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FORMULATION AND STUDY OF CONTROLLED POROSITY OSMOTIC TABLET OF ACARBOSE

[1]*Ganesh Sanker S. and [2]Dr. Molly Mathew

[1]Research Scholar, the Vinayaka Missions University, Ariyanoor, Salem, Tamilnadu-636308.

[2]Principal, Malik Deenar College of Pharmacy, Seethangoli, Bela Post, Kasaragode-671321, Kerala.

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***Corresponding Author**
Ganesh Sanker S.
Research Scholar, the Vinayaka Missions University, Ariyanoor, Salem, Tamilnadu- 636308.

ABSTRACT

In this study a controlled pore osmotic tablet of Acarbose was prepare and evaluated the various parameters. Acarbose is very high soluble anti-hypoglycemic drug which is an ideal candidate for zero order drug delivery release. The effect of osmogen, change in composition of coating solution and various physiochemical studies were conducted. The FT-IR studies revealed that no physiochemical interaction between excipients and drug. The *in vitro* study of Acarbose osmotic tablet shows a significant effect on dug release up to 12h. The drug release kinetic of optimized formulation follows zero order non fickian release mechanism. The observed data's were found to be very close to predicted values of most satisfactory formulation which demonstrates the feasibility of the optimization procedure in successful development of porous osmotic tablet of Acarbose.

KEYWORDS: Acarbose, CPOP, poly ethylene glycol, mannitol, sodium chloride, drug release kinetics.

INTRODUCTIONS

Oral osmotic drug delivery systems are new approaches for controlled release dosage form. The survey of the literature indicates that extensive work was conducted in the development and fabrication of an osmotic drug delivery system for the pharmaceutical active materials. Many attempt where made to develop osmotic pumps which produce zero order delivery for an extended period of time for many active substance. The drug release mechanism from such system can be explained by diffusion, osmotic pumping and a combination of both. Oral

controlled release system continues to be the most popular amongst all the drug delivery system. Because pharmaceutical agents can delivered in controlled pattern over a long period by osmotic pressure, there has be an increase interest in the development of osmotic device over the past two decades.[1]

In matrix system the drug delivered through diffusion mechanism, which can be altered by the pH of medium, presence of food and the physiological factors of body. In osmotic drug delivery system, the principle of osmosis as driving force to release the drug from the system and release rate is unaffected by the above reasons.[12] In the present study, an osmotic drug delivery drug delivery system for Acarbose was devised and studied to reduce the drug dosing frequency and to produce a zero order drug release system.[2,3]

In the present work, a micro-porous membrane coating because of its advantage such as a high flux of water in to tablets, better control of the permeability and porosity of membrane and easy of formulation. The release rate from this type of system is dependent on the coating, solubility of the drug in the tablet core and osmotic pressure difference across the membrane. The coating composition of CPOP includes, pore forming agent, which generates pore in contact with aqueous media. It was observed that most of the core content release through pore at constant rate, where the release mechanism primarily is osmotic with simple diffusion playing a major role.[4]

A zero order delivery pattern was designed to produce plasma level within the desired range. Different formulation variables were studied and optimized to achieve the desired release profile. To maintain the drug concentration within the therapeutic window the drug dose and during interval are optimized thus ensuring efficacy while minimizing toxic effects. The oral osmotic pump tablet have many disadvantages such as reducing risk of adverse reaction, zero order delivery rate, a high degree of *in vitro–in vivo* correlation and improve patient compliance.[5]

MATERIALS AND METHODS

MATERIALS[12]

Acarbose, Microcrystalline cellulose, PVP_{K30}, PEG 400 was received from Yarrow chem, Mumbai. Mannitol, Fructose, Magnesium stearate, Talc, Cellulose acetate was purchase from SD Fine Chem. Ltd (Mumbai, India).

METHODS

Preparation of core tablet[4,12]

The core tablets were prepared by direct compression method according to the various compositions of formulae given in table -1.

All the ingredients and drug were accurately weighed and mixed in a lab scale mixer to get a homogenized uniform mixture. The dry blend of mixture pass through sieves No: 80. Then mixture is compressed in to tablet using rotary tablet machine (Cadmach machinery, Ahmadabad) equipped with 10mm diameter, round plain and concave punch. Tablet were compressed at an average weight of 300 mg and hardness of tablet kept as 7 Kg/cm^2.

Various formulation and dissolution parameter were analyzed to optimize the core tablets.

Table 1: Preparation of core tablet.

