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FORMULATION AND EVALUATION OF CONTROLLED DRUG DELIVERY SYSTEM CONTAINING ACARBOSE

Tripathi Sanskrit, Patel Arun, Patel Shailendra
Shri Ram Group Of Institutions, Faculty Of Pharmacy, Jabalpur

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Abstract:
Oral controlled drug delivery systems refer to those products where in a release controlling technology is instigated which in turn modulates the release pattern of drug from the device into gastro intestinal tract. The tablets are coated with cellulose acetate polymer contain polyethylene glycol 400 and polyvinyl pyrrolidine K30 (20 %) as pore former in varying concentration, which is dissolved in acetone (60 %) solution. In EOP the delivery orifice had been drilled on the surface of the coated tablet by mechanical method. The stability determination recommended by ICH guidelines testing parameters were carried with designed formulation for the 12-month study reveals, the osmotic tablets were stable under the standard operational conditions. The post compression parameter like thickness, hardness, uniform drug content, in vitro release kinetics and average weight of tablets are comparable with standard reference of Acarbose. The in vitro release data of optimized formulation CP5 determined by USP type II dissolution apparatus shows 96.6 ± 0.15 % at 12 hr. The kinetic modelling of release data gives the information of release mechanism from osmotic pump was mainly by diffusion and osmosis.

Corresponding author:
Tripathi Sanskrit,
Shri Ram Group Of Institutions,
Faculty Of Pharmacy, Jabalpur

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INTRODUCTION:

Oral controlled drug delivery systems refer to those products where in a release controlling technology is instigated which in turn modulates the release pattern of drug from the device into gastro intestinal tract [1]. The term-controlled drug delivery has got a scope beyond sustained type of drug action. Controlled drug delivery products have got several advantages including the zero order drug delivery patterns and its reproducibility and predictability in terms of release kinetics [2]. When compared to the conventional release system CDDS provides uniform drug concentration which lies within the therapeutic range hence minimizing the side effects and increasing patient compliance by decreasing the dosing frequency [3]. When compared to the conventional release system CDDS provides uniform drug concentration which lies within the therapeutic range hence minimizing the side effects and increasing patient compliance by decreasing the dosing frequency [3].

Different drug delivery routes are present in the present scenario but oral route is the most preferred route of drug administration and among these CDDS systems are designed for oral administration, as it helps to increase the patient compliance, it's easy to administer and more convenient to use [4]. Oral controlled drug delivery systems refer to those products where in a release controlling technology is instigated which in turn modulates the release pattern of drug from the device into gastro intestinal tract [4]. The formulations which are given by oral route should be developed by keeping in mind the intrinsic physiology of gastro intestinal tract. Therefore, the biopharmaceutical considerations including the pharmacokinetic and dynamic parameters and the gastrointestinal physiology should be accounted during the design and fabrication of orally controlled drug delivery systems [5].

Acarbose is used in the treatment of type II diabetes mellitus. It works by competitively inhibiting intestinal alpha-glucosidase enzyme and at the same time with maximum specific inhibition against sucrose [6]. The normal dose of Acarbose for treatment for of oral hypoglycaemia is Adults may take doses of 25 mg TID, increasing to 100 mg TID. It was also found that this drug is more effective when given daily once [6]. Acarbose is available in market as 25, 50 and 100 mg tablets. The conventional tablets have several draw backs such as inconvenient dosing, slower onset of action etc [6]. Acarbose osmotic tablets have been developed on this behalf so that a controlled release preparation will be able to maintain plasma concentration in a much better way with their programmed release pattern. More over Acarbose is prescribed to patients for long durations; in this extent also the controlled release preparations will serve better. The main intend behind the formulation and characterizing a drug delivery system is to optimise a product which is therapeutically effective [7].

MATERIAL AND METHODS:

PREPARATION OF OSMOTIC TABLETS OF ACARBOSE:

The core osmotic tablets of Acarbose were prepared by direct compression technique [8, 9,10].
The following steps are involved to prepare osmotic release tablets of Acarbose [10, 11,12].

Dry mixing

All the ingredients and drug were accurately weighed and mixed in a lab scale mixer to get a homogenized uniform mixture. The dry blends of mixture pass through sieves No # 80 and collected in a clean bowl. The dried powder was finally lubricated before compression [13].

Tablet compression

The tablets were compressed using a 16-station rotary tablet compression machine (Cadmach machinery, Ahmadabad) equipped with 10 mm diameter, round plain and concave punch. Tablets were compressed at an average weight of 300 mg and hardness of tablet kept as 7 Kg/cm^2 [13].

