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FORMULATION AND EVALUATION OF PULSATILE SALUBUTAMOL SULPHATE TABLET IN CAPSULE PULSATILE RELEASE DEVICE FOR ASTHMA

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ABSTRACT

That the drug should not be released at all during the initial phase of dosage form administration. Such a release pattern is known as pulsatile release. In the present research work, we have attempted to develop a novel dosage form by using a chronopharmaceutical approach. This novel system or a technique consists of one i.e. the immediate release powder and the extended release tablet. This novel system is a so-called “tablet in capsule”. The object of this study is to formulate and evaluate pulsatile tablet in capsule device of salbutamol sulphate drug by using HPMC K100M and HPMC K15 polymers.

Keywords: pulsatile drug delivery system, salbutamol sulphate, tablet in capsule device.

INTRODUCTION

Oral controlled drug delivery systems represent the most popular form of controlled drug delivery system for the more obvious advantage of the oral routes of the administration. Pulsatile drug delivery system useful for prevention of peak-valley fluctuations, reduction in dose of drug, reduced dosage frequency, avoidance of side effects, and improved patient compliance. The principle rationale for the use of pulsatile release is for the drugs where a constant drug release, i.e., a zero-order release is not desired. The release of the drug as a pulse after a lag time (an interval of no drug release) has to be designed in such a way that a complete and rapid drug release follows the lag time. In chronopharmacotherapy (timed drug

therapy) drug administration is synchronized with biological rhythms to produce maximal therapeutic effect and minimum harm for the patient. By basing drug delivery on circadian patterns of Diseases, drug effect can be optimized and side effects can be reduced. Pulsatile release is also useful for the targeting of the drug irritating the stomach or degradable therein, as well for drugs developing biological tolerance or with an extensive first-pass metabolism.

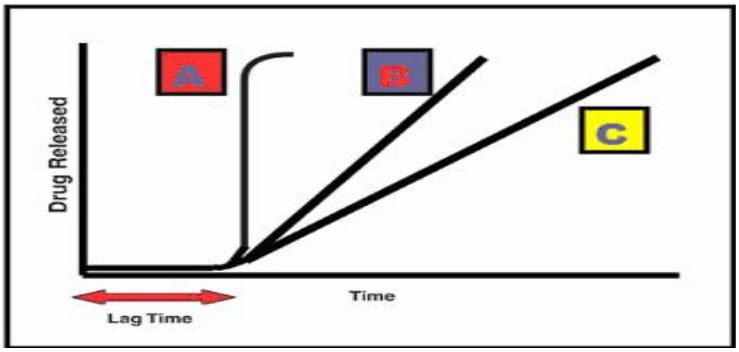

Figure No. 1: Drug release profile of pulsatile drug delivery system [1, 2]

A: Ideal sigmoidal release

B & C: Delayed release after initial lag time

The first pulsed delivery formulation that released the active substance at a precisely defined time point was developed in the early 1990s. In this context, the aim of the research was to achieve a so-called sigmoidal release pattern (pattern A in Figure). The characteristic feature of the formulation was a defined lag time followed by a drug pulse with the enclosed active quantity being released at once. Thus, the major challenge in the development of pulsatile drug delivery system is to achieve a rapid drug release after the lag time. Often, the drug is released over an extended period of time (patterns B & C in Figure). For this concept we are selected and formulate the asthmatic drug is salbutamol sulphate. The object of this study is reduce the nocturnal asthma and chronic obstructive pulmonary disease (COPD) and Drug release at particular time at particular site.

Formulation on leaving the stomach arrives at the ileocecal junction in about 5 to 6 hours after administration and difference in pH throughout GIT, a time and pH dependent pulsatile drug delivery system was designed.

Necessity of pulsatile drug delivery systems

♦ First pass metabolism.

♦ Biological tolerance.

♦ Special chronopharmacological needs.

♦ Local therapeutic need.

♦ Gastric irritation or drug instability in gastric fluid.

Advantages of pulsatile delivery

- Reduced side effects.
- Extended daytime or night time activity.
- Dosage frequency.
- Reduction in dose size.
- Improved patient compliance.
- Lower daily cost to patient due to fever dosage units are required by the patient in therapy.
- Drug adapts to suit circadian rhythms of body functions or diseases.
- Drug targeting to specific sites colon.
- Protection of mucosa from irritating drugs.
- Drug loss is prevented by extensive first pass metabolism.

Drawbacks of pulsatile delivery

- Lack of manufacturing reproducibility and efficacy.
- Large number of process variables.
- Multiple formulation steps.
- Higher cost of production.
- Need of advanced technology.

Chronopharmacotherapy

Recent studies show that diseased have predictable cyclic rhythms and the timing of medication regimens can improve outcome in selected chronic conditions. "Chronopharmaceutics" consist of two words chronobiology and Pharmaceutics [2]. Chronobiology is the study of biological rhythms and their mechanisms. There are three types of mechanical rhythms in our body, they are:

- Circadian.
- Ultradian.
- Infradian.

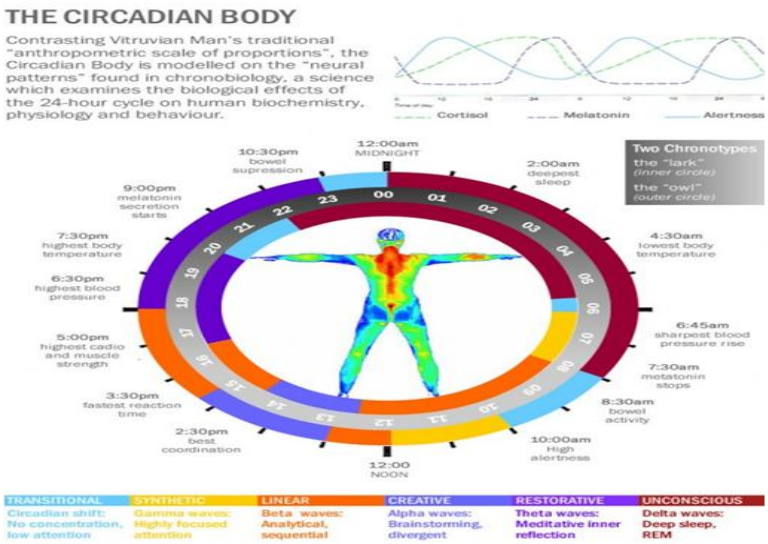

Fig 2: Diseases displaying circadian rhythm.