Sr. No	MATERIALS	CP1	CP2	CP3	CP4	CP5	CP6
1	DRUG	75	75	75	75	75	75
2	MANNITOL+NaCl	1:1.34	1:1.34	1:1.34	1:1.34	1:1.34	1:1.34
4	MCC	118.5	118.5	118.5	118.5	118.5	118.5
5	TALC	2%	2%	2%	2%	2%	2%
6	MAGNESIUM STERATE	1%	1%	1%	1%	1%	1%

Preparation of coating solution[6,9,14]

The coating solution containing Cellulose Acetate (CA) (4%, 3% & 2%) and PVP $_{K30}$ (20%) was prepared as per the formula given in table-2.

Table- 2: Preparation of coating solution.

sr. no	COATING SOLUTION	CP1 (4%)	CP2 (4%)	CP3 (4%)	CP4 (4%)	CP5 (3%)	CP6 (2%)
1	Cellulose Acetate	30	60	50	100	60	60
2	PEG 400	70	40	50	*	70	70

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.

Coating of core tablet

Coating of core tablet was done by pan coater. Coating process parameters optimized with respect to coating pan speed, coating inlet air, temperature, atomizing air pressure and spray rate.

EVAUATION OF OSMOTIC TABLET

Pre-Formulation Evaluation[9,10]

1. Angle of repose

The powder mass was allowed to flow through the funnel orifice kept vertically to a plane paper kept on the horizontal surface, giving a heap angle of powder on paper. The angle of repose was calculated by substituting the values of the base radius 'r' and pile height 'h' in the following equation:

$\Theta = \tan^{-1} h/r$

2. Bulk density[9]

Bulk density was obtained by dividing the mass of powder by the bulk volume in cm^3. It was calculated by using equation given below:

$Df = M/Vp$

Where, Df=Bulk Density

M=Weight of sample in grams

Vp=Final volume of powder in cm^3

3. Tapped density[9]

It is the ratio of total mass of the powder to the tapped volume of the powder. It is expressed in g/ml and is given by,

$Do = M/Vp$

Where,

Do=Tapped density

M=Weight of sample in grams

Vp=Final volume of powder after tapping in cm^3

4. Carr's index[9]

Carr developed an indirect method of measuring powder flow from densities. The percentage compressibility of a powder was a direct measure of the potential powder arch or bridge strength and stability. Carr's index of each formulation was calculated by,

$\%\ Compressibility = Do – Df/Df \times 100$

Where,

Df=Fluff or poured bulk or bulk density

Do=Tapped or consolidated bulk density

5. Hausner's ratio[9]

Hausner Ratio is the measure of the propensity of a powder to be compressed which is calculated using the following formulae:

Hausner ratio=Do/Df

Where,

Df=Fluff or poured bulk or bulk density

Do=Tapped or consolidated bulk density

Compatibility studies

1. Fourier transform infrared spectroscopy (FTIR)[20]

The use of FTIR technique allows pointing out the implication of the different functional groups of drug and excipients by analyzing the significant changes in the shape and position of the absorbance bands. 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 mins in a mortar and compressed into disc by applying pressure of 5 tons for 5 mins 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.

Physiochemical Evaluation

1. Appearance and shape

The general appearance of tablet includes the morphological characteristic like size, shape, colour etc.

2. Uniformity of thickness and diameter

The uniformity of the diameter and thickness was measured using vernier caliper. Ten tablets from each formulation were randomly selected and used. The average diameter and thickness of the tablet calculated and expressed in mm.

3. Hardeness

Monsanto hardness tester was used to check the hardness of tablet. Ten tablets from each formulation were randomly selected and used. The tablet placed between the jaws of tester. The two jaws placed under the tension by spring and screw gauge. By turning the screw, the load was increased and at collapse the applied pressure from the spring measured in Kg/m^2.

4. Friability

The friability test was carried out to evaluate the hardness and stability instantly in Roche Friabilator. The percent loss in weight or friability (F) was calculated by the formula,

$F= (1-W/W_o) \times 100$

Where,

F=Friability

W_o=Initial weight

W=Final weight

5. Weight Variation

To study the weight variation 20 tablets from each formulation were weighed using an electronic balance and the test performed according to the official standard method.

6. Uniform drug content[17]

To perform uniform drug content 10 tablets were weighed and crushed to a fine power using motor and pestle. Accurately weighed sample equivalent to 75 mg of Acarbose was taken in a volumetric flask. The content was dissolved in small quantity of water and then volume is made up to 100 ml with remaining volume of water. The sample were diluted to the required concentration and analyzed spectrophotometrically at 210nm.[21]

7. Dissolution study[9,8,13,13]

The *in vitro* dissolution study carried out using USP type II dissolution apparatus, operation condition were maintained at 37 ± 0.5^oC at 30 RPM. The dissolution media was phosphate buffer pH 7.4 up to the volume of 900 ml. During the study 5 ml of sample were withdrawn at every hour and same amount of fresh dissolution media was replaced. The withdrawn sample were diluted to the required concentration and analyzed spectrophotometrically at 210nm.[21]

8. Kinetics of drug release[9,17]

The dissolution profile of all batches were checked to fitted to zero order, first order, higuchi, korsemeyer and peppas to assess the kinetics modeling of drug release.