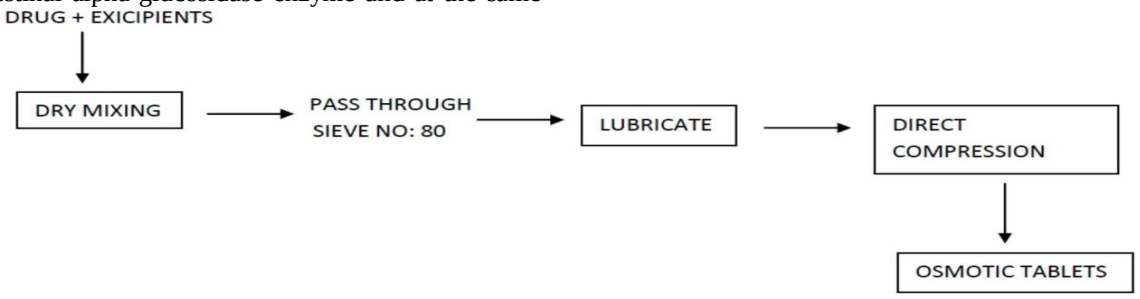

Figure 6.1: Preparation of core osmotic tablets of Acarbose

COATING OF TABLETS:

PREPARATION OF COATING SOLUTION [14]

Preparation of coating solution for Controlled Pore Osmotic Pump (CP_1-CP_6)

The coating solution containing Cellulose Acetate (CA) (4.0 %, 3.0 % & 2.0 %) and PVP K30 (20 %) was prepared as per the formula given in table- 6.1.

Accurately weighed quantity of CA and PEG 400 was added to acetone (60 %). The mixture stirred until the formulation of clear solution. The weighed quantities of PVP K30 dissolved in acetone were added to CA solution. The mixture was stirred continuously for 10 minutes [14].

Preparation of coating solution for Elementary Osmotic Pump (E1- E9)

The coating solution containing Cellulose Acetate (CA)-3.0% and PEG-400 was prepared as per the formula given in table- 6.2. Finally, the coated tablets were drilled using a micro drill of 0.5 µ in the centre part of tablets [14,15].

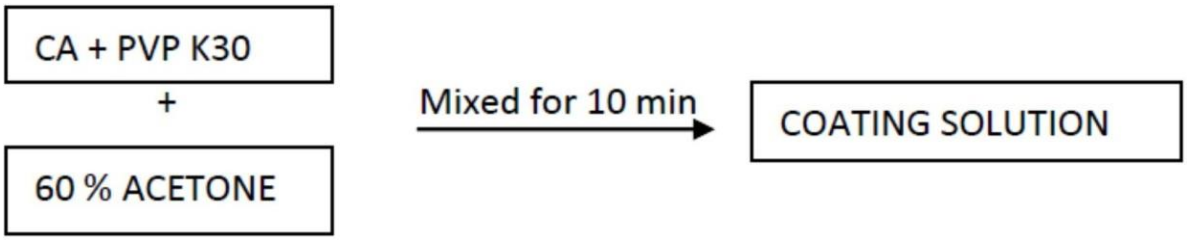

Figure 6.2: Preparation of coating solution for osmotic tablet

EXPERIMENTAL INVESTIGATIONS

Preformulation Studies [16]:

Preformulation testing is an investigation of physical and chemical properties of drug substances alone and when combined with excipients. It is the first step in the rational development of dosage forms.

The aim of preformulation study is to obtain information to develop a highly stable dosage form which is having high bioavailability.

The use of Preformulation parameters helps in formulating an acceptable, safe, efficacious and stable product.

Determination of organoleptic properties:

The physical appearance of drug was observed and compare with the pharmacopieal specification.

Determination of melting point:

The melting point of Acarbose was determined by capillary method. Fine powder was filled in glass capillary tube (previously sealed at one end). The capillary tube was inserted into the melting point apparatus and observed the temperature at which the drug started to melt by using the thermometer which was already immersed into the liquid paraffin in the apparatus [16].

Determination of solubility:

The solubility of Acarbose in different solvent were examined to find whether it is soluble in various solvents like purified water, buffer, ethanol, acetone etc.

DRUG – EXCIPIENTS COMPATIBILITY STUDIES

Fourier transform infrared spectroscopy (FTIR) [17]:

IR spectroscopic studies were carried out to identify the drug and excipients. The drug along with excipients was taken for IR studies to find out any possible interactions.

In this method individual samples as well as the mixture of drug and excipients were ground and mixed thoroughly with potassium bromide (1:100) for 3-5 min in a mortar and compressed into disc by applying pressure of 5 tons for 5 min in hydraulic press. The pellet was kept in the sample holder and scanned from 4000 to 400 cm^{-1} in FTIR spectrophotometer. Then the characteristics peak of all samples as well as mixtures were obtained. Then the peaks of optimized formulation were compared with pure drug and excipients. If there was no interaction between the peaks of drug and excipients of optimized formulation then it was said to be compatible.

DSC Study [17,18]:

Thermal analysis of pure drug and drug- excipients mixture was carried out by DSC Model Q20-TA instrument. The thermograms obtained by heating samples from 30 ºC-200 ºC at a rate of 10 ºC/min under inert nitrogen dynamic atmosphere.

