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Research/Review

Formulation and evaluation of controlled release matrix tablets of oligomeric proanthocyanidins (OPC)

V. Suresh Rao[1], D. Suchitra[2], Dr. Munija pancheddula[*]

**Vice Principal, Vision college of Pharmaceutical Sciences & Research, Boduppal, Hyderabad-500092*
[1,2]Asisstant professor, Vision college of Pharmaceutical Sciences & Research, Boduppal, Hyderabad-500092

*Author for Correspondence: P. Munija
Email: munijapharma@gmail.com

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Abstract

In the present research, an attempt has been made to formulate controlled release matrix tablets of oligomeric proanthocyanidins (OPCs). Matrix technologies have often proven popular among the oral controlled drug delivery technologies because of their simplicity, easy in manufacturing, high level of reproducibility and easy of scale up and process validation. OPCs is a natural anti oxidant used for the treatment of atherosclerosis was chosen as a model drug with an aim to develop a controlled release matrix tablet. Different formulations were prepared by wet granulation method by using different polymers like HPMC, chitosan, guar gum and xanthan gum with different ratios were used in the development of formulations. The prepared tablets were evaluated for precompression and postcompression parameters with different ratios. All the formulations showed compliance with pharmacopoeial standards. The effect of polymer loading in *in-vitro* drug release and the mechanism of release/dissolved was studied by different mathematical models. It was found that the OPCs release rate increased with a decreased amount of polymer. This can be adjusted by maintaining the concentration of the suitable polymers. The selected formulations were subjected to stability studies as per ICH guidelines at different temperature and humidity conditions. Among all the formulations the chitosan and combinations of HPMC and chitosan was considered as the optimized formulation.

Keywords: Oligomeric Proanthocyanidins, HPMC, Chitosan, xanthan gum, guar gum

INTRODUCTION

Controlled Release System[1,2,3,4]

The term Drug delivery covers a very broad range of techniques used to get therapeutic agents into the human body. Among all routes of administration, the oral route has been most popular and successful. This is, in part, because of the inherent simplicity of both the oral route and oral delivery systems. On the other hand, the oral route is constrained by short and variable GI transit time, first-pass metabolism, limited absorption in the lower part of the GI tract, and the size of the system.

The effectiveness of these drugs, however, is often limited by side effects or the necessity to administer the compound in a clinical setting, the goal in designing sustained or controlled delivery system is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required, or providing uniform drug delivery. Sustained release constitutes any dosage form that provides medication over and extended time. Controlled release, however, denotes that the system is able to provide some actual therapeutic control, whether this is of a temporal nature, spatial nature or both.

This correctly suggests that there are sustain release system that cannot be considered controlled release system. In general, the goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of drug for an extended period this is usually accomplished by attempting to obtain zero-order release from the dosage form; zero-order release constitutes drug release from the dosage form. Sustained release systems generally do not attain this type of release and provides drug is a slow first order fashion. In recent years sustained release dosage forms continue to draw attention in the search for improved patient compliance and decreased incidence of adverse drug reactions. Sustained release technology is relatively cow field and as a consequence, research in the field has been extremely fertile and has produced many discoveries. New and more sophisticated controlled release, sustained release delivery systems are constantly being developed and tested.

Sustained release, sustained action, prolonged action controlled release, extended action, timed release, depot and repository dosage forms are terms used to identify drug delivery system that are designed to achieve or prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose.

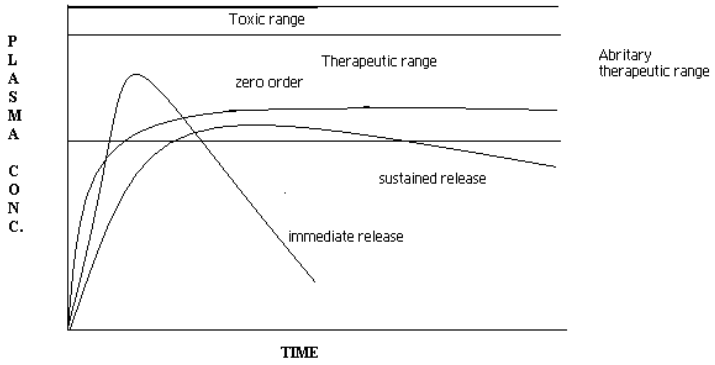

Fig 1: Drug level versus time profile showing differences between zero order, controlled releases, slow first order sustained release and release from conventional tablet.

Systems that are designed as prolonged release can also be considered as attempts at achieving sustained-release delivery. Repeat action tablets are an alternative method of sustained release in which multiple doses of drug are contained within a dosage form, and each dosage is related to a periodic interval. Delayed release systems, in contrast may not be sustaining, science often function of these dosage forms is to maintain the drug within the dosage form for some time before release. Commonly the release rate of drug is not altered and does not result in sustained delivery once drug release has begun.