RESULT AND DICUSSION

1. Powder properties

The results of preformulation parameters for formulated physical mixtures of all batches are show in table:-4. The flowability of the drug polymer mixture was found to be quite good according to the flow properties. The angle of repose ranging from 26.07± 0.42 to 27.62 ± 0.37, bulk density ranges from 0.45 to 0.449 g/cm^3, % compressibility ranges from 14.5 to 16.17%.

Table- 4: Data of various pre-formulation evaluation parameters.

Sr.No	FORMULATIONS	ANGLE OF REPOSE	BULK DENSITY	TAPPED DENSITY	HAUSNER RATIO	COMPRSSIBILITY
1	CP1	27.62 ± 0.37	0.448	0.534	1.19	16.17
2	CP2	27.46 ± 0.37	0.449	0.532	1.19	15.97
3	CP3	27.21 ± 0.36	0.45	0.534	1.15	13.69
4	CP4	26.97 ± 0.6	0.446	0.53	1.18	15.43
5	CP5	26.64 ± 0.37	0.449	0.532	1.18	15.88
6	CP6	26.07 ± 0.42	0.446	0.524	1.16	14.5

2. Fourier transforms infrared spectroscopic studies (FTIR)[20]

The FTIR spectra of drug and optimized formulation were recorded and shown in Figure-3 and 4. The major peaks were obtained at 581.27, 1034.45, 1643.96 and 3300-2930/cm^{-1} for pure drug and the same characteristic bands of the drug in optimized formulation also shown without any significant spectral changes, thus there is no interaction between drug and excipients used in the formulation.

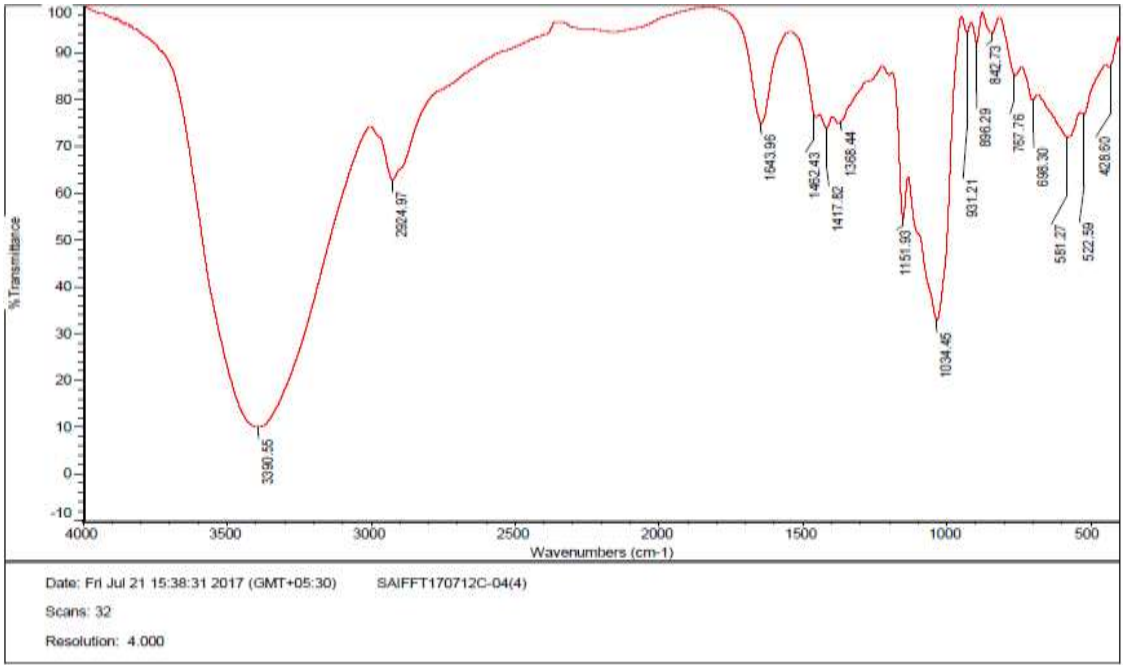

Fig- 3: FTIR spectra of pure drug (Acarbose).