Construction of standard curve of Acarbose (By UV-Spectroscopy Method)
Method of preparation of buffer pH 7.4:[19]

Preparation of 0.2 M Potassium dihydrogen phosphate solution (Primary solution): 27.218 grams of Potassium dihydrogen phosphate was weighed and dissolved in small quantity of distilled water and the volume was made upto one litre with distilled water.

Preparation of 0.2 M Sodium hydroxide solution (secondary solution):
8 grams of sodium hydroxide was weighed and dissolved in distilled water and made up to one litre with distilled water.

From the primary solution 50ml and from the secondary solution 22.4 ml was taken and made up to 200 ml with distilled water to get buffer of pH 7.4 and the pH waschecked and adjusted to 7.4.

Determination of λ_{max}:
100 of drug was weighed and transferred into 100 ml volumetric flask and made up with distilled water. From this 2 ml was transferred to 10ml volumetric flask. Itwas then made up with distilled water. From this 0.5 ml was pipetted out and transferredto a 10 ml of volumetric flask. To this added 5 ml of 0.01N Potassium permanganate which was prepared by using 0.1N NaOH solution was added and then the final volume was adjusted with distilled water. This contains 10 µg/ml of the drug. The solution was scanned by UV-visible spectrophotometery in the range of 300-750 nm. The λ_{max} of Acarbose was found to be 625 nm [19].

Procedure for construction of standard curve:
From standard stock solution of Acarbose, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5 ml wasseparately pipette out in a series of 10 ml volumetric flask and added 5 ml of 0.01 $KMnO_4$ in 0.1 N NaOH solution remaining up to mark volume was made by distilled water. It was made up to the concentration in the range of 10, 20, 30, 40, 50, 60, 70 µg/ml of the drug. The absorbance of these resultant solution was measured at 625 nm by placing 0.01 N alkaline with Acarbose in sample cell, and 0.01 N alkaline solution placed in reference cell, and a graph was plotted between absorbance v/s concentrations of the solutions. The Lambert-Beer's law was obeyed in range of 10 to 70 µm/ml at 625 nm.

Then a calibration curve was plotted by taking concentration on X-axis and absorbance on Y – axis.[93.]

EVALUATION OF OSMOTIC TABLETS
Pre compression parameters [20,21]:
Determination of Angle of Repose
Funnel method was employed to determine the angle of repose of the drug excipient mixture. The funnel was placed at a height of 6 cm from the surface. A predetermined weight of powder poured into the funnel, so that it forms a heap on the surface. The radius and height of the powder was measured. The angle of repose is calculated by using the following equation.

$\theta = \tan^{-1}(h/r)$---------Equation (6.1)

θ = angle of repose.
h = height of the pile formed on the surface.
r = radius of the pile of powder.

Table-6.3: Relationship between angle of repose and flow property.

Angle of repose (θ)	Flow property
Less than 25	Very Excellent
Between 25 & 30	Good
Between 30 & 40	Fair
Between 41 & 50	Poor
Greater than 50	Very poor

Determination of Bulk Density and Tapped Density:

Bulk density and tapped density were determined by using a bulk density apparatus. Weighed quantity of the powder (W) was poured into the graduated cylinder and the initial volume (V_o) was measured. The apparatus was then tapped for 250 times and again subjected to 500 tappings till a consistent reading was obtained (V_f). The following equations were used for calculation.

Bulk density = **W / V_o** Equation (6.2)

Tapped density = **W/V_f** Equation (6.3)

Where,

W = weight of the powder

V_o = initial volume before tappingV_f = final volume after tapping

Determination of Hausner Ratio and Carr's Index:

Hausner ratio and the Carr's Index are the measures of inter-particle friction and the potential powder arch (or) bridge strength and stability respectively which have been widely used to estimate the flow properties of powders.

Hasners ratio is the number that is correlated to the flowability of a powder or granular material. It is name after the engineer Hendry H. Hausner. The Hausner ratio was calculated by the formula,

Table-6.4: Predictable flow property of powder mixture based on Hausner ratio.

Hausner's ratio	Flow property
Between 1-11	**Excellent**
Between 1.12-1.18	**Very good**
Between 1.19-1.25	**Fairly flowing**
Between 1.26-1.34	**Passable**
Between 1.35-1.45	**Poor flow property**
Between 1.56-1.59	**Very poor**
Greater than 1.60	**unacceptable**

Carr's compressibility index directly indicates the compressibility of a powder.It is named after the scientist Raiph J Carr. The carr index was calculated by the formula,

Table -6.5: Scale of flowability of powders.

