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RESEARCH ARTICLE

DISSOLUTION BEHAVIOUR OF DICLOFENAC POTASSIUM USING DUAL RELEASE SPHEROIDS

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ABSTRACT

The objective of the present work was attempted to formulate a dual release drug delivery system comprising immediate release and delayed release pattern using solid dispersion and pellets of diclofenac potassium and to achieve a customized *in vitro* profile for developed formulation. Diclofenac potassium is chosen as a model drug, as it is classified under BCS-II with low solubility, an attempt was made to increase solubility with solid dispersion. Lactose is selected as a carrier. Solid dispersion is made with concentrations of carrier ratios (1:1,1:2,1:3,1:4,1:5). It was evident that *in vitro* drug release of the optimised batch (SD4) shows promising increase of solubility same is taken for the further studies to prepare a dual release dosage form as a immediate release formulation. Sustain release spheroids was formulated with different concentrations of polymer HPMC K 100M.The results revealed that all the values are within the range formulation D3 was selected as an ideal batch for further studies to prepare a dual release dosage form as a sustained release formulation based on the *in vitro* performance. The dual release dosage form was constructed using the optimized batches from solid dispersion (SD4) and pellets (D3). The prepared dual release dosage form was evaluated for *in vitro* release studies The release models were plotted in the dual release dosage form .It was observed that the developed dual release spheroids follow first order kinetics obeying fickian diffusion.
Keywords: Pellets, Solid dispersion, Diclofenac potassium, HPMC

INTRODUCTION

Oral administration is conventional to be leading route of drug delivery. More than 50% of drug delivery systems (DDSs) reachable in the market are oral DDSs. These dosage forms are easy to manage and increase patient compliance However the growth of such systems is prohibited by several physiological difficulties. In truth orally administered dosage forms are exposed to broad range of greatly variable conditions during their transit throughout the gastrointestinal tract[1] .Usually oral dosage forms are classified as a single unit and multiple unit dosage forms . Multiparticulate dosage forms are getting a huge concentration as alternative drug delivery system for the oral route of administration, even when the single unit dosage forms have been broadly used for decades. The most usually used pharmaceutical solid dosage forms today include granules, pellets, tablets and capsules, out of which tablets being the most popular dosage form, accounting for 70% of all moral pharmaceutical preparations produced [2]. But presently it was sensed that some of the formulating and clinical problems (free flowing property, dose dumping, dysphagia, etc.) comes along with the single dose formulations. This presently leads to the dividing of monolithic dosage forms into multiples. Multiple unit dosage forms (MUDFs) or multiparticulates, are formulated as granules, pellets, or mini tablets (1mm in diameter)[3]. The concept of this multiple unit dosage form solves several formulating problems and with a common approach to organize the release of drug as showing the reproducible release profiles when compared to single unit dosage forms. These MUDFs, can either be filled in to hard capsules or compressed into bigger tablets or can be dispensed in a dose pouches or packets. The most increasingly interesting area in the development of MUDF'S is incorporated into tablets instead of hard gelatin capsules in order to make it more economical for the consumers and gaining more attention currently[4].

The improvement of multiparticulate drug delivery systems such as mini tablets, spheroids is a promising area in pharmaceutical research concerned with a high control over the release rate of drug combined with a high flexibility on the modification of both the initial dose and the loading for maintaining the release of the drug to get steady therapeutic level[5]. Extended release products plan on releasing the drug continuously at a programmed rate in order to increase the patient compliance.

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This is estimated since the incidence of administration is reduced and peaks are cut to prevent high concentrations, locally or systemically, which can cause undesirable side effects. At the same time the dosage forms developed have following novelties improving GIT absorption, minimize local irritation, offers a high degree of flexibility, and reduces the dose dumping.

The main objective of the present work was to produce a dual release delivery system combining a fast release together with the slow release spheroids of the Diclofenac potassium. The further goal of the study was, to evaluate the *in vitro* release behavior for the developed dual release formulation.