Successful fabrication of sustained release products is usually difficult & and involves consideration of physicochemical properties of drug, pharmacokinetic behavior of drug, route of administration, disease state to be treated and, most importantly, placement of the drug in dosage form total will provide the desired temporal and spatial delivery pattern for the drug

The slow first order release obtained by a sustained release pre parathion is generally achieved by the release of the drug from a dosage form. In some cases in some cases, this achieved by making slow the release of drug from a dosage form. In some cases, this is accomplished by a continuous release process

MATERIALS AND METHODS

The seeds of Grapes are used to produce grape seed extract (GSE). GSEs are industrial derivatives from whole grape seeds. Typically, the commercial opportunity of extracting grape seed constituents has been for chemicals known as polyphenols, including Oligomeric proanthocyanidins (OPCs) recognized as Natural Antioxidants. Microcrystalline Cellulose, Magnesium stearate , Potassium dihydrogen phosphate, Guar gum, Xanthan gum are purchased from S.D.Fine Chem.Ltd., Mumbai.

Preformulation studies

Determination of Melting Point .

Melting point of OPCs was determined by capillary method. Fine powder of OPCs was filled in glass capillary tube (previously sealed on one end). The capillary tube is tied to thermo meter and the thermometer was placed in fire. The powder at what temperature it will melt was noticed.

Solubility

Solubility of OPCs was determined in ethanol (95%), methanol, chloroform, acetone, water and 0.1 N HCl. Solubility studies were performed by taking excess amount of OPCs in different beakers containing the solvents. The mixtures were shaken for 24 hrs at regular intervals. The solutions were filtered by using whattmann's filter paper grade no. 41. The filtered solutions are analyzed spectrophotometrically.

Compatibility Studies

Compatibility with excipients was confirmed by carried out FTIR studies. The pure drug and its formulations along with excipients were subjected to IR studies. In the present study, the potassium bromide disc (pellet) method was employed.

Identification of OPCs.

A solution *of* OPCs containing the concentration 10 µg/ ml was prepared in 0.1 N HCl and UV spectrum was taken using Shimadzu 1800 – Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

Preparation of Standard Calibration Curve of OPCs in water

Dissolve 100 mg of drug in 50 ml of water in beaker then sonicate it for 15 mn them make up the volume up to 100 ml in 100 ml volumetric flask with water this solution is stock 1st solution (1000 µg/ml). Pipette out 5 ml from stock 1 and make up to volume 100 ml with water in 100 ml volumetric flask this is 2nd stock solution which gives 50 µg/ml concentrations. Now pipette out 2, 4, 6, 8 ml from 2nd stock and make up the volume to 10ml with water in 10 ml volumetric flask this gives 10, 20, 30, 40 µg/ml concentration respectively. The absorbance of the solution was measured against water as blank at 280 nm using UV spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Preparation of Standard Calibration Curve of OPCs in 0.1 N HCl

Dissolve 100 mg of drug in 50 ml of HCL in beaker then sonicate it for 15 mn them make up the volume up to 100 ml in 100 ml volumetric flask with HCL this solution is stock 1st solution (1000 µg/ml). Pipette out 5 ml from stock 1 and make up to volume 100 ml with HCL in 100 ml volumetric flask this is 2nd stock solution which gives 50 µg/ml concentrations. Now pipette out 2, 4, 6, 8 ml from 2nd stock and make up the volume to 10ml with HCL in 10 ml volumetric flask this gives 10, 20, 30, 40 µg/ml concentration respectively.The absorbance of the solution was measured against 0.1 N HCL as blank at 280 nm using UV spectrophotometer. The absorbance values were plotted against concentration (µg/ml) to obtain the standard calibration curve.

Preparation of Standard Calibration Curve of OPCs in pH 6.8 phosphate buffer

Dissolve 100 mg of drug in 100 ml of 6.8 pH phosphate buffer in 100 ml volumetric flask with 6.8 pH phosphate buffer this solution is stock 1st solution (1000 µg/ml). Pipette out 5 ml from stock 1 and make up to volume 100 ml with 6.8 pH phosphate buffer in 100 ml volumetric flask this is 2nd stock solution which gives 50 µg/ml concentrations. Now pipette out 2, 4, 6, 8 ml from 2nd stock and make up the volume to 10ml with 6.8 pH phosphate buffer in 10 ml volumetric flask this gives 10, 20, 30, 40 µg/ml concentration respectively. The absorbance of the solution was measured against 6.8 pH phosphate buffer as blank at 280 nm using UV.

Angle of repose

The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$\tan \theta = h/r$

Where,

h and r are the height and radius of the powder cone respectively.