Compressibility index (%)	Flow description
Between5 -15	Excellent
Between 12-16	Good
Between 18-21	Fair
Between 23-28	Poor
Between 28-35	Poor (but cohesive powder)
Between 35-38	Very poor
More than 40	Extremely poor

Loss on Drying [20,21]:

It was done in Electronic Loss on Drying (LOD) apparatus. Weighed quantity of 1gm sample was placed in the pan and the temperature was increased to 105 ºC and the loss on drying in % was noted.

Post compression parameters:

Physical Appearance:

The physical appearance like shape, size and nature of each compressed tablets were visually examined and tabulated.

Organoleptic properties:

The organoleptic properties include colour and odour of the prepared tablets were monitored.

Thickness:

The thickness of the tablets was measured using a vernier caliper. Ten tablets from each batch were selected for the test and results were expressed in millimeter.

Hardness test:

The hardness of tablet was measured by using Monsanto hardness tester. Ten tablets from each batch were used for hardness studies and results were

expressed in Kg/cm^2 [21,22].

Weight variation test:
Twenty tablets were selected at random individually weighed in a single pan electronic balance and the average weight was calculated. The uniformity of weight wasdetermined according to I.P specification. The parameter was set as per Indian pharmacopoeia. Not more than two of individual weight would deviate from average weight by more than 5 % and none should deviate more than twice that percentage [21,22].

Table-6.6 : Maximum allowable deviation for tablets.

Average weight of tablet (mg)	Maximum percentage deviation allowed (%)
130 mg or less	± 10.0
130 – 324	± 7.5
> 324	± 5

Friability test:
The friability of the tablet was determined by Roche fabricator. In this apparatus, the tablets are dropped at a distance of six inches with each revolution. The speed of revolution is set at 25 RPM. Pre-weighed samples of 10 tablets were placed in the fabricator, which is then operated for 100 revolutions. The tablets are then dusted and reweighed. Conventional compressed tablets that lose less than 0.5 to 1.0 % of their weight are generally considered acceptable [21,22].

Drug content uniformity:
Ten tablets were weighed and taken in a mortar and crushed to powder form. A quantity of powder weighing equivalent to 75 mg of Acarbose was taken in a 100 ml volumetric flask and distilled water was added. The solution was filtered using membrane filter (0.45 µm). To this 5 ml of 0.01 N Potassium Permanganate in 0.1 N Potassium Hydroxide solution was added and then its absorbance was measured at 625 nm. The amount of drug was calculated using standard graph [21,22].

***In vitro* dissolution studies:**
In vitro drug release from the osmotic tablets of Acarbose was studied using Dissolution apparatus USP Type I rotating basket method. 900 ml of buffer solution (pH 7.4) was used as the dissolution medium. The tablet was placed inside the basket and rotated at a speed of 50 rpm maintained at a temperature of 37 ± 0.5 ^{O}C [21,22,23].

1ml of sample was withdrawn at intervals of 1 hr for 12 hr and transferred to 10 ml standard flasks. To this 5 ml of 0.01 N Potassium Permanent in 0.1 N Potassium Hydroxide solution was added and made up to 10 ml using buffer. 1ml of fresh dissolution medium was replaced after each time of withdrawal of samples. The samples were analyzed spectrophotometrically at 625 nm for the drug content against respective buffer blank [22,23].

The mean percentage of Acarbose released at various time intervals was calculatedfrom standard graph and plotted against time.

Kinetics of drug release:
To analyze the mechanism of release, the best formulation was subjected tosome statistical tests [22,23].

Peppa's plot:
It describes the drug release from the polymeric system in which release deviates from Fickian diffusion, as expressed in following equation.

$Q = Kt_n$ ----------Equation (6.10)
Where,
Q – is the amount of drug release at time 't'.
K– is the release rate constant.
n – exponent of diffusion based on release.
The data obtained from *in vitro* drug release studies were plotted as log percentage cumulative drug release Vs time. The non Flickian diffusion refers to combination of both diffusion and erosion-controlled rate release. The release mechanism of drug from dosage form can be determined from the characterization of'n' value in kinetic model which is described in table 6.7.

Table-6.7 : Diffusional release mechanism.

Release exponent (n)	Diffusion release mechanism
0.45	Flickian diffusion
0.45< n < 0.89	Anomaleous (non- Flickian) diffusion
0.89 – 1.0	Case II transport (zero order)
> 1.0	Super case II transport

Stability studies [24,25]:
The stability studies were carried out as per the ICH and WHO guidelines of stability testing. The formulations were packed in aluminium foil and kept inside the stability chamber maintained at 45^{O}C and 75 % RH for the period of 12 month. At the end of the stability study period, samples were analyzed for parameters like physical characteristics, drug content, and *in vitro* drug release.

Scanning electron microscopic studies:
Morphology of coating membrane of optimized formulation before and after complete *in vitro* dissolution where characterized by using scanning electron microscopy (Hitachi S-2400). The tablets were dried at 45 ^{O}C and stored in desiccators until examination. Samples were fixed on supports with carbon glue and coated with gold using the gold sputter model in a high vacuum evaporator. Samples were then observed with scanning electron microscopy.[102.]