Diseases and chronotherapeutics

The potential benefits of chronotherapeutics have been demonstrated in the management of a number of diseases. In particular there is a great deal of interest in how chronotherapy can particularly benefit patients suffering from allergic rhinitis, rheumatoid arthritis and related disorders, asthma, cancer, cardiovascular diseases, and peptic ulcer disease.[5-15]

Pulsatile system - to increase therapeutic efficacy of drug

In recent years considerable attention has been focused on the development of pulsatile drug delivery system. Delivery system with pulsatile release pattern has gained most popular form of controlled drug delivery system because conventional systems with a continuous release are not ideal. Oral controlled drug delivery systems are generally used due to convenient dosage form & it also releases drug in constant or variable rates. In these system drug release generally occurs within therapeutic window for prolong period of time. Hence these systems show sustained release of drug from dosage form.

METHODOLOGY

Materials for the extended release tablets

Salbutamol sulphate, HPMC K100M, HPMC K15, Sodium CMC, MCC, Magnesium stereate.

All ingredients supplied from SERIN FORMULATION PVT.LIMITED**.**

Preparation of ER Tablets (Direct compression)

- All the excipients except Mg stearate were cosifted through # 40 ASTM & blended in a poly bag for 10 min
- To the above mixture # 60 ASTM passed Mg stearate were added & lubricated by blending in a poly bag for 5 min.
- ER tablets of 100 mg weight were prepared by direct compression method using 7 mm concave punch with single station tablet compression machine.

Table 1: Formulation of Salbutamol sulphate ER tablets by direct compression Method

INGREDIENTS	F1 mg/tab	F2 mg/tab	F3 mg/tab	F4 mg/tab	F5 mg/tab	F6 mg/tab	F7 mg/tab
salbutamol	6	6	6	6	6	6	6
hpmc k100m	-	-	50	75	50	60	37.5
hpmc k15	50	75	-	-	-	-	-
sodium cmc	25	-	25	-	-		37.5
mcc	18	18	18	18	43	33	18
magnesium stereate	1	1	1	1	1	1	1
total weight	100	100	100	100	100	100	100

Preparation of IR Powder

♦ All the excipients except Mg stearate were cosifted through # 40 ASTM and blended in a poly bag for 10 min.

♦ to the above mixture # 60 ASTM passed Mg stearate were added and lubricated by blending in a poly bag for 5 min. IR Powder was prepared .

Table 2: Formulation of Salbutamol sulphate IR powder for capsule

INGREDIENTS	F1 mg/tab	F2 mg/tab	F3 mg/tab	F4 mg/tab	F5 mg/tab
salbutamol	2	2	2	2	2
mcc	50	97.57	97.57	146	72.57
lactose monohydrate	98	50.43	50.43	-	73.43
ssg	3	3	5	5	5
aerosil	1	1	1	1	1
magnesium stereate	1	1	1	1	1
total weight	155	155	157	155	155

PREPARATION METHOD: Tablet In capsule method

Prepare Immediate Release powder & next Extend Release tablet For ER tablet maintain punch 5-7Kg/cm^2 In capsule first fill ER Tablet & next with coating of erodible polymer & later filled with IR powder.

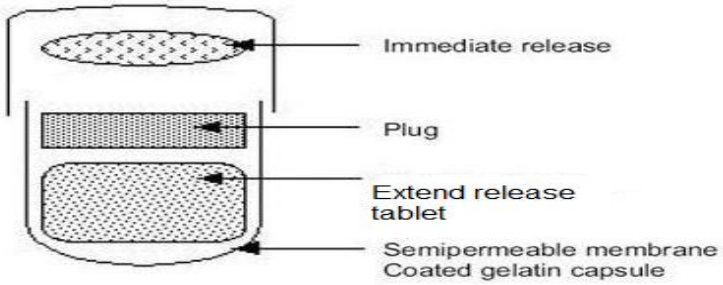

Fig 3 : tablet in capsule device

EVALUATION OF TABLETS AND POWDERS

The formulated tablets were evaluated for the following Pre, post compression quality control studies & In vitro Buoyancy studies and dissolution studies.we have to prepare ER tablets and ir powder separately. IR powder separately keep in capsule and perform dissolution. IR tablet also separately do the dissolution. After dissolution we have to keep IR powder in a capsule then ER tablet also keep in that same capsule.

A) PRE COMPRESSION STUDIES

1. Angle of Repose

It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane.

Angle of Repose of granules was determined by the funnel method. Accurately weighed powder blend was taken in the funnel. Height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. Powder blend was allowed to flow through the funnel freely on to the surface. Diameter of the powder cone was measured and angle of repose was calculated using the following equation.

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

Where:

θ = angle of repose
h = height in cms
r = radius in cms

The angle of repose has been used to characterize the flow properties of solids. It is a characteristic related to inter particulate friction or resistance to movement between particles.

Flow Properties and Corresponding Angles of Repose.

Table 3: Angle of Repose Limits

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

2. Density

a) Bulk density (BD): It is the ratio of total mass of powder to the bulk volume of powder Weigh accurately 25 g of granules, which was previously passed through 22 # sieve and transferred in 100 ml graduated cylinder. Carefully level the powder without compacting, and read the unsettled apparent volume. Calculate the apparent bulk density in gm/ml by the following formula.

Bulk density = weight of powder / Bulk volume.

$$\mathbf{D_b} = \frac{M}{V_0}$$

M = mass of the powder

V_0 = bulk volume of the powder.

b) Tapped density (TD)

It is the ratio of total mass of powder to the tapped volume of powder.

Weigh accurately 25 g of granules, which was previously passed through 22# sieve and transferred in 100 ml graduated cylinder of tap density tester which was operated for fixed number of taps until the powder bed volume has reached a minimum, thus was calculated by formula .

Tapped density = Weigh of powder / Tapped volume

$$\mathbf{Dt} = (M) / (V_f).$$

M = mass of the powder

V_f = tapped volume of the powder.