MATERIALS AND METHODS

Diclofenac potassium was obtained gift sample from Karnataka antibiotics, Bangloore. HPMC K100M, Avicel PH 101, Lactose, Aerosil, Sodium hydroxide, Dichloromethane, Methanol was purchased from S.D Fine chem..Ltd, Mumbai, India.

Formulation of diclofenac potassium solid dispersion

Diclofenac potassium solid dispersions were prepared by solvent evaporation method using lactose as carrier at different ratios. The drug and carrier were dissolved in a mixture of dichloromethane and methanol (1:1 vol/vol) and triturated in dry mortar until the solvent is evaporated. The resultant solid dispersion was scraped out with a spatula, pulverized in a mortar and pestle. Stored in an airtight container for further analysis. The compositions of different batches are shown in Table 1.

Table 1: compositions of different batches

S.NO	Drug to carrier ratio	Code of solid dispersion
1	1:1	SD-1
2	1:2	SD-2
3	1:3	SD-3
4	1:4	SD-4
5	1:5	SD-5

Formulation of diclofenac potassium pellets

The required quantity of MCC as spheronization enhancer, HPMC as polymeric material and diclofenac sodium as model drug were weighed, to this mixture sufficient quantity of water as granulating agent was added to get a wet mass[6].The solid blend passed through the extruder model RRE/EXT-65/037 to form extrudates. The formed extrudates were introduced into the spheronizer model RRE/SPH-150/010 to get spherical pellets by varying different spheronization speed shown in Table 2.

Table 2: different concentrations of HPMC used in the formulation

Batch code	DRUG (gm)	HPMC (gm)	MCC PH 101	Granulating fluid (ml)
D1	8	2	20.5	15
D2	8	3.5	19	15

Preparation of dual release dosage form

The dual release dosage form was constructed using the optimized batches from solid dispersion (SD4) and pellets (D3). The amount of pellets equivalent to 100mg of Diclofenac and the amount of solid dispersion equivalent to 50mg were filled in a gelatin capsule (size 2) the prepared dual release dosage form were evaluated for *in vitro* experiments .

Characterization of diclofenac solid dispersion Solubility studies

Take clean and washed amber coloured volumetric flasks and then dry it in oven. The Excess amount of the drug was added to 10ml of the selected solvents such as water, 6.8 phosphate buffer.The solutions were kept in an isothermal shaker for 24 hours at 37oC. After 24 hours, the solutions were centrifuged, the supernatant was taken and assayed by UV/VISIBLE spectrophotometer. Further the concentration of the drug is obtained using following formula.

Concentration of drug (µg/ml) = Absorbance/ slope × dilution factor

In vitro drug release studies

In vitro release profile of solid dispersion and pure drug were performed using USP XXII type 2 dissolution apparatus (TDP-06P, Electro lab, Mumbai, India). Sample equivalent to 50 mg of diclofenac was filled in to capsules and subjected to in vitro dissolution study using 900 ml phosphate buffer pH 6.8 maintained at 37± 0.5ºC with a stirring speed of 50 rpm. Aliquot of 5ml was withdrawn at predetermined time intervals of 0, 5, 10, 15, 20, 30, 45, 60 and 90 min. The withdrawn volume was replaced with the same volume of dissolution medium to maintain the sink condition[7].The absorbance of the samples was measured at 282 nm using UV spectrophotometer. The results shown in Table 3.

Table 3: *In vitro* dissolution studies of solid dispersion formulations

TIME (min)	PURE DRUG	SD-1	SD-2	SD-3	SD-4	SD-5
0	0	0	0	0	0	0
15	15.693±1.0	19.56±1.7	23.987±1.5	21.954±0.1	31.752±0.8	26.897±0.9
30	26.557±1.1	29.897±1.8	39.123±1.3	52.137±0.2	69.836±0.7	54.876±0.7
60	34.567±1.3	48.987±1.7	47.657±1.9	65.453±0.3	72.815±0.5	68.356±0.5
120	40.887±1.4	68.908±1.6	72.98±1.7	78.787±0.4	84.568±0.3	73.765±0.3

In Vitro Dissolution Studies for Pellets

A quantity of pellets and which will be theoretically contain a drug content of 100mg Diclofenac was filled in the capsules and subjected to *in vitro* dissolution study using USP XXII model type II (paddle). 900ml of phosphate buffer pH 6.8 was transferred to each jar and placed them in a test assembly which is maintained at 37°C.

