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RESEARCH ARTICLE

Fabrication of Chitosan and Poly-Acrylic Acid Complexes as Osmogent for Swellable Nanoporous Osmotic Pump

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Abstract:

In present study on controlled porosity osmotic tablet of Irbesartan was performed. The study involved two stages, at first stage; optimization of sodium chloride in the core tablet to optimize the release of water insoluble Irbesartan, while the second stage involved the formulation and evaluation of the CPOP (chitosan and poly-Acrylic acid osmotic pump) and study effect of different concentrations of swelling polymer (chitosan and carbopol 934 P). Irbesartan is a angiotensin II given in the treatment of hyprtension. Irbesartan is water insoluble drug so by optimization of sodium chloride in the core tablet, concentration of chitosan and carbopol 934 P in the proper weight ratios modifies the release of water insoluble Irbesartan in order to make it controlled release approach for 10 hrs.. The study reveals successful performance of optimization technique for the development of controlled porosity osmotic tablet drug delivery. When the release rate of osmotic tablets, it was found that increse3 in concentration of chitosan and carbopol 934P, the drug release was found to be increased.

KeyWords: Osmotic Tablet, Chitosan, Carbopol 934P

Introduction:

Osmotic systems have a high degree of IVIVC, because of the factors that are responsible for causing differences in release profiles *in vivo -in vitro* (e.g. variable pH, agitation) affect the systems to a much lesser extent.[1] Out of existing oral controlled release systems, elementary osmotic pump, push pull osmotic pump, and controlled porosity osmotic pump are the key systems. In elementary osmotic pump, drug core is coated with a semipermeable membrane and a delivery orifice is created with a mechanical or laser drill.[2] The push pull osmotic pump is a bilayer tablet. The upper layer consists of a drug along with osmotic agents. The lower layer consists of polymeric osmotic agents. The tablet is coated with a semipermeable membrane and a delivery orifice is created in upper layer.[3] The controlled porosity osmotic pump is a simple coated tablet. When it comes in contact with aqueous media, water-soluble component (from the coating membrane) leaches out and pores are formed, through which drug release takes place. Controlled porosity osmotic pump provides advantage over other systems is that it does not require laser drilling for drug release. Drug is released due to leaching of water-soluble component from the coating membrane.

Oral route is one of the most extensively used routes of drug administration because of its obvious advantages of ease of administration, improved patient compliance and convenience.[4] Conventional drug delivery systems have slight control over their drug release and almost no control over the effective concentration at the target site. This kind of dosing pattern may result in constantly changing, unpredictable plasma concentrations. Drugs can be delivered in a controlled pattern over a long period of time by the controlled or modified release drug delivery systems.[5]

A number of design options are available to control or modulate the drug release from a dosage form. Majority of the oral dosage forms fall in the category of matrix, reservoir or osmotic systems. Osmotic systems utilize the principles of osmotic pressure for controlled delivery of drugs.[6]

An osmotic system offers many advantages over other controlled release devices i.e. they are easy to formulate and simple in operation, improve patient compliance with reduced dosing frequency and prolong therapeutic effect with uniform blood concentration. Hypertension

is very common, occuring in over 50% of older people, and is a major risk factor for stroke and ischaemic heart disease.

Irbesartan is a water insoluble soluble drug. Because of its water insolubility, the majority of the drug fraction was released predominantly at a zero order rate. Incorporating excipients that modulate the solubility of the drug within the system could be an ideal approach to control drug release. The objective of the research work, Controlled porosity osmotic pump (CPOP) are reliable drug delivery system and could be employed as oral drug delivery system. Drug release from these systems is independent of pH and other physiological parameters. Zero order release characteristics for longer duration can be achieved by optimizing the parameters of the delivery system. The controlled porosity osmotic tablets consist of pore forming material in the coat. The core consists of drug and osmogen. Tablet is surrounded by a semipermeable material which controls the water influx and the drug release, irrespective of the surrounding environment.

The present work aims towards the formulation and evaluation of extended release formulation of Irbesartan based on chitosan and carbopol 934P as osmopolymer.