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) was determined. A quantity of 2 gm of powder blend from each formula, previously shaken to break any agglomerates formed, was introduced in to 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted. LBD and TDB were calculated using the following equations.

LBD= Weight of the powder blend/Untapped Volume of the packing

TBD=Weight of the powder blend/Tapped Volume of the packing

Compressibility Index

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

Carr's Index (%) = [(TBD-LBD) x100]/TBD

Table 1: Compressibility index

Carr's index(%)	Type of flow
5-15	Excellent
12-18	Good
18-23	fair to passable
23-35	poor
35-38	Very poor
>	Extremely poor

Total Porosity

Total porosity was determined by measuring the volume occupied by a selected weight of a powder (V_{bulk}) and the true volume of the powder blend (The space occupied by the powder exclusive of spaces greater than the intermolecular spaces, V).

$$\text{Porosity (\%)} = V_{bulk}\text{-}V/\ V_{bulk} \times 100$$

Post compression parameters

Weight variation test.

To study weight variation twenty tablets of the formulation were weighed using a Essae electronic balance and the test was performed according to the official method. Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation.

Table 2: IP Standards of Uniformity of weights

Sl.No	Avg.wt.of tablet	% deviation
1	80mg or < 80	10
2	>80 to < 250mg	7.5
3	>250 or more	5

Drug content

Ten tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in pH 6.8 Phosphate buffer, the drug content was determined measuring the absorbance at 280 nm after suitable no. dilution using a Shimadzu1800-Double beam UV/VIS Spectrophotometer.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined.

Thickness

The thickness of the tablets was determined by using digital vernier calipers. Five tablets were used, and average values were calculated.

Friability Test

The friability of tablets was determined by using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (W_0) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W). The % friability was then calculated by – $\%F = 100\ (1\text{-}W_0/W)$

% Friability of tablets less than 1% are considered acceptable no.

***in vitro* dissolution studies**

In- vitro dissolution studies were carried out using eight stage dissolution rate tests USP Type II apparatus (TDT-08T Electro lab). The dissolution medium consisted of pH 1.2 (0.1 N hydrochloric acid) for first 2 hrs and phosphate buffer (pH 6.8) for subsequent 10 hrs. A quantity of 900 ml of the dissolution fluid was maintained at 37 ± 1° with a stirring speed of 75 ± 2 rpm used for the study. Aliquots of 5 ml were withdrawn at predetermined time intervals and an equivalent amount of fresh buffer maintained in the same temperature was replaced. Then absorbance was measured at about 280 nm with UV/ Visible Spectrophotometer (Model UV 1800 ENG240V). The content of drug was calculated using the equation generated from standard curve of OPCs. All dissolution studies were performed in triplicate.

Short term Stability studies of OPCs tablet

The International Conference of Harmonization (ICH) Guidelines titled, "stability testing of New Drug substance and products" (QIA) describes the stability test requirements for drug registration application in the European Union, Japan and the United States of America. ICH specifies the length of study and storage conditions. Long-term testing: - $25^0C \pm 2^0C$ / 65% RH ± 5% for 12 months. Accelerated testing: - $40^0C \pm 2^0C$/ 75% RH± 5% for 6 months. Stability studies were carried out at 30^0C / 65% RH (as per QIC) and 40^0C / 75% RH for the following optimized formulations for 45 days.

RESULTS AND DISCUSSION

In the present work, an attempt has been made to prepare controlled release matrix tablets of OPCs, an antioxidant along with different polymers like HPMC, chitosan, xanthan gum, and guar gum

In the present study 13 formulations with variable concentration of polymer were prepared and evaluated for physicochemical parameters, *in vitro* release studies and stability studies. The formulated batches were shown in Table 3.

Table 3: Different Composition of Controlled Release Tablets of OPCs

INGREDIENTS	Code of formulations												
(mg/tab)	FA_1	FA_2	FA_3	FB_1	FB_2	FB_3	FC_1	FC_2	FD_1	FD_2	FE_1	FE_2	FE_3
OPCs	100	100	100	100	100	100	100	100	100	100	100	100	100
HPMC(K100M)	100	–	50	–	50	50	–	50	–	50	50	25	–
Chitosan	–	100	50	–	–	–	–	–	–	–	–	–	–
EC	–	–	–	100	50	42.5	–	–	–	–	–	–	–
PEG 4000	–	–	–	–	–	7.5	–	–	–	–	–	–	–
Guar Gum	–	–	–	–	–	–	100	50	–	–	25	37.5	50
Xanthan Gum	–	–	–	–	–	–	–	–	100	50	25	37.5	50
PVP k 30	10	10	10	10	10	10	10	10	10	10	10	10	10
MCC	35	35	35	39	39	39	35	35	35	35	35	35	35
Magnesium Stearate	5	5	5	1	1	1	5	5	5	5	5	5	5
Total	250	250	250	250	250	250	250	250	250	250	250	250	250

Melting Point Determination: Melting point of OPCs was determined by capillary method. The melting point of OPCs was found to be in the range 220°C.