Pharmacological studies [28,29]:
Ethical clearance:
Anti-hyperglycemic effects of optimized formulation (CPOP) were studied using diabetic rabbits. The animal used in the study in accordance with a protocol approved by the Institutional Ethical Committee (letter approval number: Ganesh Sanker S/Ph.D/VU/J863600002 &10/06/2015), at the central animal hous**e facilities of K. M. College of pharmacy, Uthangudi, Melur road, Madurai – 625107.** The experiments were conducted as per Committee for Prevention, Control and Supervision of Experimental Animals guidelines.

Selection of animals [29,30]:
The adult New Zealand white rabbit's selected from either sex was used in pharmacological study. Rabbits having weight between 1-1.5 Kg were used in the study.The animals were housed in wooden cages under standard conditions (light period: 12 hr, relative humidity and temperature 25 ± 2 ^{O}C). The animals were provided free access to food (green fodder, leaves and pulses) and water *ad libitum.*

In clinical practice, Acarbose are administered orally. Hence, the human therapeutic doses were extrapolated to rabbits based on their body weight and administered orally for the study.

Diabetes mellitus was induced by a single intraperitoneal injection of Alloxan monohydrate (100 mg/kg, body wt.), was given to the selected groups of rabbits. Hyperglycemia was confirmed by elevated glucose levels in blood, which was determined at 72 hr, following 7th day after injection.

Study design [29,30]:
New Zealand white rabbits of either sex weighing between 1-1.5 kg were divided into four groups of 6 animals each. The animals were fasted for a period of 18 hr prior to experimentation and water supplied *ad libitum.* Group I was treated with the vehicle (diabetic control), Group II was treated with Acarbose 5.25 mg/kg, Group III was treated with optimized formulation (5.25 mg/kg), Group IV was treated with optimized formulation contain dose 2.10 mg/kg.

On the first day of treatment, fasted-treated rabbits were administered with standard drug and test tablets through intragastric tube and this was repeated for three consecutive days (orally) and the alloxan treated rabbits were given vehicle.

Blood glucose determination [30,31]:
Blood samples were collected at 0 hr, 2nd hr, 4th hr, 6th hr, 8th hr, 12th hr, 18th hr and 24th hr of drug treatment from the marginal ear vein of the rabbits. The collected blood was used to determine blood glucose level.

Body Weight Measurement [30,31]:
Body weight of animals in each group was recorded on 0, 7th 14th, 21th and 28th day and difference in weight were noted.

Urine Excretion [30,31]:
During the study period, total urinary excretion volume (ml) before and after induction of alloxan was determined for each group.

Statistical Analysis [31]:
Results are reported as mean and standard deviation. Student's *t*-test was used tocompare the groups and ANOVA was used for repeated longitudinal measurements with commercially available statistical software (GraphPad Instat Software). A *P*-value of *<0*.05 was considered significant.

RESULTS AND DISCUSSION:
The present study was undertaken to formulate Acarbose osmotic tablets. The study involved pre-formulation of drugs-excipient mixture, formulation, processing development along with evaluation of the tablets and pharmacological study of optimized formulation using suitable animal models.

Pre-formulation study of drug:
Determination of various organoleptic properties like physical appearance of drug was observed and reported on table 7.1.

Table 7.1: Determination of organoleptic properties of pure Acarbose.

Sample	Acarbose
Colour	White/ off White
Odour	odourless
Texture	Amorphous powder

Determination of solubility of Acarbose with various solvents which aresubjected to use for further stages of formulation development.

Table 7.2: Determination of solubility of pure Acarbose.

Solvent	**Solubility**
Distilled water	Freely soluble
Ethanol	Sparingly soluble
Buffer pH 7.4	Freely soluble
Acetone	Slightly soluble

Determination of melting point: The melting point of Acarbose was determined by capillary method. The result from the experiment, which was compared with standard specification.

Table 7.3: Melting point determination of pure Acarbose.

Sample	**Specification/ limit**	**Observation**
Acarbose	140-162 ^{O}C	141.2 ^{O}C

The Acarbose was subjected to drug-excipients compatibility study with excipients like mannitol, sodium chloride, micro crystalline cellulose, ethyl cellulose, Eudragit, hydroxyl propyl methyl crystalline cellulose, polyvinyl pyrrolidone, talc and magnesium stearate. The mixtures shown to have no colour change.

Good flow of powders / granules is essential in tableting because the compressibility & flow properties of the drugs likely to influence the compression process in the preparation of tablets.

Evaluation of powder mixture:

The prepared dry blend of the formulations was evaluated for the parameterslike angle of repose, bulk density, tap density, Hausner ratio and compressibility index.