3.Carr's Index

Compressibility index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the BD and TD of a powder and the rate at which it packed down. The formula for Carr's index is as below:

$$\textbf{Compressibility index} = 100 \times \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}}$$

4. Hausner's Ratio

Hausner's Ratio is a number that is correlated to the flow ability of a powder.

$$\textbf{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Scale of Flow ability (USP29-NF34)

Table 4: Compressibility Index Limits

Compressibility Index (%)	Flow Character	Hausner's Ratio
≤ 10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very Poor	1.46-1.59
> 38	Very, very Poor	> 1.60

B) POST COMPRESSION STUDIES

1. **General appearance:** The formulated tablets were assessed for its general appearance and observations were made for shape, colour, texture and odour.
2. **Average weight/Weight Variation:** 20 tablets were selected and weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to assure whether it was within permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 300 mg tablets and none by more than double that percentage.

$$\textbf{Average weight} = \frac{\textbf{weight of 20 tablets}}{\textbf{20}}$$

$$\textbf{\%weight variation} = \frac{\textbf{average weight - weight of each tablet}}{\textbf{Average weight}} \times 100$$

Acceptance criteria for tablet weight variation (USP 29-NF 34)

Table 5: Weight variation tolerance for uncoated

Average weight of tablet(mg)	% difference allowed
130 or Less than	± 10
130-324	± 7.5
More than 324	± 5

6. Assay Procedure

tablets

3. Thickness: Thickness of the tablets (n=3) was determined using a Vernier calipers

4. Hardness test: Hardness of the tablet was determined by using the Monsanto hardness tester (n=3) the lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

5. Friability test: This test is performed to evaluate the ability of tablets to withstand abrasion in packing, handling and transporting.

Initial weight of 20 tablets is taken and these are placed in the Friabilator, rotating at 25rpm for 4min.

The difference in the weight is noted and expressed as percentage.

It should be preferably between 0.5 to 1.0%.

$$\%\text{Friability} = [(W_1-W_2)/W_1] \times 100$$

Where, W_1= weight of tablets before test,

W_2 = weight of tablets after test

Weigh and finely powder not less than 20 tablets. Transfer an accurately weighed portion of the powder equivalent to about 10mg of model drug a 10 ml volumetric flask. Add approximately 6ml of 0.1N HCl and shake and sonicate for 10 min to complete the extraction. Dilute the methanol to volume and mix. Pipette 1ml aliquot into a 10ml volumetric flask, dilute with mobile phase to volume, mix and filter. From it withdraw take 1ml aliquot and make up to mark with buffer.

Calculate the quantity in mg of model drugHydrochloride in the portion taken by the formula

assay = test absorbance/standard absorbance*standard concentration/sample concentration*purity of drug/100*100

7. In vitro Dissolution Study

i) 900 ml of 0.1N HCl was placed in the vessel and the USP-II apparatus (Paddle method) was assembled. The medium was allowed to equilibrate to temperature of 37^0C±0.5^0C. A tablet was placed in the vessel and was covered; the apparatus was operated up to 12 hrs at 50 rpm. At definite time intervals, 5 ml of dissolution medium was withdrawn; filtered and again replaced with 5 ml of fresh medium to maintain sink conditions. Suitable dilutions were done with dissolution medium and were analyzed spectrophotometrically at λ_{max} =276 nm using a UV-spectr ophotometer (Lab India).

Table 6: Dissolution parameters for 0.1 N HCL.

Parameter	Details
Dissolution apparatus	USP -Type I (basket)
Medium	0.1N HCl.
Volume	900 ml
Speed	50 rpm
Temperature	37± 0.5 ºC
Sample volume withdrawn	5ml
Time points	0,10,15,30,45 mins
Analytical method	Ultraviolet Visible Spectroscopy
λ_{max}	276 nm

ii) 900 ml of 6.8 phosphate buffer was placed in the vessel and the USP-II apparatus (Paddle method) was assembled. The medium was allowed to equilibrate to temperature of 37^0C±0.5^0C. A tablet was placed in the vessel and was covered; the apparatus was operated up to 12 hrs at 50 rpm. At definite time intervals, 5 ml of dissolution medium was withdrawn; filtered and again replaced with 5 ml of fresh medium to maintain sink conditions. Suitable dilutions were done with dissolution medium and were analyzed spectrophotometrically at λ_{max} =276 nm using a UV-spectrophotometer (Lab India).

Table7: dissolution parameters for 6.8 phosphate buffer

Parameter	Details
Dissolution apparatus	USP -Type II (paddle)
Medium	6.8 Phosphate buffer
Volume	900 ml
Speed	50 rpm
Temperature	37± 0.5 ºC
Sample volume withdrawn	5ml
Time points	1,2,4,6,8,10,12hr
Analytical method	Ultraviolet Visible Spectroscopy
λ_{max}	276nm

C) In vitro Release Kinetics Studies

The analysis of drug release mechanism from a pharmaceutical dosage form is important but complicated process and is practically evident in the case of matrix systems. The order of drug release from FDDS was described by using zero order kinetics or first order kinetics. The mechanism of drug release from FDDS was studied by using Higuchi equation and the Peppa's-Korsemeyer equation.

1. Zero Order Release Kinetics

It defines a linear relationship between the fractions of drug released versus time.

$$Q=k_0t.$$

Where, Q is the fraction of drug released at time t and $k_o$is the zero order release rate constant. A plot of the fraction of drug released against time will be linear if the release obeys zero order release kinetics.

2. First Order Release Kinetics

Wagner assuming that the exposed surface area of a tablet decreased exponentially with time during dissolution process suggested that the drug release from most of the slow release tablets could be described adequately by the first-order kinetics. The equation that describes first order kinetics is

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

Where C is the amount of drug dissolved at time t,

C_o is the amount of drug dissolved at t=0 and

k is the first order rate constant.

A graph of log cumulative of log % drug remaining vs time yields a straight line.

Will be linear if the release obeys the first order release kinetics.

3. Higuchi equation

It defines a linear dependence of the active fraction released per unit of surface (Q) and the square root of time.

$$Q=K_2t^{1/2}$$

Where K_2 is release rate constant. A plot of the fraction of drug released against square root of time will be linear if the release obeys Higuchi equation. This equation describes drug release as a diffusion process based on the Fick's law, square root time dependent.

4. Peppa's-Korsemeyer equation (Power Law)

In order to define a model, which would represent a better fit for the formulation, dissolution data was further analysed by Peppa's-Korsemeyer equation (Power Law).

$$Mt/\mathbf{M}_\infty = K.t^n$$

Where, Mt is the amount of drug released at time t

M_α is the amount released at time α,

M_t/M_α is the fraction of drug released at time t,

K is the kinetic constant and n is the diffusion exponent.