Table 4: *In vitro* Dissolution Profile of Diclofenac potassium pellets of D-1 to D-3 with different concentration of polymer

TIME	Percentage cumulative release		
	DI %CLR	D2 %CLR	D3 %CLR
0	0	0	**0**
0.083	31.75±1.7	18.52±0.6	**7.07±1.3**
0.42	48.12±0.3	24.65±0.1	**17.9±1.9**
0.74	58.11±0.8	35.96±0.8	**27.9±1.5**
2	80.46±1.3	45.78±1.6	**32.7±2.9**
3		52.83±1.3	**36.4±1.9**
4		65.98±1.8	**43.7±2.1**
5		72.56±0.5	**47.5±1.0**
6		84.87±1.1	**52.6±1.2**
7			**56.8±0.4**
8			**63.5±1.7**
10			**68.6±0.8**
12			**83.3±1.4**

The capsules were placed in the jar and the assembly was brought down to static position[8].

The medium was stirred at 50 rpm. 5ml of samples were withdrawn at different time intervals up to 12 h (0.083, 0.42, 0.74, 2, 3, 4, 5, 6, 7, 8, 10 and 12). Equal quantity of fresh medium was replaced after each sampling. The sample was diluted to 10 times and absorbance was measured at 282 nm. The results shown in Table 4.

Drug release kinetics [9,10] :

In order to investigate the mode of release data were fitted into zero-order, first-order, Higuchi, Korsmeyer-Peppas equations .The regression equations were calculated and the correlation coefficients were determined.

RESULTS AND DISCUSSION

Infrared spectroscopy

The FTIR spectra of the drug with polymer and excipients (HPMC, MCC, and lactose) showed there was no major shifting, loss or appearance of functional peaks between the spectra of drug, physical mixture of drug and excipients. It is concluded that the drug and excipients were compatible with each other without any chemical interaction. Figure 1.