Angle of Repose (Ø):

Table 7.4: Determination of Angle of repose of powder mixture

Sl.No	**FORMULATIONS**	**ANGLE OF REPOSE (Ø)**
1	**CP1**	27.62 ± 0.21
2	**CP2**	27.46 ± 0.21
3	**CP3**	27.21 ± 0.21
4	**CP4**	26.97 ± 0.35
5	**CP5**	26.64 ± 0.21
6	**CP6**	26.07 ± 0.24
7	**E1**	26.72 ± 0.16
8	**E2**	27.80 ± 0.24
9	**E3**	26.32 ± 0.36
10	**E4**	26.15 ± 0.08
11	**E5**	26.22 ± 0.08
12	**E6**	26.30 ± 0.29
13	**E7**	26.56 ± 0.14
14	**E8**	26.89 ± 0.07
15	**E9**	27.21 ± 0.21

*n=3, All values expressed in ± SEM

Table 7.5: Determination of physical characteristics of powder mixture

Sl. No	FORMULATIONS	BULK DENSITY(g/cm^3)	TAPPED DENSITY(g/cm^3)	HAUSNER RATIO
1	**CP1**	0.448 ± 0.00	0.534 ± 0.00	1.19 ± 0.00
2	**CP2**	0.449 ± 0.00	0.532 ± 0.00	1.19 ± 0.01
3	**CP3**	0.450 ± 0.00	0.534 ± 0.00	1.15 ± 0.01
4	**CP4**	0.446 ± 0.00	0.530 ± 0.00	1.18 ± 0.00
5	**CP5**	0.449 ± 0.00	0.532 ± 0.00	1.18 ± 0.00
6	**CP6**	0.446 ± 0.00	0.524 ± 0.00	1.16 ± 0.00
7	**E1**	0.441 ± 0.02	0.526 ± 0.00	1.19 ± 0.03
8	**E2**	0.443 ± 0.00	0.528 ±0.00	1.05 ± 0.06
9	**E3**	0.446 ± 0.00	0.517 ± 0.00	1.05 ± 0.06
10	**E4**	0.445 ± 0.00	0.526 ± 0.00	1.06 ± 0.06
11	**E5**	0.441 ± 0.00	0.524 ± 0.00	1.06 ± 0.07
12	**E6**	0.453 ± 0.00	0.530 ± 0.00	1.05 ± 0.05
13	**E7**	0.446 ± 0.00	0.522 ± 0.00	1.05 ± 0.06
14	**E8**	0.450 ± 0.00	0.526 ± 0.00	1.05 ± 0.06
15	**E9**	0.447 ± 0.00	0.530 ± 0.00	1.06 ± 0.06

*n=3, All values expressed in ± SEM

Table 7.6: Determination of % Compressibility of powder mixture

Sl. No	FORMULATIONS	COMPRSSIBILITY (%)
1	**CP1**	16.16 ± 0.13
2	**CP2**	15.65 ± 0.51
3	**CP3**	15.65 ± 0.69
4	**CP4**	15.77 ± 0.32
5	**CP5**	15.77 ± 0.16
6	**CP6**	14.88 ± 0.30
7	**E1**	16.17 ± 2.05
8	**E2**	15.97 ± 0.46
9	**E3**	13.69 ± 0.89
10	**E4**	15.43 ± 0.17
11	**E5**	15.86 ± 0.64
12	**E6**	14.58 ± 0.35
13	**E7**	14.58 ± 0.12
14	**E8**	14.41 ± 0.03
15	**E9**	15.52 ± 0.18

*n=3, All values expressed in ± SEM

The physical characteristics of powder mixture of various formulations (CP1-CP6and E1-E9) are given below:
Angle of repose for all the prepared formulations fall in the range of 26.07 ± 0.245 to 27.80 ± 0.247o.
Hausner ratio was found to be 1.05 ± 0.05 to 1.19 ± 0.03.

Carr's index was found to be in the range of 13.69 ± 0.89 to 16.17 ± 2.05 %.
All these values indicated that the powder mixtures have good flow property and compressibility property.

Hardness:
The hardness of the different formulations of CPOP ranged from 6.96 ± 0.121kg/cm^2 to 7.25 ± 0.104 kg/cm^2 and for EOP ranged from 6.96 ± 0.109 kg/cm^2 to 7.23± 0.179 kg/cm^2. The data's of various formulations were shown in table-7.13 & 7.14.The tablets have enough hardness to withstand stress during handling and transportation.