To characterize the mechanism for both solvent penetration and drug release n can be used as abstracted . A plot between log drug release upto 60% against log of time will be linear if the release obeys Peppa's-Korsemeyer equation and the slope of this plot represents "n" value.the kinetic data of the formulations were included .Nature of release of the drug from the designed tablets was inferred based on the correlation coefficients obtained from the plots of the kinetic models. The data were processed for regression analysis using MS EXCEL.

Table 8: Drug release kinetics mechanism

Diffusion exponent(n)	Mechanism
0.45	Fickian diffusion
0.45 < n <0.89	Anomalous(Non- Fickian) diffusion
0.89	Case II transport
n > 0.89	Super Case II transport

RESULTS AND DICUSSION

1. Construction of Standard calibration curve of Salbutamol sulphate in 0.1N HCl

The absorbance of the solution was measured at 276nm, using UV spectrometer with 0.1N HCl as blank. The values are shown in table no 20. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer's law in the concentration range 2 to 10 µg/ml.

Table 9: Standard Calibration graph values of Salbutamol sulphate in 0.1N HCL at λ_{Max} = 276 nm

Conc.(µg / ml)	Absorbance at λ_{Max} = 276 nm
0	0
2	0.097
4	0.18
6	0.27
8	0.35
10	0.45

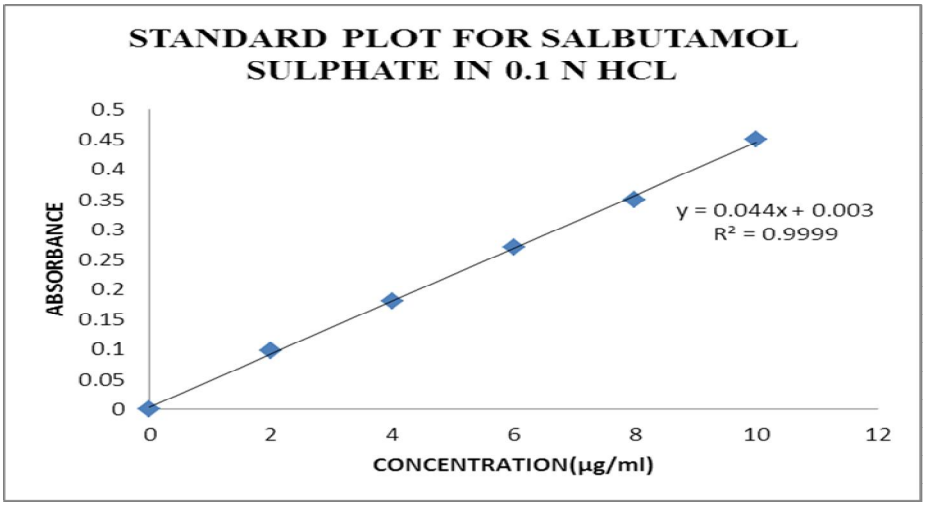

Figure 4: Standard calibration curve of Salbutamol sulphate in 0.1N HCL at λ_{Max} = 276 nm.

Inference : The standard calibration curve of Salbutamol sulphate in 0.1N HCl showed good correlation with regression value of 0.9999.

2. Construction of Standard calibration curve of Salbutamol sulphate in 6.8 phosphate buffer

Table 10: Standard Calibration graph values of Salbutamol sulphate 6.8 phosphate buffer at λ_{Max} = 276 nm

Conc.(µg / ml)	Absorbance at λ_{Max} = 276 nm
0	0
10	0.061
20	0.126
30	0.186
40	0.239
50	0.302

The absorbance of the solution was measured at 276nm, using UV spectrometer with 6.8 phosphate buffer as blank. The values are shown in table no 20. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer's law in the concentration range 10 to 50 µg/ml.

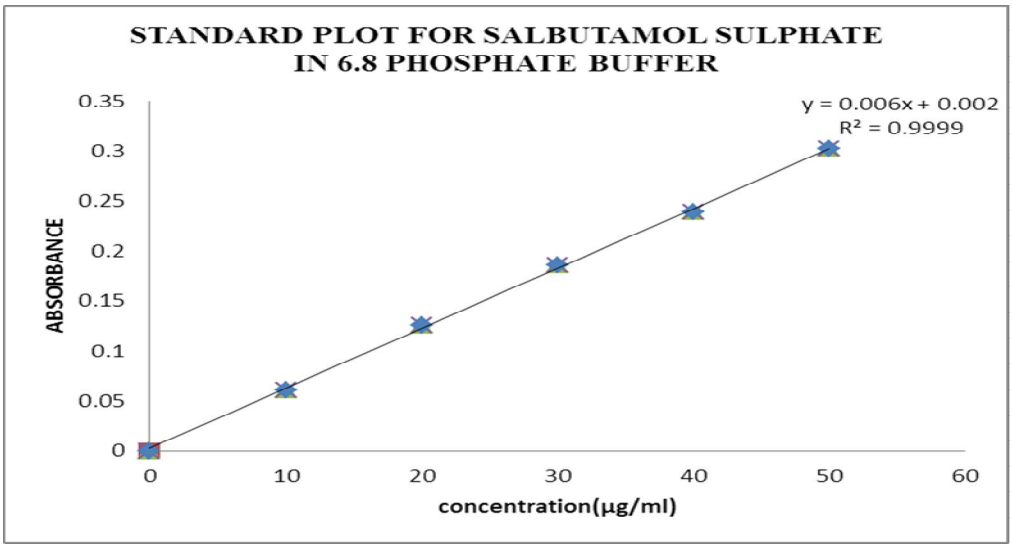

Figure 5: Standard calibration curve of Salbutamol sulphate in 6.8 phosphate buffer at λ_{Max} = 276 nm

Inference: The standard calibration curve of Salbutamol sulphate in 6.8 phosphate buffer showed good correlation with regression value of 0.9999.

Evaluation of Tablets and Powders

A) Pre Compression studies for ER Tablets.