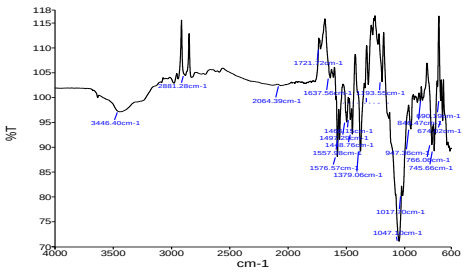

Figure:1(a) FTIR of HPMC

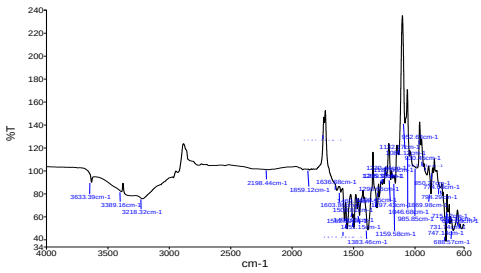

Figure:1 (b) FTIR of Lactose

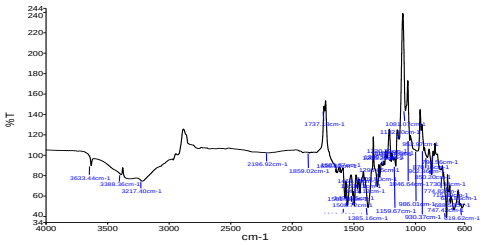

Figure:1(c)FTIR of Diclofenac

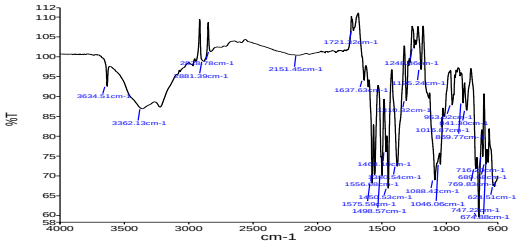

Figure:1(d)FTIR of Diclofenac+hpmc+lactose

Differential Scanning Calorimetry

The DSC thermogram of diclofenac potassium exhibited an endothermic peak o at 286.48 OC, which corresponds to the melting Point of diclofenac potassium. The carrier lactose showed an endothermic peak at 217.66 O C which corresponds to the melting point of lactose .There was only one endothermic peak observed for solid dispersions prepared using drug: carrier ratio, 1:4 at 217.66 OC. which corresponds to the melting of lactose . The disappearance of endothermic peak of drug (Diclofenac potassium) in solid dispersion gives an idea that diclofenac might be in dissolve state in melted lactose. This could be attributed to higher lactose concentration and uniform distribution of drug in the crust of lactose resulting in complete miscibility of molten drug in lactose. The disappearance of endothermic peak in solid dispersion formulations confirms the amorphous state of drug in prepared solid dispersion formulations. Figure 2.

