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Development & Release Kinetic Study of Hydrophilic Matrix System Based Unit Dosage Form of Acarbose

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Abstract

Matrix systems are the satisfactory platform for the sustained release system; as it is an approach in which the dissolved or dispersed drug is divided homogenously in an inert matrix. The inert matrix may be hydrophilic or hydrophobic. Sustained release is a mechanism used in oral dosage form to dissolve slowly and release a drug over time. Acarbose is a water-soluble drug. It is usually prescribed to patients who are diabetic or prone to diabetes. Development of gastro retentive doses form is required so as to enhance the retention of drug in the body, controlled release & to maintain uniform drug concentration in the body. Acarbose is an oral hypoglycemic agent which is reversible inhibitor of alpha-glucosidase enzymes in the brush border of small intestine and pancreatic alpha-amylase. So as to develop a gastro retentive dosage form using Acarbose as an ideal candidate an attempt is made to formulate Acarbose as sustained release tablet using HPMC K100 M as polymer in various ratios. Cellulose derivatives have been extensively used in formulation of hydrophilic matrix tablet for sustained drug delivery. The present study was carried out to perform preformulation, formulation, assessment & study of release kinetics of Acarbose sustained release matrix tablet. Sustained release matrix tablet was successfully prepared by direct compression technique. The batch F5 showed the best results when compared with other batches prepared, with having drug content 98.40 %, cumulative % drug release 76.28 % up to 8 hours and hardness 5.7 Kg/cm^3& swelling index 131.06 ± 0.72 % which shows good swelling index and shows that the diffusion mechanism was followed. Release kinetics showed that the in-vitro release curve was fitted under Higuchi model having R2 value of 0.996 which was highest when compared to other models showed that the drug released from diffusion mechanism.

Key words: HPMC, Sustained Release Tablet, Swelling Index, Matrix System, Acarbose

Introduction

Oral ingestion is the most prevalent and natural route for drug delivery due to its least sterility constraints and but in many cases conventional oral drug delivery system do not provide rate controlled delivery and may cause dose dumping. The revolutionary generation of controlled drug delivery system enhances the patient compliance Controlled drug delivery systems overcome such problems associated with the conventional systems. Sustained release systems are those, which achieves slow release of drug over an extended period of time and in this drug is initially made available to the body in amount to cause the desired pharmacological response. It is a type of dosage form which maintains the plasma drug concentration in therapeutic window. This system emerges with the advancement of avoidance of multiple dosing & side effects[1-3].

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Diabetes mellitus is a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defect in insulin secretion, insulin action, or both. Acarbose is an oral hypoglycemic agent which is reversible inhibitor of alpha-glucosidase enzymes in the brush border of small intestine and pancreatic alpha- amylase, Acarbose delays the digestion of ingested carbohydrate, thereby resulting in a smaller rise in the plasma blood glucose level following meals. As a consequence of plasma glucose reduction, Acarbose reduces level of glycosylated hemoglobin in patients with type 2 diabetes mellitus. Acarbose having shorter half life 2 hours, lower bioavailability (1-2 %), and having a usual dose of 50 mg thrice a day. So that it requires frequent dosing when it is given in conventional doses form, formulation in the sustained release tablet makes it gastro retentive so that it deliver the drug for prolong period of time, so that it can maintain constant drug level in the body and also improves patient compliance.

Soluble polymer hydroxypropylmethyl cellulose is used as release retardant to form an inert matrix[4-7]

Material and Methods

Acarbose (sun pharma, Mumbaim, HPMC K 100 M (J.B Chemicals, Ankelshswar), Anhydrous Lactose (J.B. Chemicals, Ankelshwar), Microcrystalline Cellulose & Methanol from LOBA Chemie, Mumbai, Aerosil (OTTO Chemie, Mumbai), Magnesium Stearate (SD Fine Chemicals, Mumbai)

Characterization of Drug & Excipients[8-10]

FT-IR Spectroscopy

It was employed to ascertain the compatibility between acarbose and the selected excipients. The pure drug and the drug with excipients were scanned separately .FT-IR spectrum of acarbose was compared with the FT-IR spectrum of acarbose with the excipients An Infra red spectrum of the drug was taken using KBr pellets. The pellets were placed in the holder and the spectrum was taken by using FTIR spectrophotometer (jasco-470 plus), which showed the characteristics peaks of various functional groups of drug sample.