Table: 11: Pre compression studies of Salbutamol sulphate ER tablets

Formulation Code	Bulk density (Kg/cm^3)	Tapped density (Kg/cm^3)	Cars index	Hausners ratio	Angle of repose (˚)
F1	0.40	0.48	16	1.2	12.73
F2	0.39	0.48	18	1.23	11.96
F3	0.50	0.58	13	1.16	11.58
F4	0.44	0.50	12	1.1	9.92
F5	0.37	0.41	9.75	1.1	11.14
F6	0.36	0.39	7.6	1.0	11.03
F7	0.41	0.45	8.8	1.0	11.85

Inference

- The blends prepared for Dry granulation of tablets were evaluated for their flow properties; the results for the blends of compression tablets were shown in Table:15.
- The bulk density and the tapped density for all formulations were found to be almost similar.
- The Carr's index and Hausner's ratio were found to be in the range of ≤ 18 and 1.0 to 1.23 respectively, indicating good flow and compressibility of the blends.
- The angle of repose for all the formulations was found to be in the range of 9.92-12.73˚ which indicating Excellent flow.

B) Pre compression studies for IR Powder

Table 12: pre compression studies of salbutamol sulphate IR powder

Formulation Code	Bulk density (Kg/cm^3)	Tapped density (Kg/cm^3)	Cars index	Hausners ratio	Angle of repose (˚)
F1	0.610	0.714	14	1.17	17.9
F2	0.590	0.685	13	1.16	22.8
F3	0.640	0.667	15	1.15	20.02
F4	0.621	0.756	17	1.12	24.09
F5	0.652	0.653	15	1.14	24.08

Inference

- The blends prepared for immediate release powder were evaluated for their flow.

  Properties; the results for the blends of powder were shown in table 16.
- The bulk density and the tapped density for all formulations were found to be almost similar.

- The Carr's index and Hausner's ratio were found to be in the range of ≤ 18 and 1.12 to 1.17 respectively, indicating good flow and compressibility of the blends.
- The angle of repose for all the formulations was found to be in the range of 17.9-24.09˚ which indicating Excellent flow.

C) Post compression studies

Table: 13 Post compression studies of ER tablets

Formulation Code	% weight vaiation	Thickness± SD n=3 (mm)	%*friability	%Drug Content± SD n=3	Hardness (Kg/cm^2) Avg wt hardness ± SD n=3
F1	pass	5.03±0.05	0.132	99.6±1.5	4.63 ±0.057
F2	pass	5.03±0.15	0.143	98.9 ±2.3	4.2 ±0.057
F3	pass	4.93±0.05	0.110	100.2± 1.7	4.7 ±0.1
F4	pass	5.1±0.1	0.133	100.5± 1.4	4.53 ±0.057
F5	pass	5.06±0.11	0.142	101.3 ±1.2	4.56 ±0.057
F6	pass	5.06±0.15	0.151	102.3 ±1.7	5.03 ±0.115
F7	pass	5.03±0.057	0.62	100.1 ±1.2	5 ±0.1

*Test for Friability was performed on single batch of 20 tablets

Inference

- The variation in weight was within the range of ±7.5% complying with pharmacopoeia specifications of USP.
- The thickness of tablets was found to be between 4.9-5.2 mm.
- The hardness for different formulations was found to be between 4.2 to 5.0 kg/cm^2, indicating satisfactory mechanical strength
- The friability was < 1.0% W/W for all the formulations, which is an indication of good mechanical resistance of the tablet.
- The drug content was found to be within limits 98 to 102 %.

D) Invitro Dissolution Studies Of Salbutamol Sulphate ER Tablet and IR Powder

Dissolution profile for 6.8 phosphate buffer

Table14:dissolution profile(6.8 phosphate buffer)

Parameter	Details
Dissolution apparatus	USP -Type II (paddle)
Medium	6.8 Phosphate buffer
Volume	900 ml
Speed	50 rpm
Temperature	37± 0.5 ºC

Sample volume withdrawn	5ml
Time points	1,2,4,6,8,10,12hr
Analytical method	Ultraviolet Visible Spectroscopy
λ_{max}	276nm

Dissolution parameters for 0.1 N HCL

Table :15 Dissolution profile (0.1N HCL)

Parameter	Details
Dissolution apparatus	USP -Type I (basket)
Medium	0.1N HCl.
Volume	900 ml
Speed	50 rpm
Temperature	37± 0.5 ºC
Sample volume withdrawn	5ml
Time points	0,10,15,30,45 mins
Analytical method	Ultraviolet Visible Spectroscopy
λ_{max}	276 nm

Inference

- The standard calibration curve of Salbutamol sulphate in 6.8 phosphate buffer showed Good correlation with regression value of 0.9999. 6.8 phosphate buffer for ER Tablets in- vitro dissolution studies.
- The standard calibration curve of Salbutamol sulphate in 0.1 N HCL buffer showed Good correlation with regression value of 0.9999. 0.1N HCL buffer for IR Powder. in- vitro dissolution studies.

Table 16: Invitro Dissolution Studies for an Salbutamol sulphate IR Powder

Time (mins)	% drug released in 0.1 N HCL, USP I, 50 rpm				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
10	35	50	60	50	52
15	65	75	75	76	76
30	82	82	90	90	91
45	86	87	96	94	95