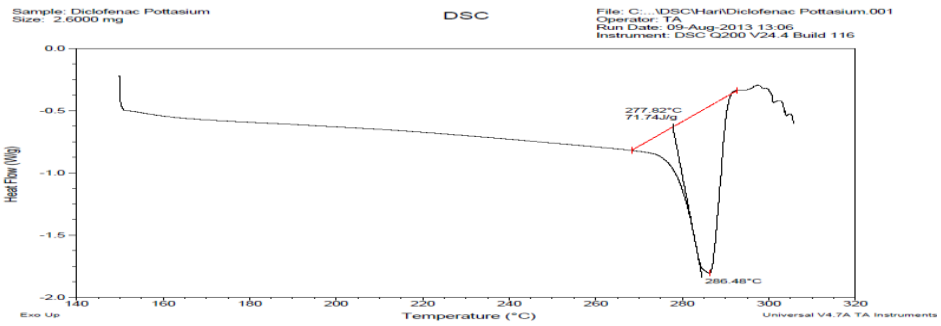

Figure 2(a): DSC of Diclofenac potassium

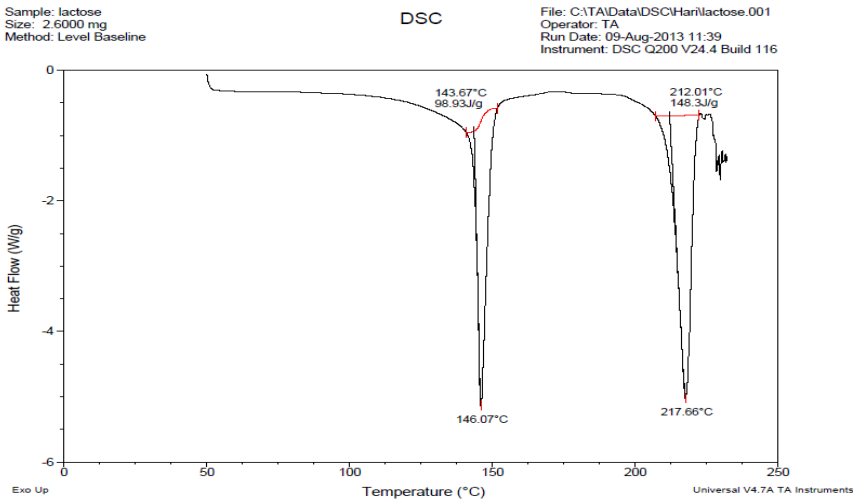

Figure 2(b): DSC Of Lactose

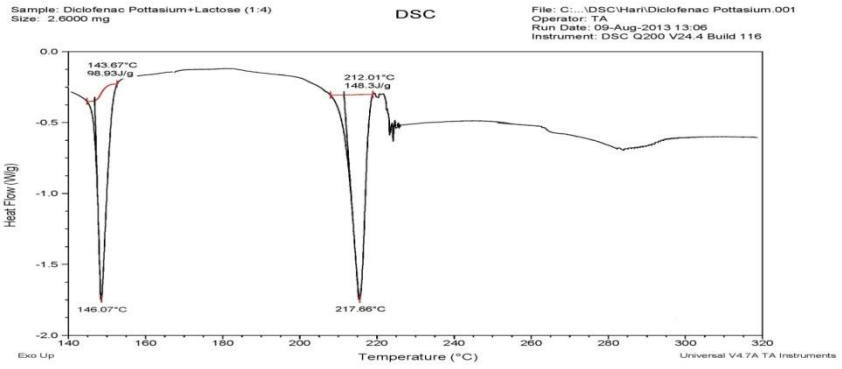

Figure 2(c): DSC of Diclofenac potassium+ Lactose

Drug content of solid dispersions

Percent drug content of various solid dispersion formulations i.e. SD1, SD2, SD3, SD4,and SD5 were found to be 95.9%, 97.4%, 96.8%, 97.9%, and 96.7%, respectively. The dissolution behavior of Diclofenac potassium from various SD formulations and the pure drug in PBS (pH 6.8) was examined in comparison with the intact drug by plotting the percentage of drug released against time shown in Figure 3. The drug release from different SD formulations prepared by solvent evaporation method followed the order: SD4 >

SD5 > SD3 > SD2 > SD1. It is evident that the rate of dissolution of pure drug is very low, only 40.8 % of the drug being dissolved within 2 h. Dispersion of the drug in the hydrophilic carrier's considerably enhanced dissolution compared to the pure drug. This was supposed to be due to the effect of molecular dispersion of the drug in lactose, and the decreased crystallinity of diclofenac potassium existing in SDs.

The dissolution rate of the solid dispersion formulations was higher compared to pure diclofenac potassium. From the *In vitro* drug release profile for different SD formulation, it is evident that amongst the SD formulated, there was an increase in dissolution up to the ratio 1:4, but after this there is no significant increase in the dissolution of the drug. This might be due to complete dispersion of drug with lactose at 1:4 ratio. Further, increase in carrier concentration, a decrease in dissolution rate was observed. This might be due to formation of the viscous boundary layer around the drug particles, leading to decrease in the dissolution rate. So, formulation SD4 was selected for further studies. Possible mechanisms of increased dissolution rates of drug in solid dispersions could be improved wettability and dispersibility of drug from the dispersion, solubilization effect of the carrier, absence of the aggregation of drug, reduction of drug crystallinity, dissolution of the drug in the hydrophilic carrier and conversion of the drug to the amorphous state. The results are shown in Table 5.

Table 5: Comparison of *In vitro* drug release of optimized dual release formulation (pellets) with marketed formulations

TIME (h)	MARKETED IR	SOLID DISPERSION	MARKETED SR	D3	IR + SR (% CR)(H5)	IR + SR (AMOUNT CR)
0	0	**0**	0	0	0	0
0.083	21.642±0.6	31.752±0.8	1.39±0.9	7.07±1.3	16.54±0.9	24.812
0.42	43.1284±0.7	69.836±0.7	3.85±1.0	17.9±1.9	37.29±1.4	55.936
0.74	49.1148±0.8	72.815±0.5	8.84±1.1	27.9±1.5	59.61±1.8	89.415
2	76.4672±0.9	84.568±0.3	10.66±1.5	32.7±2.9	64.24±0.3	96.368
3			14.01±1.3	36.4±1.9	68.6±1.1	102.9
4			17.98±1.2	43.7±2.1	74.06±1.2	111.1
5			20.58±0.5	47.5±1.03	79.8±0.5	119.7
6			32.63±1.6	52.6±1.2	81.8±1.9	122.7
7			38.55±1.3	56.8±0.4	85.6±1.6	128.4
8			49.02±1.8	63.5±1.7	88.26±0.4	132.4
10			53.60±1.0	68.6±0.8	90.26±0.9	135.4
12			59.53±1.8	83.3±1.4	94.73±0.5	142.1