Ultraviolet spectroscopy

Standard stock solution was prepared by dissolving 10mg accurately weighed drug in 100 ml filtered distill water, in a calibrated 10 ml volumetric flask. 1 ml of standard stock solution was pipette out carefully and transferred in a 10 ml volumetric flask. 1 ml of 0.01M Potassium Permanganate (coloring agent), and 1 ml of 0.5 M NaOH was added into it, and volume was made up to 10 ml with filtered distill water, the solution contains 10 µg/ml the absorbance was scanned by shimadzu UV visible spectrophotometer (model 1700he absorption maximum of the drug was determined by running the spectrum of the drug solution. Solvent which is having high solubility for the drug compound is generally used.

HPLC Technique

The HPLC equipment comprised of a solvent delivery system (Younglin). The separation was achieved on a reversed phase column (Nucleosil 100-5 C_{18}; 250x4.6 mm, 5µm i.d.) kept at room temperature. The flow rate of mobile phase was 1.2 ml/min. The mobile phase consists of 0.1 M phosphate buffer (pH-6.8) / Acetonitrile (25:75 v/v) and detection was performed at 293 nm.

DRUG EXCIPIENT INTERACTION STUDIES

Differential Scanning Calorimetry (DSC Analysis)

Compatibility of the drug with excipients was determined by differential scanning calorimetry (DSC) analysis. This study was carried out to detect any change on chemical constitution of the drug after combination with the excipients. The study was done by using differential scanning calorimeter Jade Perkin Elmer DSC (Pyris 6 DSC). Accurately weighed 4 mg sample was used, and heated at constant rate of 10^0C/min over a temperature range of 30-300 ^{0}C/min. inert atmosphere was maintained by purging nitrogen gas at a flow rate of 20.0 ml/min.

Infra Red Spectroscopy

An Infra red spectrum of the drug was taken using KBr pellets. The pellets were placed in the holder and the spectrum was taken by using FTIR spectrophotometer (jasco-470 plus), which showed the characteristics peaks of various functional groups of drug sample.An Infra red spectrum of the drug was taken using KBr pellets. The pellets were placed in the holder and the spectrum was taken by using FTIR spectrophotometer (jasco-470 plus), which showed the characteristics peaks of various functional groups of drug sample

Preparation of Tablets

Tablet containing Acarbose was prepared by direct compression method. Acarbose, HPMC K100M, and microcrystalline cellulose were passed through the sieve no. # 60, then talcum, magnesium stearate and aerosil were sifted through # no. 60 seperately. All the sifted material and pass through the mesh no. 60 and mixed properly for 15 minutes in polyethene bag and then compressed by single punch tablet punching machine weight of tablet adjusted to 350 mg containing 100 mg Acarbose. After the compression the tablet was then checked for its physical parameter. The tablets were compressed to a hardness of 5-7 kg/cm^2. To cover all the variables 5 different formulations were studied. Matrix tablets of each composition were tested for their hardness, weight variation, friability, drug content, and drug release characters with the required number of tablets for each test.

Evaluation Tablets[11-16]

All the prepared Sustained release tablets were evaluated for following parameters for the evaluation of basic properties of the sustained release preparations and the best batch is selected on the basis of acceptability of the following parameters; hardness, drug content & *in vitro* dissolution

Hardness test

Monsanto hardness tester was used to evaluate hardness of tablet. Hardness or the tablet crushing strength (f_c) is the force required to break a tablet in a diametric compression. It is expressed in kg/cm^2.

Drug Content

Three tablets were selected randomly from each batch were weighed and powdered separately. The powdered tablet equivalent to 100 mg drug in one tablet was taken and transferred in a 100 ml flask containing 100 ml of phosphate buffer 6.8 and filtered. 10ml of this filtrate was taken and appropriate dilution was made and coloring

agent alkaline potassium permanganate was added. The samples were analyzed at 610 nm using UV visible spectrophotometer. The drug content was determined from the standard curve prepared at λ max 610 nm.

***In Vitro* Dissolution Studies:**

In Vitro dissolution study was carried out using USP I apparatus (basket type) in 900 ml of 0.1 N Hcl for the first hour and phosphate buffer pH 6.8 for the rest of period for 12 hours. The temperature of the dissolution medium was kept at 37± 0.5ºC and the basket was set at 100 rpm. 1 ml of sample solution was withdrawn at specified interval of time and replace with dissolution medium. The absorbance of the withdrawn samples after suitable dilution was measured at λ_{max} 610 nm using UV visible spectrophotometer. The concentration was determined from the standard curve of Acarbose prepared in phosphate buffer pH 6.8 at λ max 610 nm. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.

Precompression Parameter of Powder Blend Used For Preparation of Optimized Batch

The blend which is made into sustained release matrix tablet by direct compression method was evaluated for bulk density, tapped density, angle of repose, carr's index & hausner's ratio.