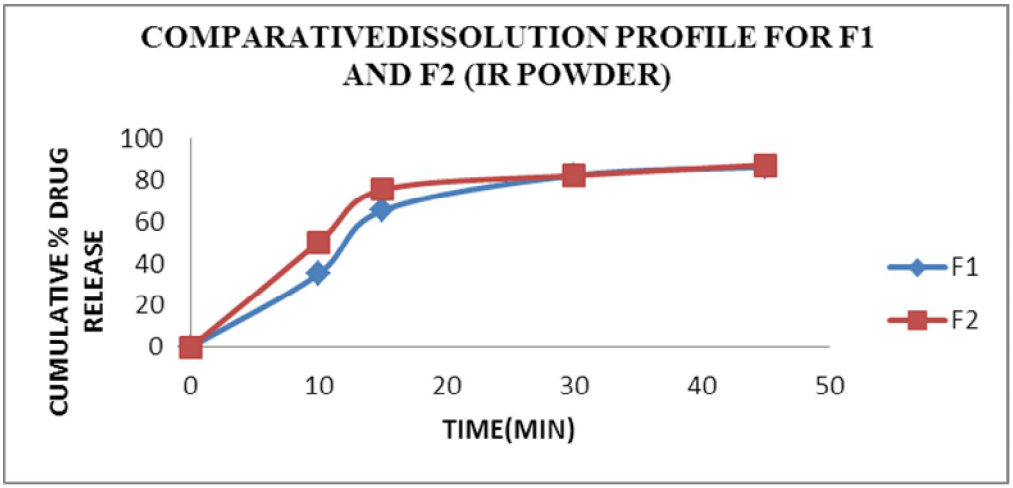

Figure 6: comparative dissolution profile for F1 and F2 IR powder

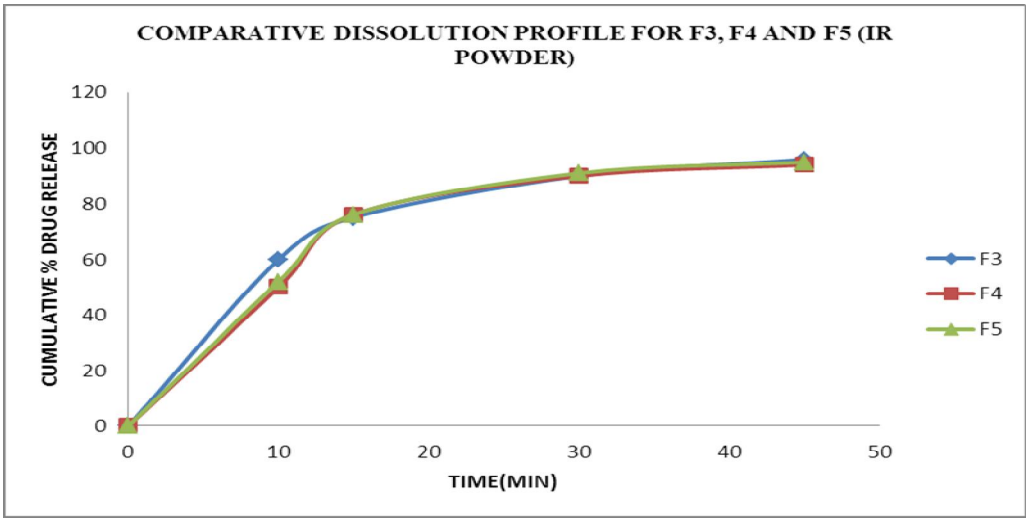

Figure 7: comparative dissolution profile for F3, F4 and F5 IR powder

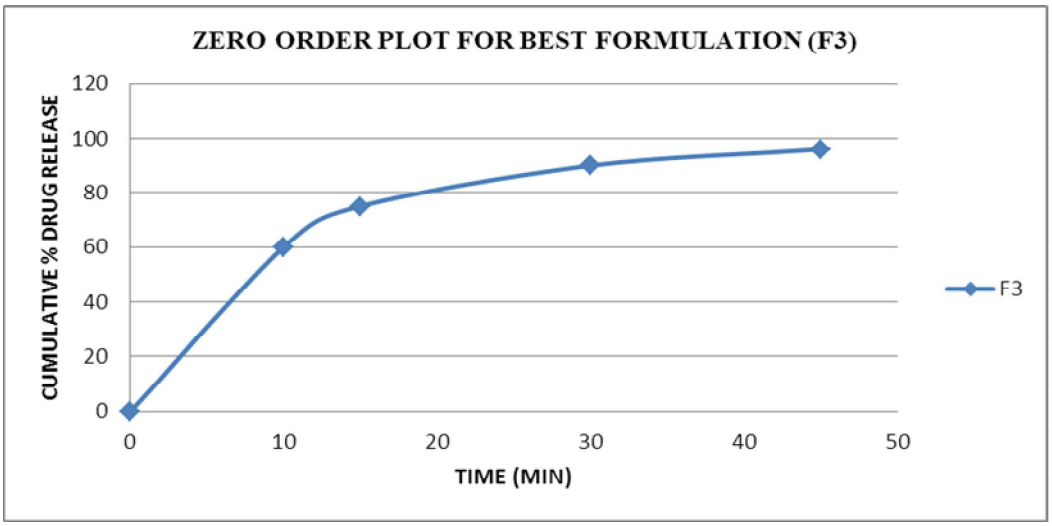

Figure 8: Zero order plot for best formulation F3 for IR powder

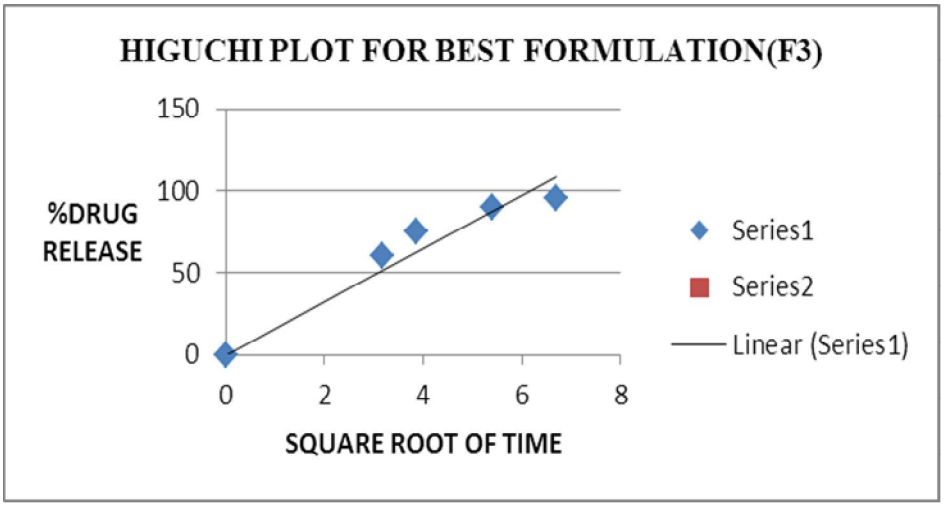

Figure: 9 Higuchi plot for best formulation F3 for IR Powder

Table 17: Invitro Dissolution Studies for an Salbutamol sulphate ER Tablet

%DRUG RELEASED IN 6.8 PH BUFFER, USP II, 50 rpm							
TIME (hrs)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
0	0	0	0	0	0	0	0
1	8	8	5	4	6	6	8
2	15	17	10	10	15	15	17
4	40	35	21	18	29	24	30
6	60	50	34	28	43	40	42
8	82	64	50	41	54	51	55
12	93	77	61	53	65	61	70
16	94	88	75	66	81	75	84
20	-	96	94	80	96	91	95
24	-	98	96	84	97	93	96