Table 7.13: Hardness of controlled pore osmotic tablets

Sl.No	FORMULATIONS	HARDNESS (kg/cm^2±SEM)
1	**CP1**	6.96 ± 0.121
2	**CP2**	7.02 ± 0.122
3	**CP3**	7.12 ± 0.167
4	**CP4**	7.20 ± 0.057
5	**CP5**	7.12 ± 0.173
6	**CP6**	7.25 ± 0.104

*n=3, All values expressed in ± SEM

Table 7.14: Hardness of Elementary osmotic tablets

Sl.No	FORMULATIONS	HARDNESS (kg/cm^2±SEM)
1	**E1**	7.07 ± 0.108
2	**E2**	7.06 ± 0.138
3	**E3**	7.18 ± 0.181
4	**E4**	7.18 ± 0.106
5	**E5**	7.23 ± 0.179
6	**E6**	7.20 ± 0.151
7	**E7**	6.96 ± 0.109
8	**E8**	7.01 ± 0.167
9	**E9**	7.00 ± 0.187

*n=3, All values expressed in ± SEM

Friability:
The friability of tablet ranges between 99.20 ± 0.26 to 99.50 ± 0.22 %. All theformulations exhibited less than 1 % friability.

Table 7.15: Friability of controlled pore osmotic tablets

Sl.No	FORMULATIONS	FRIABILITY (% ± SEM)
1	**CP1**	99.33 ± 0.19
2	**CP2**	99.40 ± 0.28
3	**CP3**	99.40 ± 0.25
4	**CP4**	99.40 ± 0.25
5	**CP5**	99.36 ± 0.15
6	**CP6**	99.36 ± 0.25

*n=3, All values expressed in ± SEM

Table 7.16: Friability of Elementary osmotic tablets

Sl.No	FORMULATIONS	FRIABILITY (% ± SEM)
1	**E1**	99.30 ± 0.25
2	**E2**	99.40 ± 0.25
3	**E3**	99.36 ± 0.25
4	**E4**	99.40 ± 0.25
5	**E5**	99.36 ± 0.24
6	**E6**	99.40 ± 0.22
7	**E7**	99.43 ± 0.21
8	**E8**	99.50 ± 0.22
9	**E9**	99.20 ± 0.26

*n=3, All values expressed in ± SEM

Average Weight:

Depending upon the ingredients of different formulations, the weight of tabletwas fixed. In each formulation, weight variation was within the I.P limit.

Table 7.17: Average Weight of controlled pore osmotic tablets

Sl.No	FORMULATIONS	AVERAGE WEIGHT (mg ± SEM)
1	**CP1**	300.40 ± 0.81
2	**CP2**	300.70 ± 0.88
3	**CP3**	300.54 ± 1.15
4	**CP4**	300.45 ± 1.01
5	**CP5**	300.20 ± 1.52
6	**CP6**	300.65 ± 1.27

*n=3, All values expressed in ± SEM

Table 7.18: Average Weight of Elementary osmotic tablets

Sl.No	FORMULATIONS	AVERAGE WEIGHT(mg ± SEM)
1	**E1**	300.40 ± 0.62
2	**E2**	300.30 ± 0.55
3	**E3**	300.40 ± 1.09
4	**E4**	300.65 ± 0.92
5	**E5**	300.40 ± 0.48
6	**E6**	300.45 ± 0.38
7	**E7**	300.05 ± 1.13
8	**E8**	300.60 ± 0.83
9	**E9**	300.10 ± 0.57

*n=3, All values expressed in ± SEM

Test for Uniformity of Drug Content:

The content uniformity test for Acarbose was carried out. The results werefound to be 98.73 ± 0.01 % to 99.00 ± 0.28 % for CPOP and 98.70 ± 0.15 % to 99.12± 0.24 % for EOP respectively. The results were found to be within the I.P. Limits[90 -110 %]. It shows that the drug was distributed uniformly throughout the tablets.

Table 7.19: Uniformity of Drug Content of controlled pore osmotic tablets

Sl.No	FORMULATIONS	UNIFORM DRUG CONTENT (% w/w ± SEM)
1	**CP1**	98.73 ± 0.01
2	**CP2**	99.00 ± 0.28
3	**CP3**	98.87 ± 0.21
4	**CP4**	98.86 ± 0.41
5	**CP5**	98.99 ± 0.49
6	**CP6**	98.82 ± 0.40

*n=3, All values expressed in ± SEM

Table 7.20: Uniformity of Drug Content of Elementary osmotic tablets

Sl.No	FORMULATIONS	UNIFORM DRUG CONTENT (% w/w ± SEM)
1	**E1**	98.70 ± 0.15
2	**E2**	98.88 ± 0.25
3	**E3**	99.12 ± 0.24
4	**E4**	98.63 ± 0.30
5	**E5**	98.75 ± 0.30
6	**E6**	98.74 ± 0.30
7	**E7**	98.80 ± 0.30
8	**E8**	98.79 ± 0.46
9	**E9**	98.78 ± 0.46

*n=3, All values expressed in ± SEM

Construction of Standard Curve of Acarbose:

***IN - VITRO* DISSOLUTION STUDIES**

Table 7.22: *In vitro* dissolution data of various formulation of controlled poreosmotic tablet (CP1-CP3)