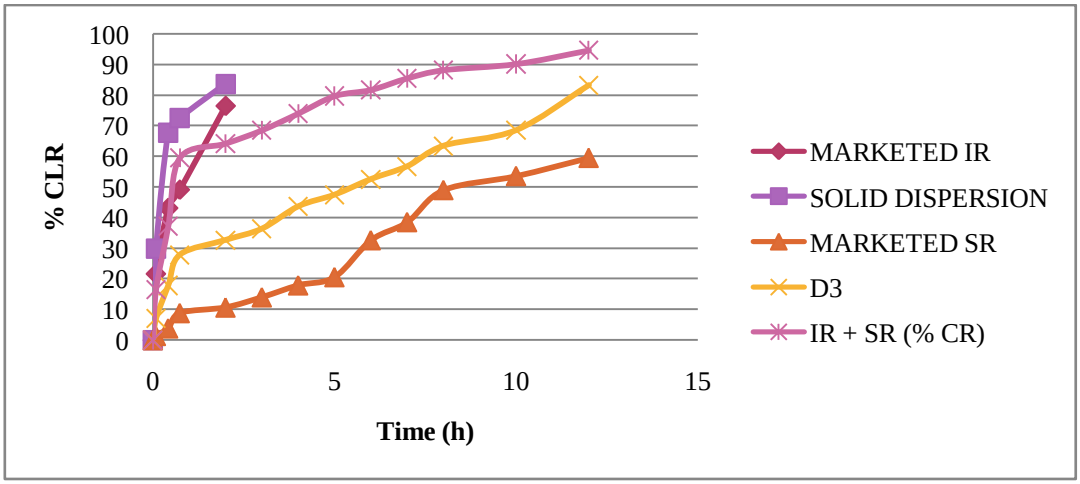

Figure 3: In vitro drug release studies of solid dispersion and spheroids

Drug release kinetics:

In order to investigate the mode of release data were fitted into zero-order, first-order, Higuchi, Korsmeyer-Peppas equations Figure 4-7. .The regression equations were calculated and the correlation coefficients were determined and shown in Table 6.