Solubility: OPCs was found to be freely soluble in ethanol (95%), methanol and soluble in water with sonication.

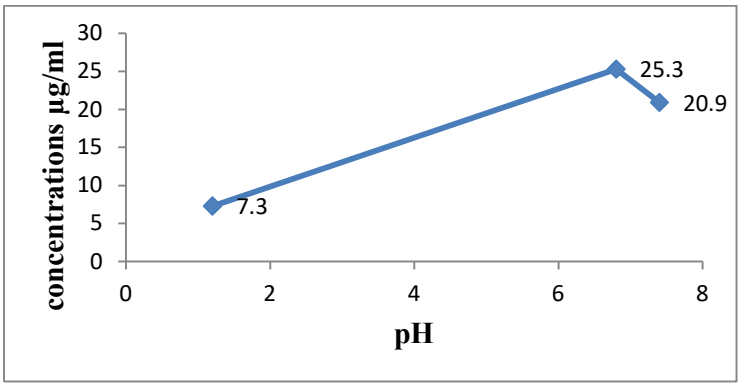

Fig 2: Solubility curve of OPCs in different pH Vs Conc

Compatibility studies

Compatibility studies were performed using FTIR spectrophotometer. The FTIR spectrum of pure drug and physical mixture of drug and polymers were studied. Drug- excipient interactions play a vital role with respect to release of drug from the formulation amongst others. FTIR techniques have been used here to study the physical and chemical interaction between drug and excipients used. In the present study, it has been observed that there is no chemical interaction between drug and the polymers used which is shown in the figure no.3 to 5. It was observed that there were no changes in these main peaks in FTIR spectra of mixture of drug and polymers, which show there were no physical interactions because of some bond formation between drug and polymers. The peaks obtained in the spectra's of each polymer correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components.

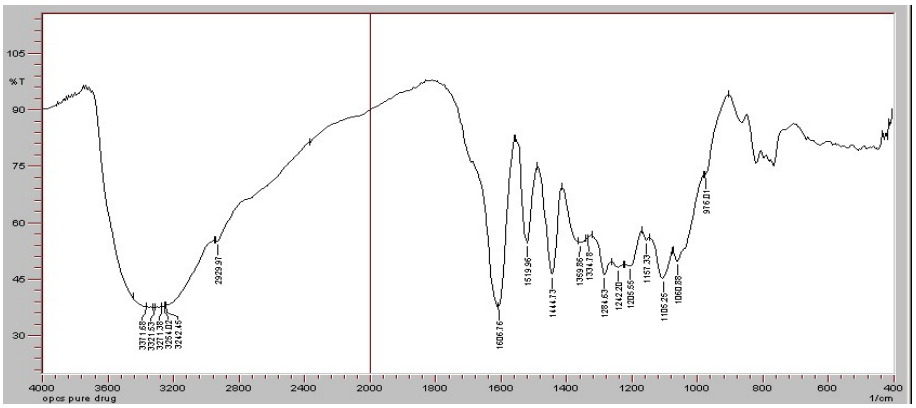

Fig 3: FTIR Spectrum of OPCs (Pure Drug).

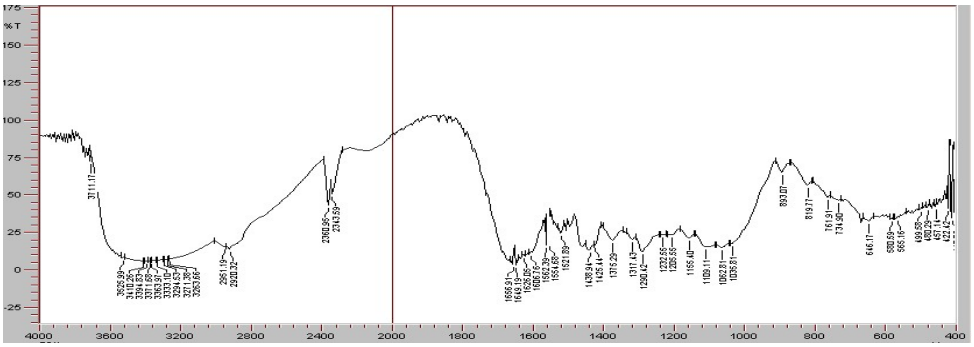

Fig 4: FTIR Spectrum of Optimized FA_2 (OPCs and chitosan).