Evaluation of optimized batch

The optimized batch was further subjected to the evaluation parameter of sustained release matrix tablet. All the prepared Sustained release tablets were evaluated for following official and unofficial parameters;. Hardness, Friability, Weight Variation, Drug Content, Swelling Index, *In-vitro* Dissolution

Swelling index

The swelling index of tablets was determined in distilled water at room temperature. After each interval the tablet was removed from beaker, removes the excess dist. Water by using filter paper and weighed again up to 8 hrs

$$\textbf{Swelling index (SI)} = \frac{(W_t - W_0)}{W_0} \times 100$$

Where, W_t = Weight of tablet at time t.

W_0 = Initial weight of tablet.

Weight Variation

Twenty tablets were sampled randomly. Tablets were weighed individually and average weight was calculated. Then deviation of each tablet from average weight was calculated and percent deviation was computed. The deviation was compared with the Pharmacopoeial limits.

Friability

Friability of the tablets was determined by using friabilator (Roche Friabilator). The device subjects the tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at a height of 6 inches in each revolution. Tablets were weighed and placed in the friabilator and subjected to 100 revolutions for 4 minute. Tablets were then de-dusted and reweighed. The observed value should not be more than 1%.

Calculation: Calculate the Friability in %, using the formula: -

$$\textbf{Friability} = \frac{(W_1 - W_2)}{W_1} \times 100$$

Where, W_1 = Initial weight of the tablets taken,

W_2 = Final weight of the tablets after testing.

Analysis of Release Mechanism of Optimized Formulation

In vitro dissolution profile has been recognized as an important element in drug development under certain assessment of bioequivalence. Several theories/kinetics models describe drug dissolution from immediate and modified release dosage forms. There are several models to represent the drug dissolution profiles where f_t is a function of't' (time) related to the amount of drug dissolved form the pharmaceutical dosage system. In order to examine the release mechanism of drug sample from the prepared matrix tablet formulation (F5), the result of dissolution study i.e. % cumulative drug release was examined in accordance to kinetic models such as zero order, first order, Higuchi equation, korsemeyer-Pappas equation, and Hixson-Crowell equation.

Results and Discussion

Optimization study was done on the basis of experimental design**.** Sustained release matrix tablets were prepared by using direct compression technique. Optimization was done by using HPMC K100M at different concentration. Concentration of the release retarding polymer was increased in definite amount for the preparation of different batches of matrix tablet, which showed that the increase in concentration of HPMC K100M retards the release of the drug from matrix tablet with time and hence, increase in % cumulative drug release up to 8 hours, and will surely delivered the drug up to 12 hours. The parameters considered for the optimization were hardness, drug content and release rate or drug release profile.

On the basis of the results obtained from different studies the optimization was done, drug content was determined for all the formulations and drug content (%) of formulation F5 was 98.40 ± 1.02 which show a better release profile, hardness was found out by Monsanto hardness tester and data obtained varied from 4.8- 5.7 kg/cm^2 which showed the effect of

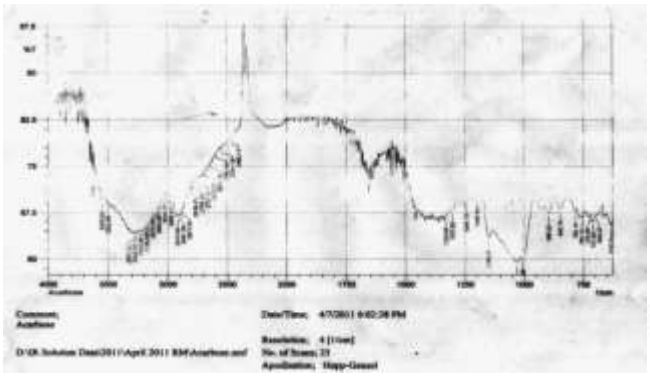
diluents on the hardness of tablet. *In vitro* dissolution study of all the formulation was done by USP Type I (Basket apparatus) and formulation F4 showed 90.43 ±1.66 % drug release and batch F5 showed maximum % cumulative drug release up to 10 hours is 76.28 ± 0.88.

Formulation F4 and formulation F5 both released the drug above 8 hours hence both formulations released drug in sustained release fashion but F5 released drug for longer period of time. On the basis of combined results of selected parameters *in-vitro* drug release, drug content and hardness of the tablet the formulation F5 which contains 55% HPMC K100M was selected as optimized batch for further evaluation and stability studies.