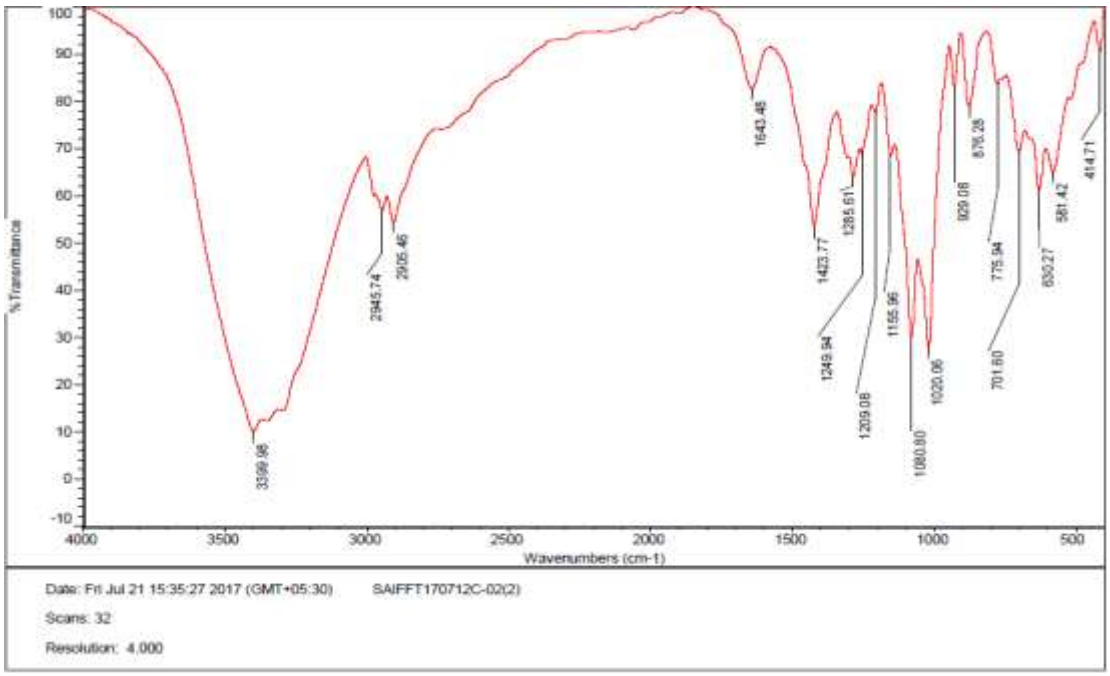

Fig- 4: FTIR spectra of optimized formulation contains pure drug (Acarbose) and polymers.

3. Appearance and shape

The physical evaluation of the formulation was carried out for their appearance, shape and identification, which was shown in table:-3. The shape and size are identical for all the formulation and its colour varies from white to off white.

Table- 3: Physical evaluation of the formulations CP1 –CP6.

FORMULATIONS	Appearance	Shape	Identification
CP1	White/off white coloured	Circular tablet	Passes
CP2	White/off white coloured	Circular tablet	Passes
CP3	White/off white coloured	Circular tablet	Passes
CP4	White/off white coloured	Circular tablet	Passes
CP5	White/off white coloured	Circular tablet	Passes
CP6	White/off white coloured	Circular tablet	Passes

4. Physiochemical properties

The physiochemical properties like;- hardness, thickness, uniform drug content, friability of prepared core tablets were recorded in table:-5. The hardness of tablet was found to be between 6.96 ± 0.12 to 7.12 ± 0.10 kg/cm^2, while the friability of tablet ranges between 298 ± 0.74 to 298.2 ± 0.79%. The tablets have enough hardness to withstand stress during handling and transportation. The uniform drug content of various formulations between 98.73 ± 0.96 and 99 ± 0.25%w/w.

Table- 5: Data of various physiochemical evaluation parameters.

Sl.No	FORMULATIONS	THICKNESS	HARDNESS	FRIABILITY	AVERAGE WEIGHT	UNIFORM DRUG CONTENT
1	CP1	3.379± 0.036	6.96±0.12	298±0.74	300.4±1.27	98.73±0.96
2	CP2	3.376± 0.042	7.05±0.12	298.2±0.79	300.7±0.92	99±0.25
3	CP3	3.376± 0.040	7.11±0.15	298.2±0.79	300.55±1.05	98.87±0.32
4	CP4	3.377± 0.042	7.11±0.10	298.2±0.79	300.45±1.05	98.86±0.47
5	CP5	3.372± 0.044	7.12±0.10	298.1±0.74	300.2±1.91	98.99±0.57
6	CP6	3.371± 0.041	7.22±0.08	298.1±0.74	300.65±1.93	98.82±0.44

5. Dissolution study

In porous osmotic pump tablets the drug release rate depends on the concentration of the osmotic agents and the pore former used. The osmotic agent concentration increases then the osmotic pressure created inside the tablet also increases, the core compartment imbibes aqueous fluids from the surrounding environment across the membrane and dissolves the drug so the release of the dug also will increase. The pore former concentration increases then the number of pore formed or the pore size also increases it will cause easy leaching out of the drug from the formulation. These two factors will cause the release of the drug in diffusion manner.