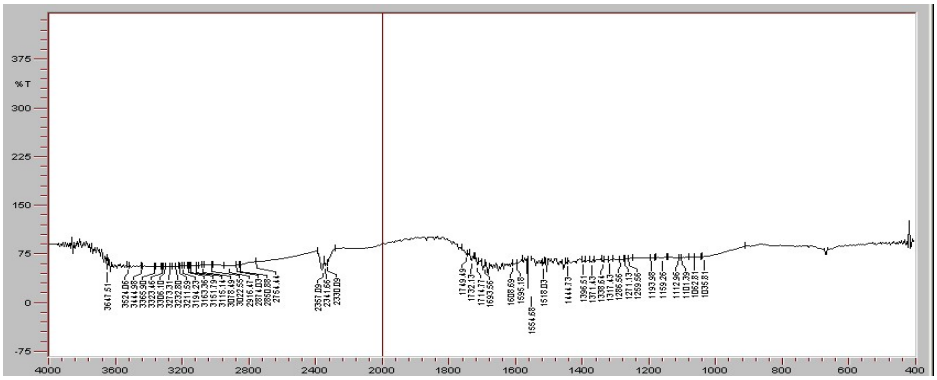

Fig 5: FTIR spectrum of Optimized FA_3 (OPCs+chitosan+HPMC).

Standard Calibration Curve of OPCs

The scanning of drug solution in UV region (200–400 nm) to find out the wavelength of maximum absorption (λ_{max}). The λ_{max} was found to be at 280 nm. So the Standard calibration curve of OPCs was developed at this wave length. The calibration curve was linear between 10-50 µg/ml concentration ranges. The standard calibration curve of OPCs was determined in both phosphate buffer and 1.2 pH (0.1 HCl), by plotting absorbance against concentration at 280 nm. Results were tabulated in table no 6. The r^2 and slope were found to be 0.992 and 0.011 respectively and in phosphate buffer (6.8) r^2 and slope were found to be 0.997 and 0.026 respectively.