The stability study of formulations was carried out according to the ICH guidelines for zones III and IV. The formulations were stored at 40 ± 2°C/75 ± 5% RH for 3 months by storing the samples in a stability chamber. At the end of 3 months tablets were tested for hardness, drug content and disintegration. In-vitro dissolution was carried out for selected formulation. Samples were withdrawn at an interval of 7 days for 3 months and were studied for *in- vitro* drug release, drug content uniformity and disintegration time.

On the basis of stability study it was concluded that there is no significant change in parameters like drug content, drug release and hardness of tablet therefore optimized formulation was found to be stable under the specified temperature and humidity conditions.

Characterization of Drug & Excipients



.Figure 1: FTIR of sample drug

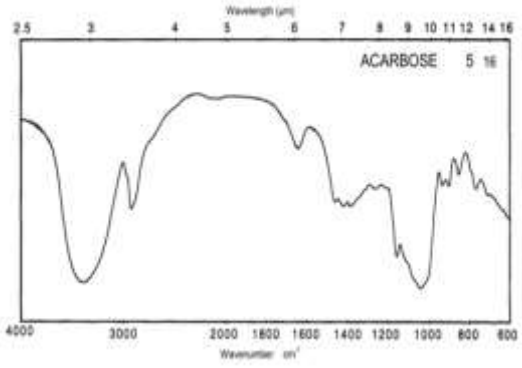


Figure 2: FTIR of Pure drug

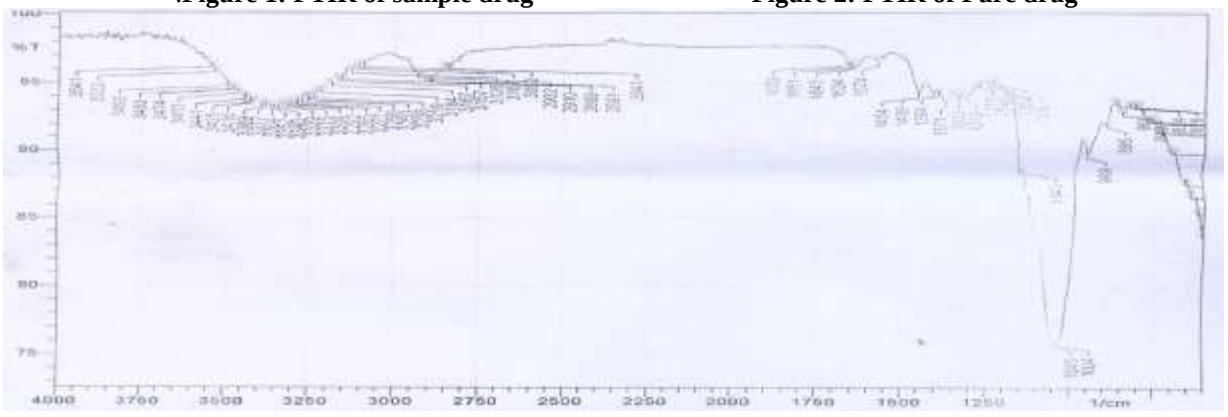


Figure 3: I.R spectra of Drug + excipient

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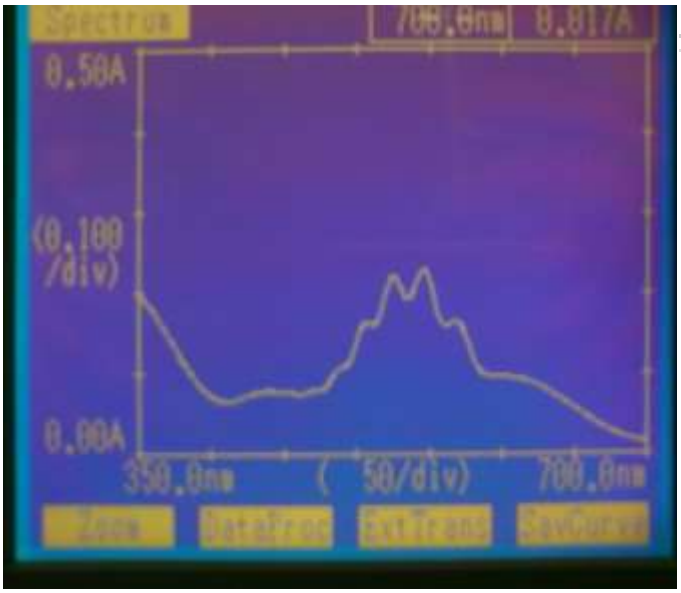