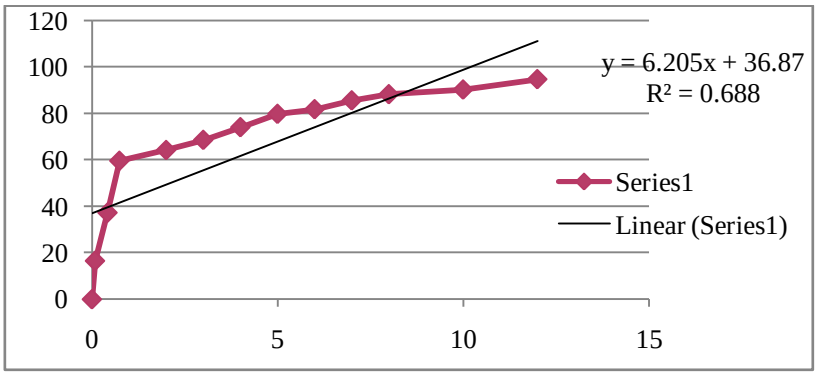

Figure 4: Zero order kinetics

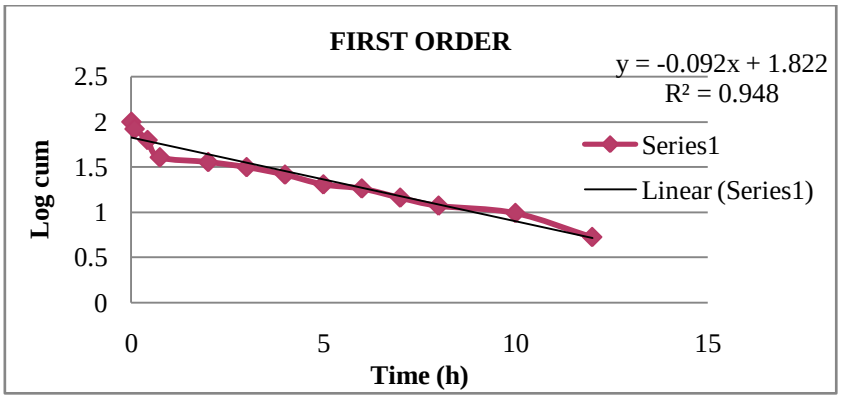

Figure 5: First order kinetics

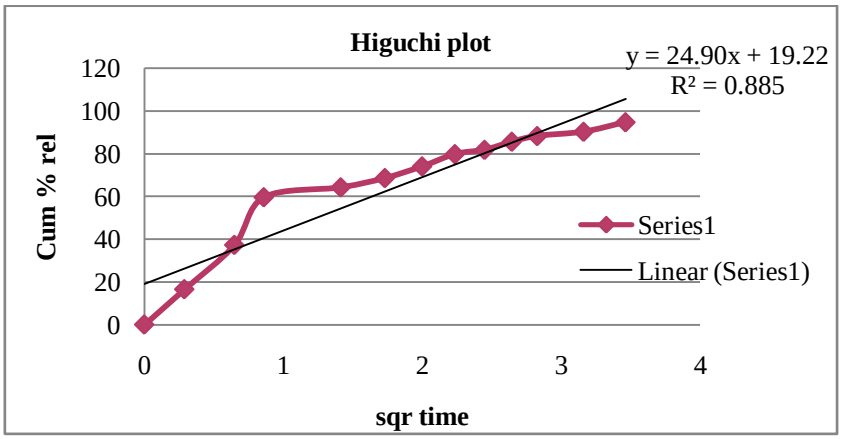

Figure 6: Hieguchi plot

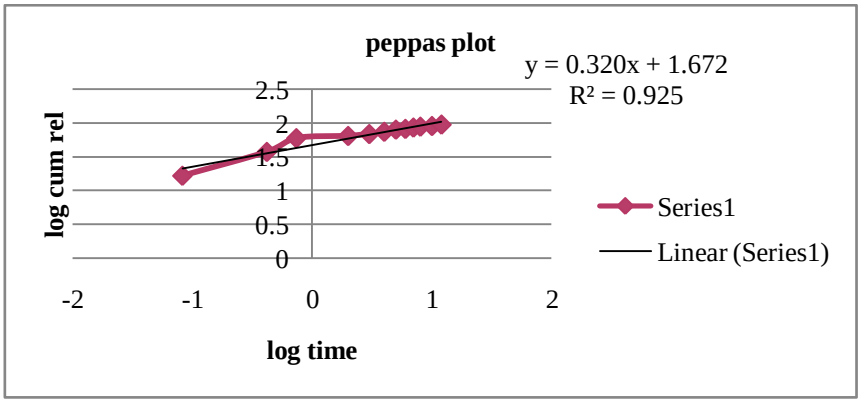

Figure 7: Peppa"s plot

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Table 6: Regression Co-Efficient of Zero order, First order, Higuchi and Peppa's

Name of the formulation	Zero order	First order	Higuchi	Peppa's	
				R2	N
Pellets	0.6882	0.9482	0.8858	0.925	0.320

CONCLUSION

From the experimental results it can be concluded that the dual release dosage form was constructed using the optimized batches from solid dispersion (SD4) and pellets (D3). As evident from the *in vitro* release studies the dual release spheroids combine the advantages of both IR and SR formulations. Thus the absorption lag time associated with SR formulations could be minimized using these formulations. The developed dual release system can able to deliver a first fraction of the dose in short time (a few minutes) and to deliver a second fraction for a longer period of time at a constant rate to overcome significant daily drug concentration variation reference to single unit conventional drug delivery systems and to improve patient compliance.

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