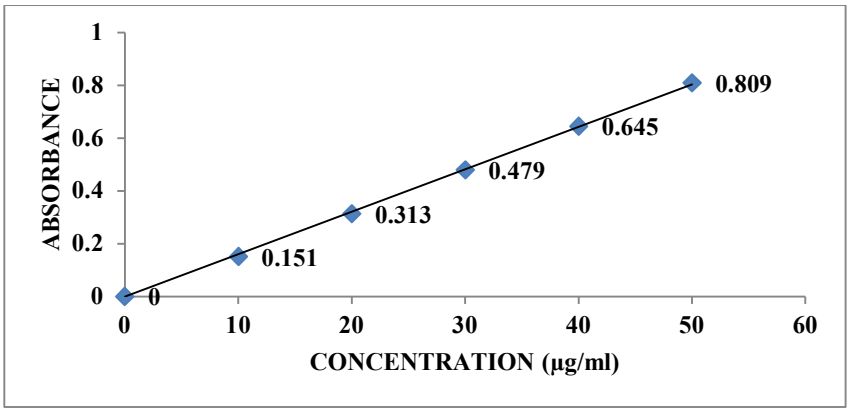

Fig 6: Standard Calibration curve of OPCs in distilled water

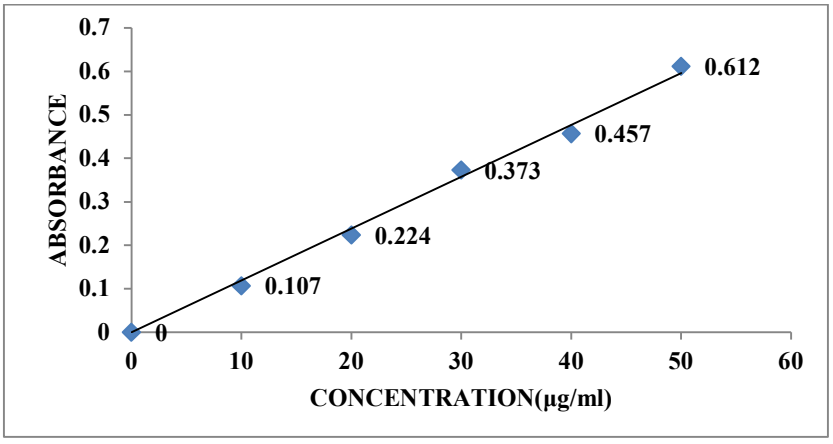

Fig 7: Standard calibration curve of OPCs in pH 1.2

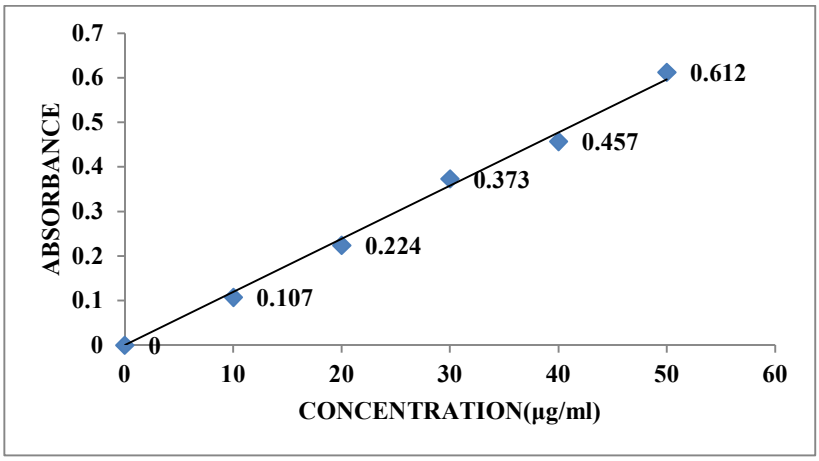

Fig 8: Standard Calibration Curve of OPCs in pH 6.8 phosphate buffer

Angle of Repose (θ).

The angle of repose for the formulated blend was carried out and the results were shown in Table no.6. It concludes all the formulations blend was found to be in the range $24^0 98'$ to $32^0 25'$.

Carr's Index

Compressibility index was carried out, it was found within the official limits i.e. 15.61% to 19.01%, indicating the granules blend has the required flow property for compression.

Table 4: Micromeritic properties of OPCs granules

Code of formulations	Parameters					
	Angle of Repose (o)*	Bulk Density (g/ml)*	Tapped Density (g/ml)*	Carr's Index. (%)*	Hausner ratio*	Total Porosity (%)*
FA_1	32.38±0.13	0.36±0.02	0.43±0.02	16.48±0.13	1.21±0.01	16.54±0.09
FA_2	27.52±0.28	0.35±0.02	0.40±0.04	16.08±0.04	1.19±0.01	14.40±0.11
FA_3	26.39±0.19	0.39±0.00	0.49±0.01	18.41±0.11	1.23±0.02	15.48±0.19
FB_1	27.67±0.16	0.34±0.01	0.41±0.01	15.43±0.15	1.22±0.01	12.41±0.14
FB_2	28.62±0.21	0.39±0.01	0.48±0.00	16.10±0.05	1.17±0.02	13.59±0.29
FB_3	29.22±0.23	0.38±0.01	0.47±0.01	18.61±0.13	1.23±0.01	14.66±0.15
FC_1	26.57±0.22	0.34±0.02	0.42±0.02	16.51±0.14	1.22±0.01	12.71±0.12
FC_2	25.44±0.08	0.38±0.01	0.47±0.02	16.30±0.16	1.18±0.01	12.14±0.05
FD_1	24.47±0.36	0.32±0.00	0.41±0.00	14.35±0.08	1.21±0.01	13.73±0.06
FD_2	27.64±0.18	0.33±0.00	0.43±0.00	19.12±0.09	1.21±0.01	14.14±0.05
FE_1	26.33±0.18	0.36±0.01	0.44±0.01	17.30±0.05	1.22±0.00	12.36±0.04
FE_2	26.56±0.31	0.37±0.00	0.45±0.01	16.44±0.18	1.23±0.01	15.16±0.05
FE_3	28.21±0.05	0.33±0.00	0.41±0.01	19.36±0.11	1.21±0.01	15.07±0.05

***** Mean ± S.D., n=3 (All the values are the average of three determination)

1. Shape of the tablets: Microscopic examinations of all the tablets formulations were found to be circular shape with no cracks.

2. Colour of the tablets: The colour of the tablet was dark red (The colour of pure drug is dark red)

3. Diameter: Diameter of the tablets was found to be 9.25 mm

4. Thickness: Thickness of the tablets was found to be 4.10 to 4.20 mm

5. Hardness test: The crushing strength of the tablets of each batch ranged between 4.5to 4.7 kg/cm^2 (Table no.7).This ensures good handling characteristics of all batches.

6. Friability Test: It is ranging from 0.030±0.026 to 0.138±0.032. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable

7. Weight Variation Test: All the formulated tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

8. Drug Content Uniformity: The percentage of drug content for all formulation was found to 97.02% to 98.52% of OPCs.

9. *In vitro* Dissolution Studies and Kinetic modeling of drug release.