Figure 4: Absorption maximum (λ_{max}) of Acarbose

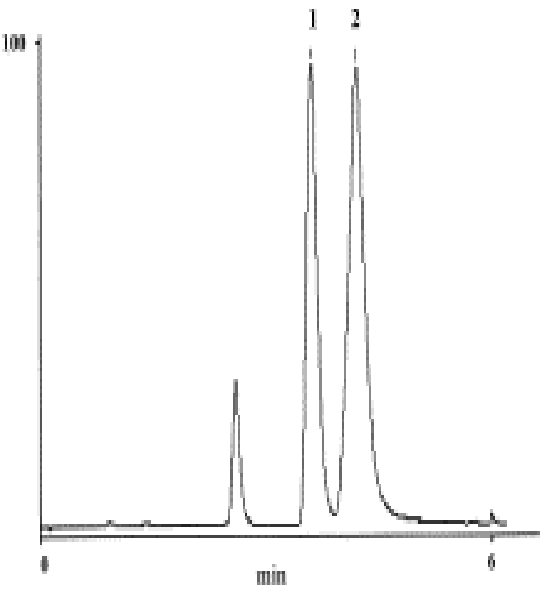

Figure 5: HPLC spectra of Acarbose

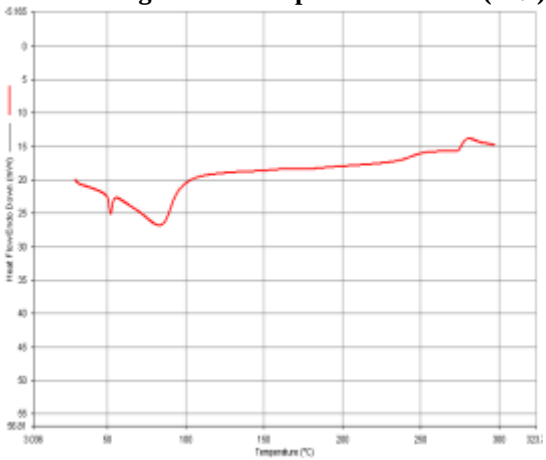

Figure 6: DSC thermogram of drug

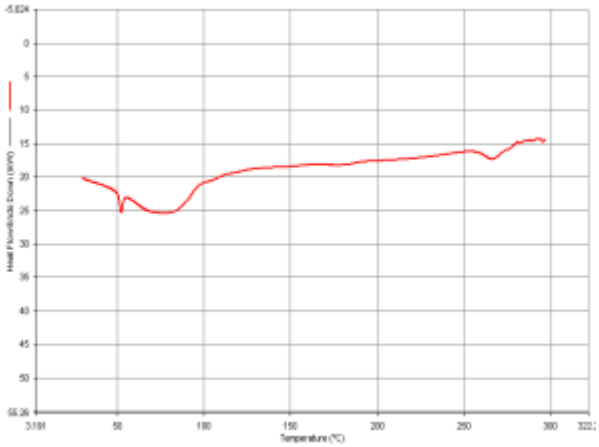

Figure 7: DSC thermogram of physical mixture

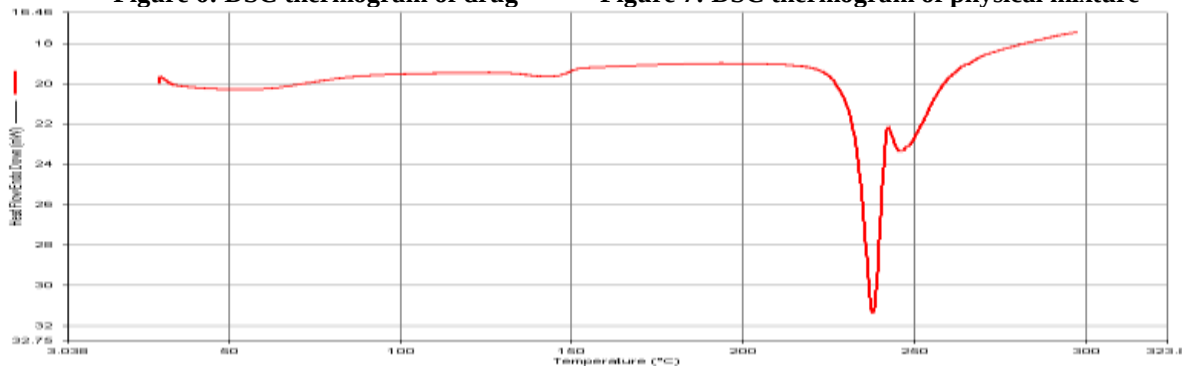

Figure 8: DSC Thermogram of HPMC K 100 M

Table 1: formulation of matrix tablet

S.NO	Ingredients(mg)	F1	F2	F3	F4	F5
1	Acarbose	100	100	100	100	100
2	HPMC K-100 M	52.5	87.5	122.5	157.5	192.5
3	Lactose	143.2	108.2	73.2	38.2	3.2
4	MCC	42	42	42	42	42
5	Talc	7	7	7	7	7
6	Magnesium Stearate	3.5	3.5	3.5	3.5	3.5
7	Aerosil	1.5	1.5	1.5	1.5	1.5