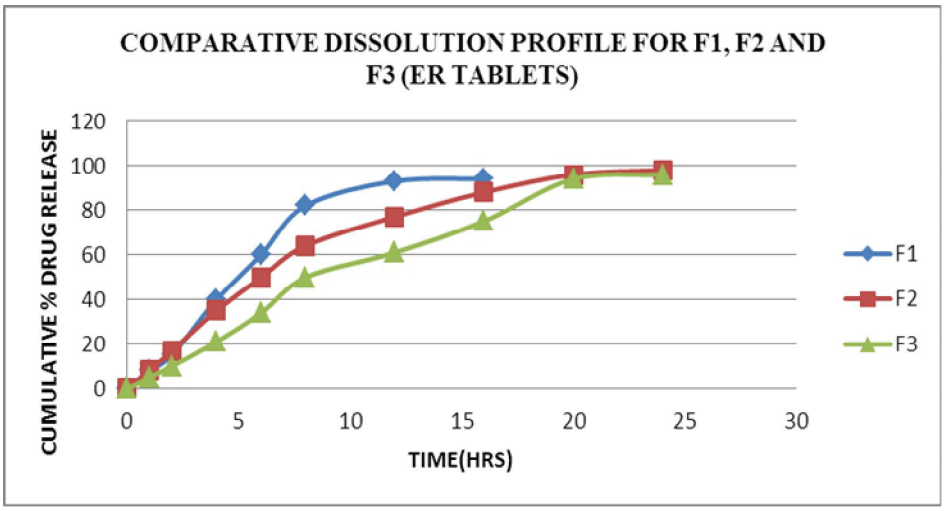

Figure 10: comparative dissolution profile for F1, F2 and F3 ER Tablets

Table 18: R^2 value and n result table

Formulation code	R square value				n value
	Zero order	First order	Higuchi plot	Pepas plot	
F2	0.948	0.99	0.986	0.98	0.791

