies of F-6

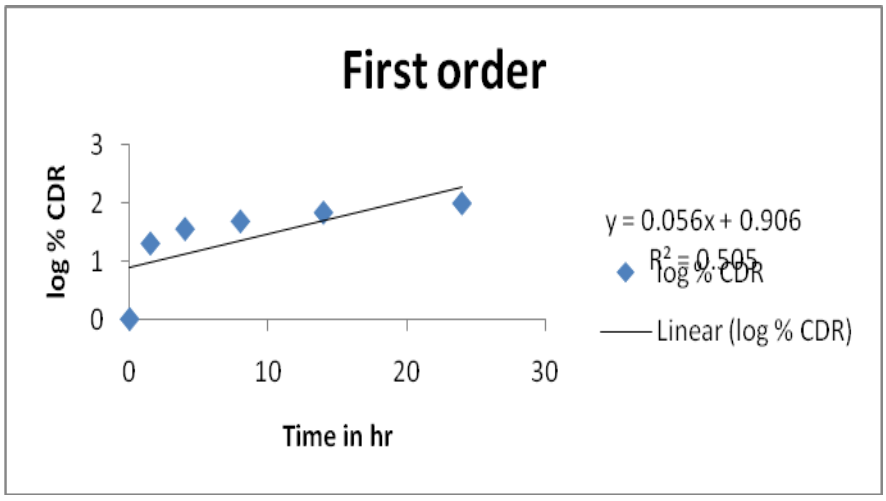

Fig.4. Graphical representation of First order kinetic studies of F-6

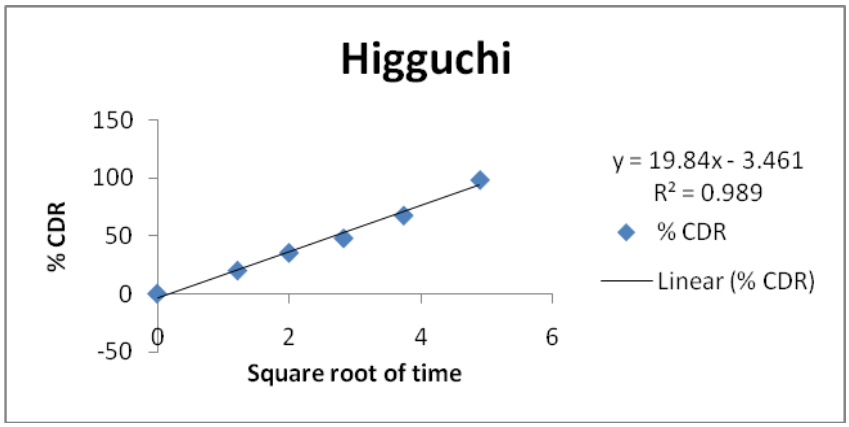

Fig.5. Graphical representation of Higuchi mechanism of release of F-6

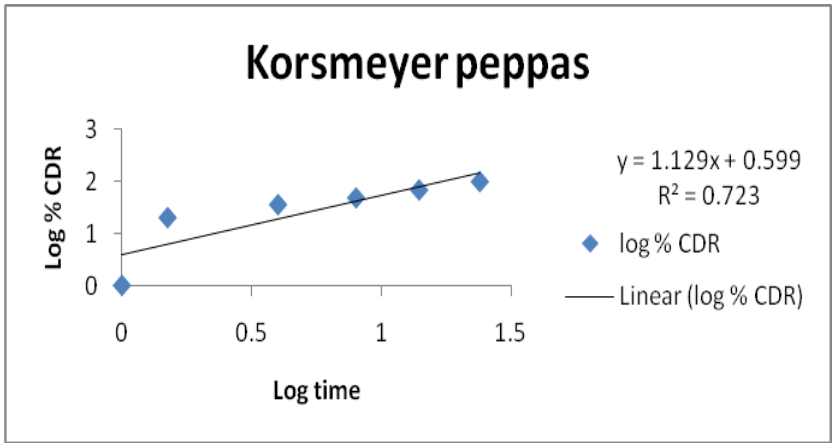

Fig.6. Graphical representation of Peppas mechanism of release of F-6

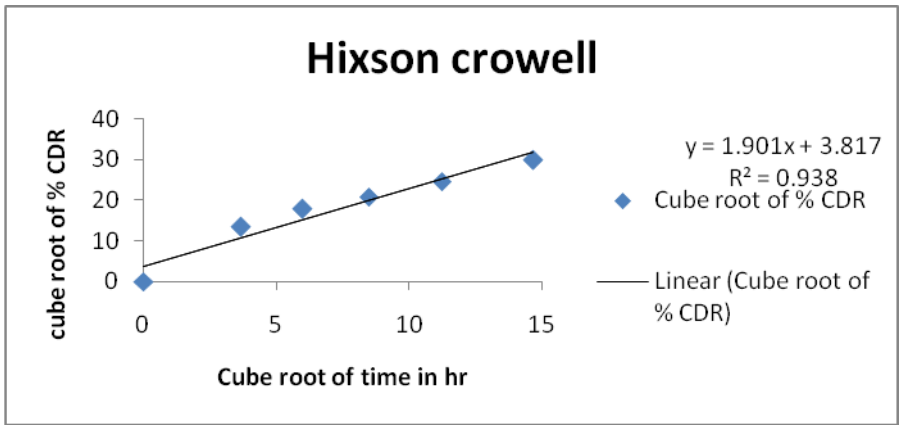

Fig.7. Graphical representation of Hixson&Crowell mechanism of release of F-6

DISCUSSION

Evaluation of physical parameters of pellets:

The important parameters in the production of pellets were evaluated and reported in Table 1.3 and Table 1.4. The bulk density and tapped density varied from 0.37 to 0.41 and 0.45 to 0.49 respectively. Hausner`s s ratio and carr`s index varied from 1.16 to 1.22 and 14 to 18 respectively. The results showed that good flow property and compressibility. Loss on drying varied from 1.8-2.2%.

Dissolution Studies

Based on the objectives of the present investigation, the pellets were evaluated for release of Propranolol HCl. Dissolution studies were attempted. The results are shown in Table 1.5

The dissolution data reveals that the rate of dissolution was decreasing linearly with increasing concentration of polymer. By using the polymers like HPMC E-5 and Ethyl cellulose 7cps results were found. In kinetic data formulation F-6 (98.9%) were follows Zero order means describes the systems where the drug release rate is independent of its concentration of the dissolved substance and Higguchi mechanism of drug release

CONCLUSION

The present investigation carried out to develop a extended release pellets of Propranolol HCl. Pellets were prepared by using drug layering technique. The release of Propranolol HCl from the formulations is proportional to the concentration of polymers. As the concentration of polymers increases, the drug release rate decreases. Result of the study based on in vitro performance clearly suggests that extended release can be achieved by incorporating hydrophobic and hydrophilic polymers.

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