Table 2: Evaluation parameters of the tablets

Parameter	Formulation Batch number				
	F1	F2	F3	F4	F5
Hardness (Kg/cm^2)	4.7 ± 0.70	5.1 ± 0.58	5.5 ± 1.05	5.4 ± 0.86	5.7 ± 0.88
Drug content (%)	97.52 ± 1.34	96.64 ± 2.08	98.82 ± 0.78	97.46 ± 1.20	98.40 ± 1.02

Table 3: Drug release study of formulations

S.No	Time (Hour)	Cumulative % drug release				
		F1	F2	F3	F4	F5
1	0	0	0	0	0	0
2	0.5	44.25 ± 2.00	40.08 ± 1.55	37.62 ± 1.42	26.15 ± 1.01	23.24 ± 1.48
3	1	61.04 ± 1.80	55.62 ± 1.03	49.51 ± 1.12	38.11 ± 1.17	29.68 ± 1.36
4	2	73.41 ± 0.94	64.74 ± 1.95	54.61 ± 1.15	47.71 ± 0.82	40.27 ± 1.26
5	3	94.62 ± 1.37	83.12 ± 1.08	61.02 ± 1.64	56.28 ± 1.44	47.18 ± 0.98

6	4	98.72 ± 0.71	96.56 ± 0.85	78.47 ± 0.92	64.82 ± 0.98	52.48 ± 1.02
7	5		98.01 ± 0.87	88.21 ± 0.93	70.14 ± 1.28	59.96 ± 1.24
8	6			94.62 ± 0.76	79.63 ± 0.94	65.72 ± 0.89
9	7			99.11 ± 0.65	84.21 ± 1.67	71.81 ± 0.68
10	8				90.43 ± 1.66	76.28 ± 0.88

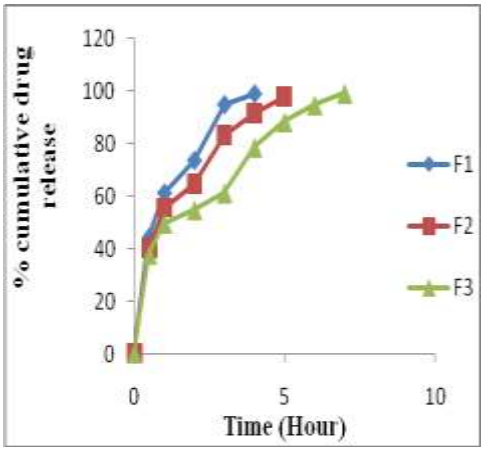

Figure 9: % cumulative drug release F1, F2, F3

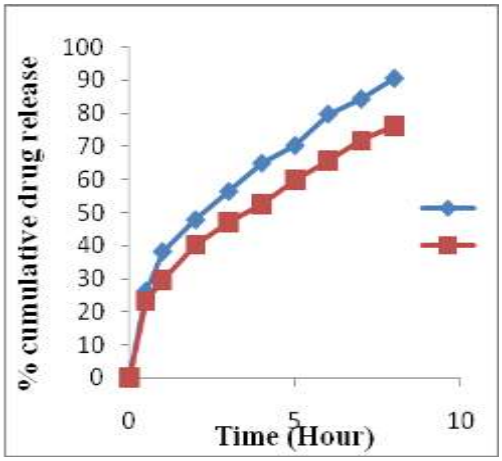

Figure 10: % cumulative drug release of of formulation formulation F4 & F5

Table 4: Pre-compression parameters of optimized batch

S. No	Batch code	Hausner's ratio	Carr's index (%)	Angle of repose (degree)
1	**F5**	1.20 ± 0.113	16.8 ± 0.098	$30^0 78'' \pm 1.932$

Table 5: Post-compression parameters of optimized batch

S.No.	Batch No.(F5)	Values
1	**Hardness Kg/cm^2**	5.7 ± 0.86
2	**% Friability**	0.330 ± 0.17
3	**Weight variation**	353.06 ± 2.23
4	**% Drug content**	98.40 ± 1.02