Table- 6: Cumulative drug release data of formulation CP1-CP6.

TIME (Hr)	% CDR					
	CP1	CP2	CP3	CP4	CP5	CP6
0	0	0	0	0	0	0
1	7.5	8.2	9.6	2.8	8.1	12.5
2	14.25	15.9	15.6	6.9	17.9	27.5
3	21.6	22.6	26.4	12.6	25.4	43.7
4	29.4	30.1	32.7	15.4	41.7	56.9
5	35.1	34.65	38.6	25.7	47.2	68.9
6	43.24	41.8	43.4	29.9	55.4	79.7
7	49.6	49.4	49.5	36.6	60.8	91.2
8	56.3	55.7	54.7	40.4	67.3	94.2
9	63.8	64.23	60.2	44.7	76.5	
10	69.7	72.56	67.4	47.5	82.3	
11	75.4	79.8	71.4	49.7	89.5	
12	79.2	85.5	71.9	50.9	96.6	

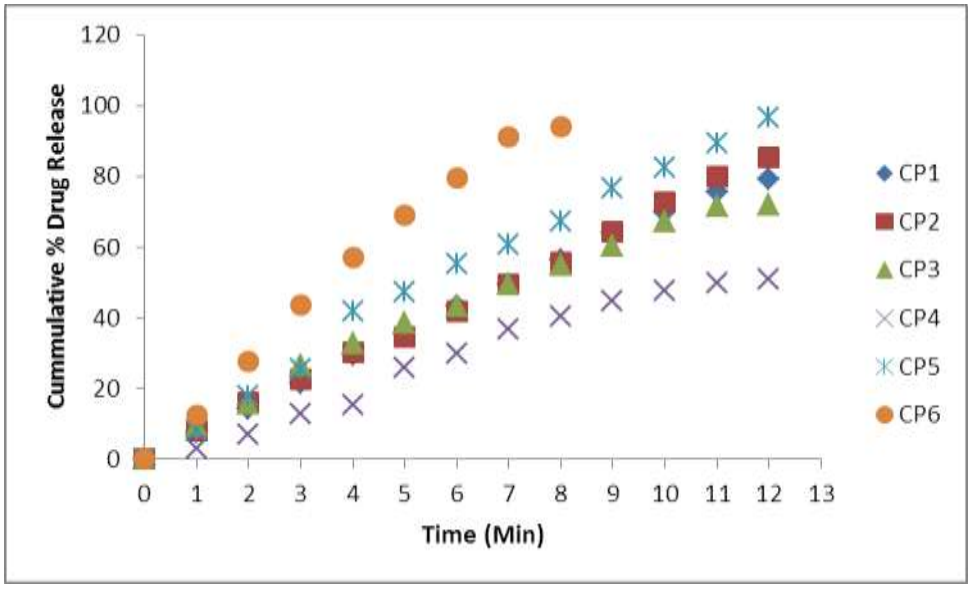

Fig- 1: *In vitro* drug release from formulation CP1 –CP6.

6. Kinetics of drug release[9]

The *in vitro* release data was fitted to various kinetic models like higuchi, zero order, first order and peppas. When the data were plotted according to first order equation shows comparatively poor linearity with regression values of 0.838. Whereas the regression value for zero order equation was 0.99, which indicated that 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, indicates that the drug release from the formulation by non fickian mechanism.

Table- 7: *In vitro* drug release kinetics of formulation CP1 – CP6.

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	0.990	0.985

CONCLUSION

The controlled porosity osmotic pump tablet of Acarbose had been successfully prepared. The optimal controlled porosity osmotic pump tablet was able to deliver Acarbose at the rate of approximate zero order up to 12 h, independent of release media and agitation rate. Membranes were found to develop pores after coming in contact with aqueous environment. Finally, it can be concluded that preparation of osmotic pump tablet can be simplified by coating the core tablet with a pore forming agent which is likely to be more cost effective than laser drilling. A more comprehensive pharmacokinetic study should be conducted, in the future, to confirm the obtained results.

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