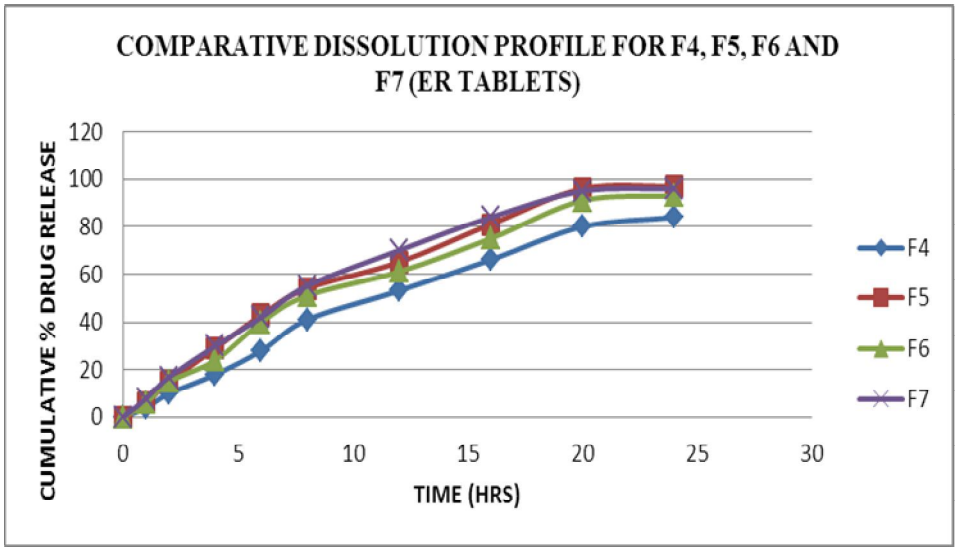

Figure 11: comparative dissolution profile for F4, F5, F6 and F7 ER Tablets

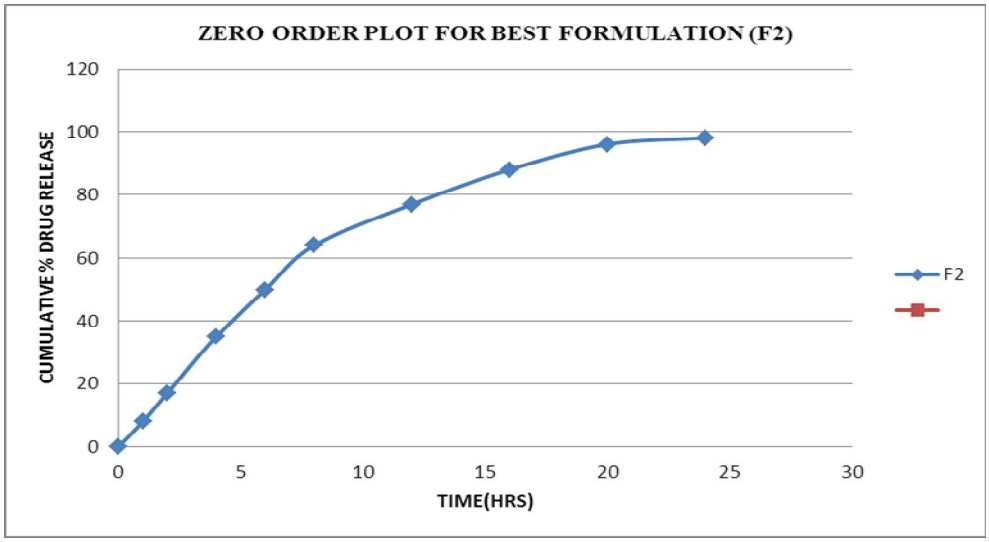

Figure 12: Zero order plot for best formulations F2 for ER Tablets

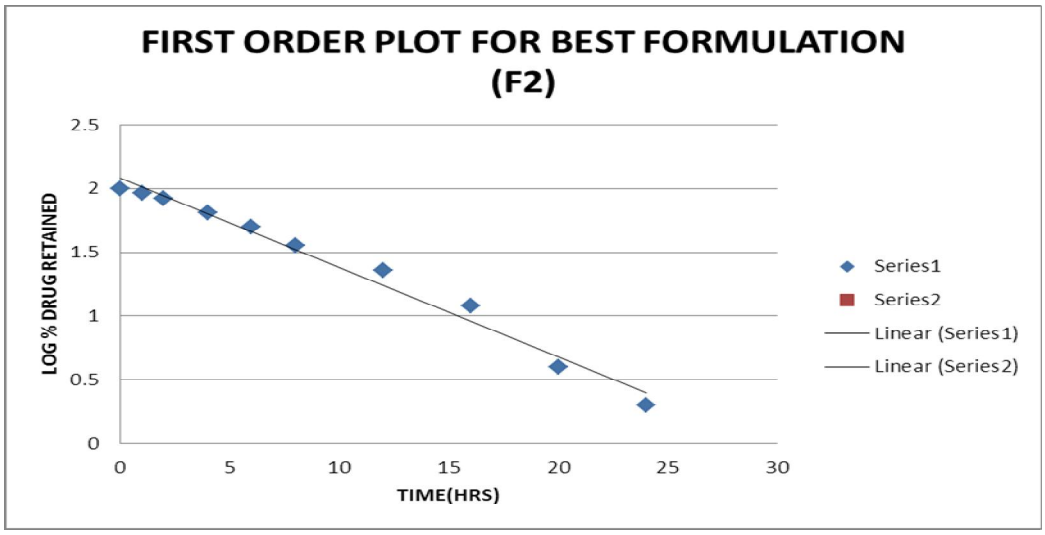

Figure 13: First order plot for best formulation F2 for ER tablets

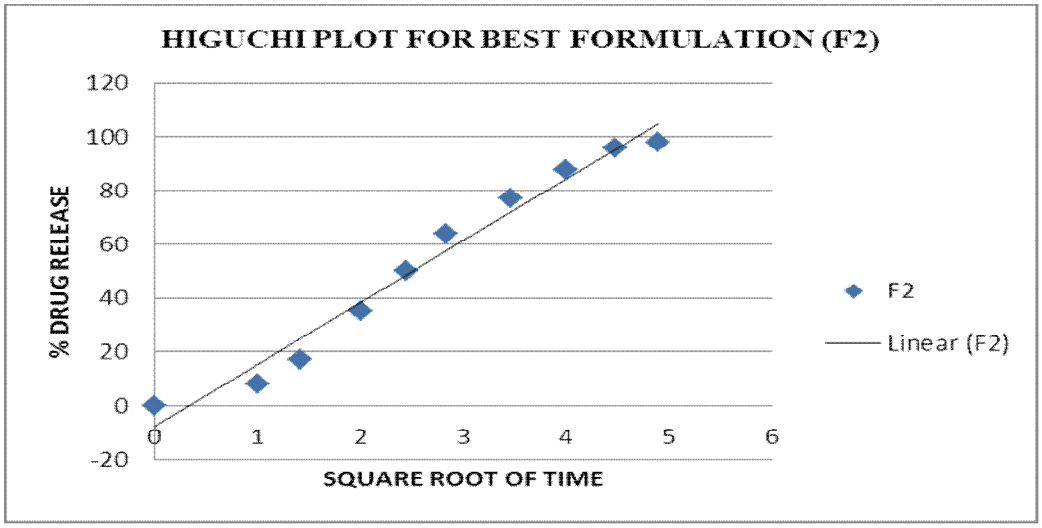

Figure 14: Higuchi plot for best formulation F2 for ER tablets

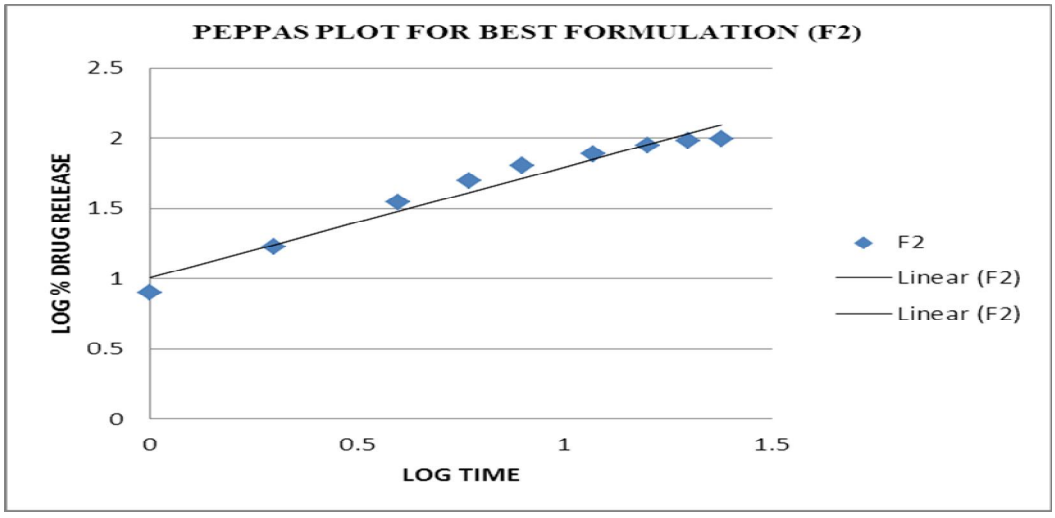

Figure 15: kors mayers pepas plot for best formulation F2 for ER tablets

Inference for ER Tablets

- Among the different control release polymers HPMC k15m was showing highest drug release retarding capacity
- F2was showing the satisfactory results and having better sustainability
- When we plot the release rate kinetics for best formulation F2 was following first order because correlation coefficient value of first order is more than zero order to value.
- F2 formulation diffusion exponent n value is 0.45 < n >0.89 so they are following Anomalous(Non- Fickian) diffusion
- Higuchi plots F2 formulation is having good correlation values so the drug is releasing diffusion mechanism.

Inference for IR Powder

- Among the different Diluents and binders 97.57 mg/tab and 50.43 mg/tab showing highest drug release retarding capacity.
- F3 was showing the satisfactory results.
- Higuchi plots F3 formulation is having good correlation values so the drug is releasing diffusion mechanism
- When we plot the release rate kinetics for best formulation F3 was following zero order.

SUMMARY AND CONCLUSION

From the experimental data, it can be concluded that

- HPMC K15M was respectively showed better Pulsatile drug release of Salbutamol sulphate by using direct compression method.
- When drug : polymer concentration increases the release rate decreases this is because of reason when the concentration of polymer increases the diffusion path length increases
- Formulated tablets showed satisfactory results for various Post compression evaluation parameters like: tablet thickness, hardness, weight variation, floating lag time, total floating time, content uniformity and *in vitro* drug release.
- Formulation F2 gave better-controlled drug release and in comparison to the other formulations.
- The release pattern of the F2 formulation was best fitted to Korsmeyer-Peppas model, Higuchi and first-order model.
- The most probable mechanism for the drug release pattern from the formulation was Anomalous(Non- Fickian) diffusion
- F3 better formulation for IR Powder.

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