Table 6: Swelling index of optimized formulation

S.No	Time Interval (Hour)	Swelling Index
1	0	0
2	1	43.74 ± 1.64
3	2	59.76 ± 0.82
4	3	74.54 ± 1.26
5	4	85.50 ± 2.21
6	5	96.22 ± 0.74
7	6	106.26 ± 0.87
8	7	119.34 ± 0.65
9	8	131.06 ± 0.72

Table 7: Drug release study of optimized formulation

S.NO	Time (Hour)	% Drug release
1	0	0
2	0.5	23.24 ± 1.48
3	1	29.68 ± 1.36
4	2	40.27 ± 1.26
5	3	47.18 ± 0.98
6	4	52.48 ± 1.02
7	5	59.96 ± 1.24
8	6	65.72 ± 0.89
9	7	71.81 ± 0.68
10	8	76.28 ± 0.88

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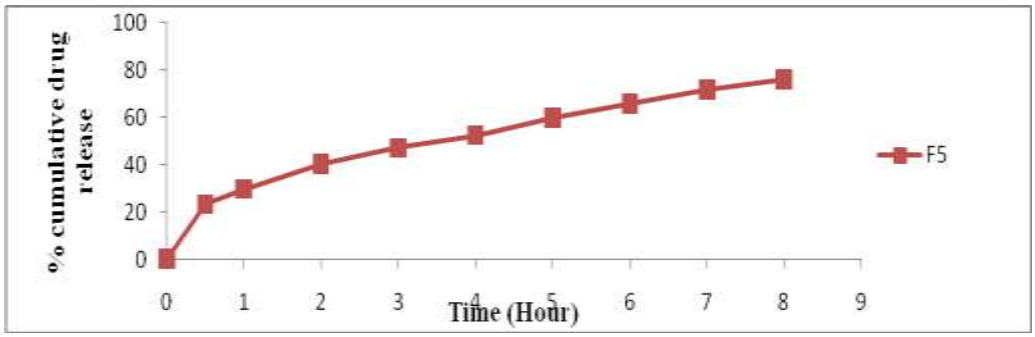