TIME (Hr)	% CDR		
	CP1	**CP2**	**CP3**
0	0	0	0
1	7.51 ± 0.06	8.23 ± 0.21	9.62 ± 0.25
2	14.25 ± 0.03	15.90 ± 0.32	15.61 ± 0.36
3	21.61 ± 0.29	22.61 ± 0.10	26.40 ± 0.25
4	29.43 ± 0.35	30.10 ± 0.17	32.72 ± 0.31
5	35.12 ± 0.25	34.65 ± 0.09	38.61 ± 0.21
6	43.24 ± 0.18	41.82 ± 0.30	43.40 ± 0.31
7	49.61 ± 0.26	49.41 ± 0.12	49.54 ± 0.35
8	56.31 ± 0.15	55.73 ± 0.21	54.73 ± 0.31
9	63.82 ± 0.21	64.23 ± 0.06	60.21 ± 0.40
10	69.73 ± 0.35	72.56 ± 0.33	67.42 ± 0.25
11	75.41 ± 0.32	79.81 ± 0.32	71.41 ± 0.31
12	79.22 ± 0.31	85.51 ± 0.15	71.90 ± 0.35

*n=3, All values expressed in ± SEM

In controlled porosity osmotic pumps the drug release rate depends on the concentration of the osmogent and the concentration of pore former used. As the concentration of osmogent and pore former increases the release rate also increases. These two factors will cause the release of the drug in diffusion manner which is further proven by kinetic studies. Among the various formulation of CPOP the formulation CP5 was found to be optimized as it showed a release rate of 96.62 ±0.15 % at the end of 12 hours. The formulation CP5 contained Cellulose acetate 3 % and PEG 400 in the ration of 60:40.

In case of an EOP the rate of drug release depends on the composition of coating, miscibility of the drug in the tablet core, and difference in osmotic pressure across the membrane. The drug release mechanism was primarily by simple diffusionat a constant release rate through the orifice. Among the nine formulations prepared the formulation E5 was found to be the optimized one, which contained Eudragit RL 100 and drug in 1:1 ratio. The polymer Eudragit RL 100 in 1:1 ratio was found to bea better release retardant than HPMC K100 and EC. The formulation E5 was able to release 94.10 ± 0.21 % at the end of 12 hours.

Kinetics of drug release:

The *in vitro* drug release data was analysed with various kinetic models likeHiguchi model, zero order, first order and Peppas which was given in table 7.26.

Table 7.26: *In vitro* drug release kinetics of Controlled Pore Osmotic Pump andElementary Osmotic Pump

FORMULATIONS	ZERO ORDER	FIRST ORDER	HIGUCHI	PEPPAS &KOSYMEYER	
	R^2	R^2	R^2	R^2	N
CP1	0.997	0.886	0.935	0.999	0.966
CP2	0.998	0.895	0.920	0.998	0.940
CP3	0.984	0.864	0.962	0.993	0.833
CP4	0.977	0.864	0.962	0.985	1.201
CP5	0.990	0.838	0.946	0.989	0.981
CP6	0.985	0.895	0.941	0.99	0.985
E1	0.977	0.965	0.971	0.983	0.638
E2	0.982	0.934	0.967	0.994	0.671
E3	0.993	0.916	0.958	0.998	0.782
E4	0.982	0.899	0.967	0.998	0.759
E5	0.965	0.855	0.973	0.991	0.733
E6	0.997	0.933	0.915	0.993	0.899
E7	0.964	0.927	0.987	0.999	0.639
E8	0.962	0.937	0.984	0.993	0.586
E9	0.972	0.931	0.975	0.993	0.637

When the data were plotted according to first order equation show comparatively poor linearity with regression values of 0.838 to 0.965, whereas the regression value for zero order equation was 0.965 to 0.997, which indicated that the drug release from optimized formulation was independent of drug concentration.

In controlled pore osmotic pump the n value for Peppas model was found to be in between 0.833 and 1.201, indicating that the drug release from the formulation by non fickian mechanism. The optimized formulation from controlled pore osmotic pump (CP5) shows a regression value 0.990 for zero order kinetics with 'n' value 0.981which indicates zero order diffusion mechanism.

In elementary osmotic pump the 'n' value for Peppas model was found to be in between 0.586 and 0.899, indicating a non fickian diffusion mechanism of drug release from the formulations. The regression value for zero order kinetics range from 0.962 to 0.993 and 0.838 to 0.895 for first order kinetics respectively, which indicate the drug release in controlled release mechanism. The optimized formulation (E5) from elementary osmotic pump follows non fickian diffusion release mechanism.

Stability Studies:

The optimized formulations were analyzed for parameters like physical characteristics, drug content, and *in vitro* drug release. From the obtained data for the various parameters, it was observed that, there will not be any considerable variations from the standard limits. The comparisons of various parameters are given in table 7.27 & 7.28.

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