Table 5 (A): *In vitro* dissolution studies profile of different formulations

Time (hrs)	FA_1	FB_1	FB_2	FB_3	FC_1
0	0	0	0	0	0
1	4.47±0.71	6.65±0.46	6.59±0.30	3.34±0.37	2.62±0.25
2	8.54±0.86	8.09±0.78	8.43±0.27	6.98±0.92	5.56±0.36
3	60.60±2.22	70.77±0.75	65.82±0.99	13.83±0.38	10.75±0.47
4	68.95±0.85	78.10±0.45	71.45±0.34	23.07±0.69	17.54±0.44
5	79.23±0.34	82.36±0.25	76.32±0.34	30.75±0.46	25.66±0.24
6	88.52±0.95	88.56±0.54	80.55±0.35	36.59±0.33	30.72±0.40
7	95.26±0.55	93.43±0.32	86.32±0.73	42.53±0.38	36.38±0.30
8	96.30±0.12	94.41±0.22	90.41±0.20	50.25±0.58	44.48±0.30
9	96.32±0.08	95.54±0.26	90.78±1.00	58.35±0.36	51.53±0.29
10	96.58±0.29	96.98±0.52	94.09±0.45	66.45±0.21	61.06±0.61
11	96.56±0.35	97.56±0.38	95.47±0.25	75.51±0.27	65.18±0.89
12	97.26±0.17	97.83±0.44	95.95±0.41	83.72±1.42	72.63±1.03

Table 5 (B): *In vitro* dissolution studies profile of different formulations

Time (hrs)	FC_2	FD_1	FD_2	FE_1	FE_2	FE_3
0	0	0	0	0	0	0
1	2.73±0.46	3.46±0.34	3.87±0.32	3.15±0.29	2.89±0.46	2.50±0.39
2	6.65±0.31	5.90±0.66	6.68±0.57	5.65±0.41	4.40±0.40	3.59±0.42
3	13.36±1.81	12.69±0.63	10.89±0.61	11.72±0.63	8.28±0.33	7.62±0.32
4	19.31±0.49	19.13±0.81	16.36±0.39	17.39±0.33	15.39±0.70	12.75±0.56
5	26.27±0.64	25.88±0.70	22.69±0.65	25.45±0.38	20.91±0.61	16.73±0.42
6	31.73±0.90	33.66±0.49	30.98±0.65	32.63±0.60	26.25±0.52	21.53±0.41
7	37.45±0.38	41.18±0.42	38.54±0.52	40.85±0.59	33.30±0.69	28.52±0.40
8	42.96±0.50	50.58±0.44	46.62±0.71	46.38±0.93	40.74±0.58	33.98±0.80
9	51.34±0.75	58.88±0.46	56.86±1.11	53.35±0.30	47.14±0.51	41.85±0.99
10	58.72±0.66	66.41±0.37	62.99±0.60	60.67±0.64	56.16±0.90	51.24±0.70
11	69.41±0.63	72.59±0.43	71.61±0.94	68.54±0.34	62.53±0.47	58.60±0.49
12	78.22±0.18	81.03±0.62	79.67±0.88	76.44±0.31	70.86±0.87	66.34±0.58

***** Mean ± S.D., n=6 (All the values are the average of six determination)

Table 6: *in vitro* dissolution studies of Optimized Formulation FA_2

Time (hrs)	% Release	CPR	log t	SQ RT	% drug remaining	log %drug remaining	log CPR
0	0	0	0	0	0	0	0
1	3.67	3.67	0.00	1.00	100.00	2.00	0.31
2	8.27	8.27	0.30	1.41	91.73	1.96	0.92
3	10.88	14.13	0.48	1.73	85.87	1.93	1.15
4	15.93	19.18	0.60	2.00	80.82	1.91	1.28
5	24.09	27.34	0.70	2.24	72.66	1.86	1.44
6	31.47	34.72	0.78	2.45	65.28	1.81	1.54
7	37.30	40.55	0.85	2.65	59.45	1.77	1.61
8	46.63	49.87	0.90	2.83	50.13	1.70	1.70
9	59.06	62.30	0.95	3.00	37.70	1.58	1.79
10	76.15	79.40	1.00	3.16	20.60	1.31	1.90
11	86.65	89.89	1.04	3.32	10.11	1.00	1.95
12	93.64	96.89	1.08	3.46	3.11	0.49	1.99

All the thirteen formulations of prepared tablets of OPCs were subjected to *in vitro* release studies using USP dissolution apparatus II, (In different pH 0.1N HCL pH 1.2 and Phosphate buffer pH 6.8.).The *in vitro* release of formulations FA_1,FB_1, FB_2 does not showed satisfactory release it release more than 60% of drug in third hour only. While the CPR of the formulation FB_3, FC_1, FC_2, FD_1, FD_2, FE_1, FE_2, FE_3 was found to be 83.72, 72.63, 78.22, 81.03, 79.67, 76.44, 70.86, 66.34 respectively. While the formulation A2 and A3 gives CPR 96.89% and 92.22% respectively, so we focused on this two formulation only.