Figure 11: Drug release study of formulation F5

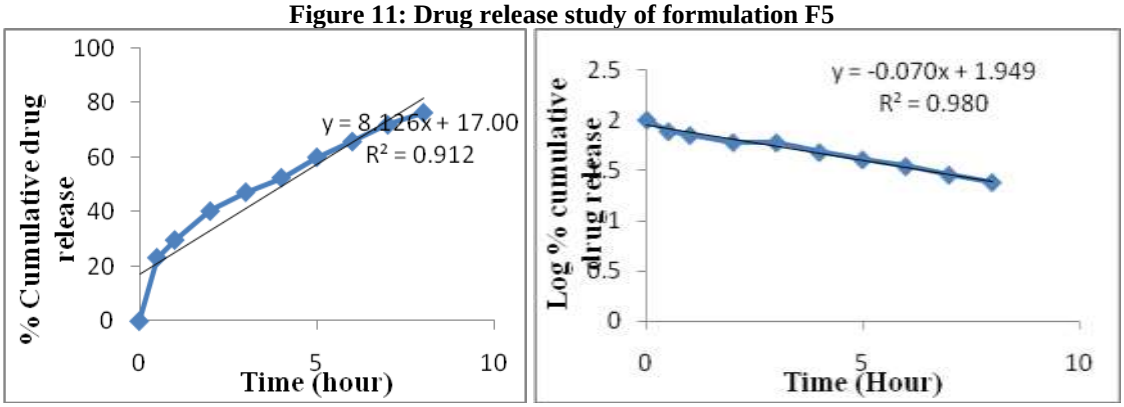

Figure 12: Zero- order release & first- order release model of formulation F5

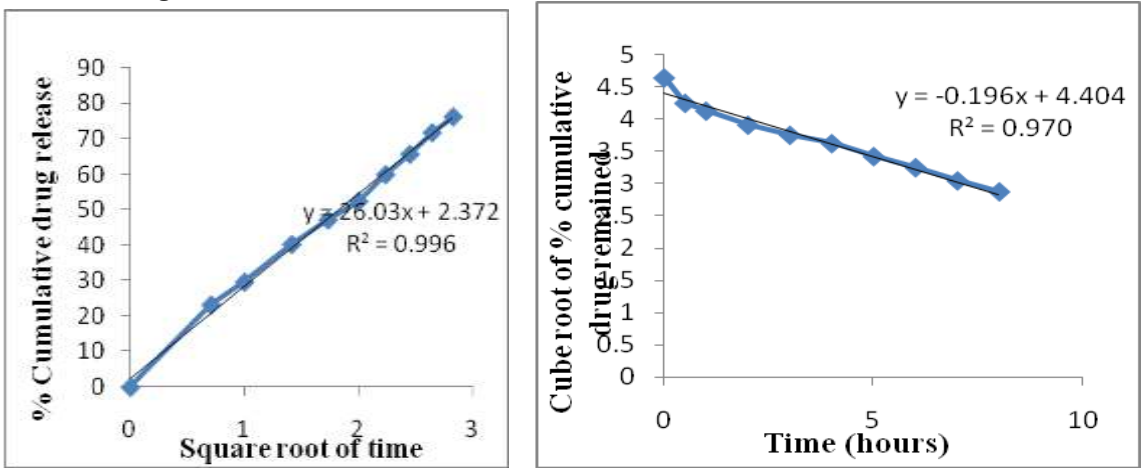

Figure 13: Higuchi & Hixson-Crowell model of formulation F5

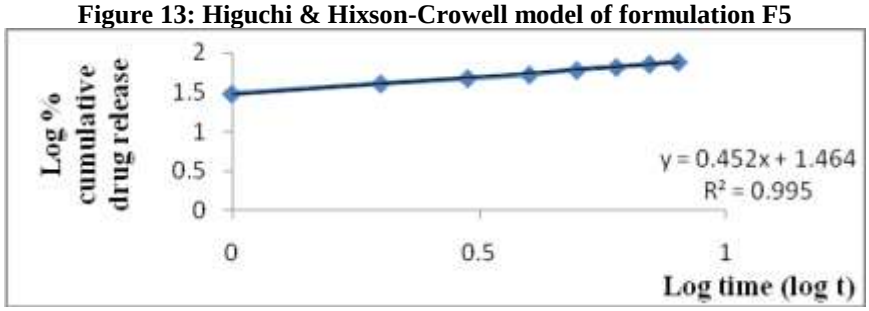

Figure 14: Korsmeyer and peppas model of formulation F5

Table 8: Analysis of drug release Kinetic data (F5)

S.No	Time t (hr)	CDR Q (mg)	√t	Log t	% CDR %Q	Log %Q	%Drug remained $\%Q_r$	Log $\%Q_r$	$\sqrt[3]{\%Q_r}$
1	0	0.00	0.000	-	0.00	0.000	100.00	2.000	4.642
2	0.5	23.24	0.707	-	23.24	1.366	76.76	1.885	4.249
3	1	29.68	1.000	0.000	29.68	1.472	70.32	1.847	4.127
4	2	40.27	1.414	0.301	40.27	1.604	59.73	1.776	3.908
5	3	47.18	1.732	0.477	47.18	1.673	52.82	1.772	3.752
6	4	52.48	2.000	0.602	52.48	1.719	47.52	1.676	3.622
7	5	59.96	2.236	0.698	59.96	1.777	40.04	1.602	3.421
8	6	65.72	2.449	0.778	65.72	1.817	34.28	1.535	3.248
9	7	71.81	2.645	0.845	71.81	1.856	28.19	1.450	3.043
10	8	76.28	2.828	0.903	76.28	1.882	23.72	1.375	2.873

Table 9: R^2 Value of Drug Release Kinetic Model

S. No.	Model	R^2
1	Zero- order	0.912
2	first- order	0.980
3	Higuchi	0.996
4	Hixson-Crowell	0.970
5	Korsmeyer and peppas	0.995

Conclusion

The sustained release Matrix tablets of Acarbose with combination of hydrophilic polymers HPMC K 100(Powder form) were developed by direct compression method. The results of this study enable us to state that ratio of polymer with various proportions affects the drug release and thus the matrix tablet formulation will be the effective pharmaceutical formulations. The objective of this study was to develop Matrix Tablets of Acarbose with Polymer HPMC K100 M and the study of influence of polymer on the drug release. Acarbose as short half life drug required frequent dosing but sustained release matrix tablet of it solves this problem. First formulations of F1, F2, F3, F4 shows the slow release of drug due to lower concentration of HPMC K 100 M and increasing the concentration of HPMC K100M for F5, formulation, drug release up to 10hrs was about 78 %.The development was initiated with standard calibration curve using UV Spectrophotometric method as it is required to routine analysis of drug. The UV Spectrophotometric method was developed in0.01 M Potassium Permanganate solution & 0.5 M NaOH solution at 610nm.

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