Mathematical Modeling of Drug Release Profile

Table 7*: In vitro* dissolution studies of Optimizes Formulation FA_3

Time (hrs)	% Release	CPR	log t	SQ RT	% drug remaining	log %drug remaining	log CPR
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	2.76	2.76	0.00	1.00	100.00	2.00	0.31
2	7.35	7.35	0.30	1.41	92.65	1.97	0.87
3	13.60	16.85	0.48	1.73	83.15	1.92	1.23
4	22.92	26.17	0.60	2.00	73.83	1.87	1.42
5	27.59	30.83	0.70	2.24	69.17	1.84	1.49
6	36.91	40.16	0.78	2.45	59.84	1.78	1.60
7	45.07	48.32	0.85	2.65	51.68	1.71	1.68
8	57.89	61.14	0.90	2.83	38.86	1.59	1.79
9	64.89	68.13	0.95	3.00	31.87	1.50	1.83
10	76.15	79.40	1.00	3.16	20.60	1.31	1.90
11	81.98	85.23	1.04	3.32	14.77	1.17	1.93
12	88.98	92.22	1.08	3.46	7.78	0.89	1.96

Table 8: Drug Release Kinetic Data Derived From Various Mathematical Models

Optimized Formulations	Zero order R^2	First order R^2	Higuchi equation K	Pappas equation "n" Value
FA_2	0.964	0.044	-22.29	1.647
fA_3	0.992	0.016	-24.14	1.628

The results obtaining in vitro release studies of A2 and A3 were plotted in different model of data treatment as follows:

1. Cumulative percent drug released vs. time (zero order rate kinetics)
2. Log cumulative percent drug released vs. time (First Order rate Kinetics)
3. Cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)
4. Log of cumulative % release Vs log time (Pappas Exponential Equation)

All *in vitro* studies results of formulation A2 and A3 are discussed in table no. 9 and 10 respectively

The kinetic values obtained for formulation A2, A3 were shown in Table no.11. The values of *in vitro* release were attempted to fit into various mathematical models. Plots of zero order, first order, Higuchi matrix and Peppas model of A2 and A3 were depicted. The r^2 value of zero order for A2 and A3 was found to be 0.964 and 0.992 which indicates that the drug release follows zero order

Swelling index

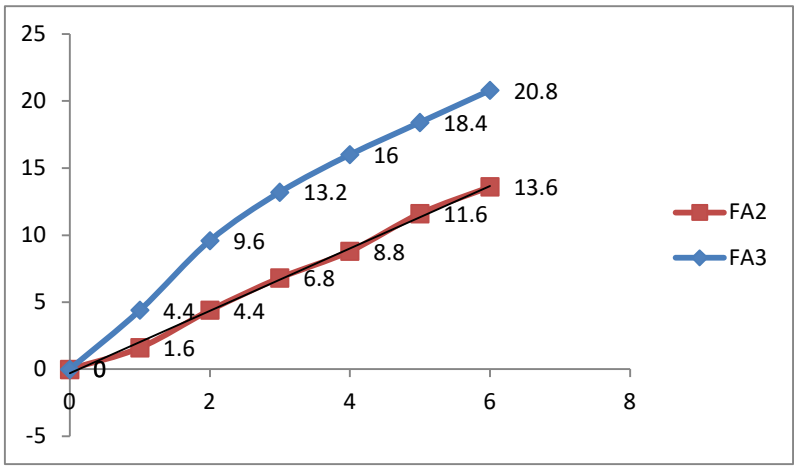

Fig 9: Swelling Behavior of Optimized Formulations FA_2 and FA_3

Stability Study

No significant difference in the drug content between initial and the formulations stored at 25°C and in photo stability chambers but a small difference were found between initial and formulations stored at 40°C. Therefore it is recommended that these formulations should be stored at 25°C.

CONCLUSION

OPCs is an anti oxidant using in the treatment of atherosclerosis, which has a short biological half-life of 4.5 hours. Its dose is 50 to 150 mg daily in divided doses. Because of frequent administration and short biological half-life OPCs is considered as an ideal drug for designing a controlled release formulation. In the present study, an attempt was made to prepare matrix tablets of OPCs by wet granulation method using polymers like HPMC, chitosan, guar gum and xanthan gum as matrix material with magnesium stearate, microcrystalline cellulose as co-excipients. Prepared matrix tablets were evaluated for hardness, friability, weight variation, drug content uniformity, drug-polymer interaction, in vitro drug release and short-term stability studies. Among the various formulations prepared, formulation A2 (drug: chitosan=1:1), formulation A3 (drug: chitosan: HPMC=1:0.5:0.5) containing microcrystalline cellulose and magnesium stearate as co-excipient showed comparatively good release. Hence, HPMC, chitosan can be used for designing OPCs drug delivery systems of OPCs.

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