MATERIALS AND METHODS

Materials:

Irbesartan was obtained as a gift sample from Mission Vivacare Ltd., Indore. Chitosan purchased from Himedia laboratories Pvt. Ltd, Mumbai. Sodium Chloride, MCC and Lactose were procured from Glenmark Pharmaceuticals Ltd., Colvale, Goa. Remaining chemical were procured from Himedia laboratories Pvt. Ltd, Mumbai.

Methods:

Preparation of Chitosan and Carbopol 934P Interpolymer Complex (IPC)

The 3.3% w/v polymeric mixtures of chitosan and carbopol 934P in the ratio of 2:1 were prepared by dissolving chitosan and carbopol 934P in 1 M acetic acid. The mixture is stirred continuously for 2 hr. The pH of the resultant mixtures was adjusted to 5.0 by adding ortho-phosphoric acid. The mixtures were kept at room temperature overnight and then filtered. The filtrate was washed with distilled water, and the remaining wet mass dried at 50°C for 24 h and pulverized to a fine powder by using morter and pestle.[7]

Optimization of Sodium Chloride in Core Tablet

Incorporating sodium chloride can modulate the release of drug within the system to control drug release. For the optimization of sodium chloride in the core tablet preliminary formulations were prepared by incorporating sodium chloride into the core tablet in 5, 10, 15, 20, 25, 30, 35 mg. increments. The tablets were prepared by wet granulation technique. The ingredients were weighed accurately as per the formula given in the Table.1. [8,9]

All the ingredients except magnesium stearate and talc were sieve through # 40 and then it is triaturated in mortar and pestle for 15-20 min, with concomitant addition of isopropyl alcohol as granulating fluid. After preparation of dummy mass, this dummy mass was passed through sieve no. # 20. An obtained granules were kept in hot air oven until loss on drying reduces to 2 %. Then magnesium stearate and talc were added finally and mixture is further triatured in morter and pestle. The core tablets were compressed at an average weight of 265 mg using 10 mm concave punches and 6-7 kg/cm^2 hardness

Table 1: Optimization of Sodium Chloride in Core Tablet

Ingredients	**S1 (mg)**	**S2 (mg)**	**S3 (mg)**	**S4 (mg)**	**S5 (mg)**	**S6 (mg)**	**S7 (mg)**
Irbesartan	150	150	150	150	150	150	150
CS-PAA	30	30	30	30	30	30	30
Sodium Chloride	5	10	15	20	25	30	35
MCC	70	65	60	55	50	45	40
Lactose	2	2	2	2	2	2	2
Magnesium Stearate	5	5	5	5	5	5	5
Talc	3	3	3	3	3	3	3
Total weight	265	265	265	265	265	265	265

Coating Process

Preparation of Coating Solution[10]

The coating solution containing cellulose acetate, pole-ethylene glycol 400 (pore former) was prepared as per the formula given in the Table.13. Accurately weighed quantity of cellulose acetate (6.3 % w/w), PEG 400 (0.7 % w/w) and deionized water (4 % w/w) was added to acetone (89 % w/w). The mixture was stirred continuously for 30 min.

6.7.2 Dip Coating[11,12]

Tablets were coated by dip coating process. 6.3 % w/w cellulose acetate solution was used for coating. The coating of core tablet was done manually by holding each tablet with the help of forcep. The coated tablets were dried by keeping them at room temperature for 24 hr. The tablets were evaluated by studying the release study for 10 hr, in 900 ml dissolution medium using USP Apparatus 2 (Paddle) with 50 rpm.

Table 2: Formulation of Coating Solution

Ingredients	Concentration (%w/w)
Cellulose acetate	6.3
PEG 400	0.7
Deionized water	4
Acetone	89

Precompression Studies

Bulk Density[13]

Approximately weighed 10 gm sample of powder was placed into 25 ml measuring cylinder. Volume occupied by the powder was noted without disturbing the cylinder and the bulk density was calculated using the equation,

Bulk density = Weight of sample / Bulk volume

Tapped Density

Accurately weighed 10 gm of powder sample was placed in 25 ml measuring cylinder. The cylinder was subjected to a fixed number of taps (~100), till there was no change in volume with further tapping. The final volume was recorded and the tap density was calculated by the following equation,

Tapped density = Weight of drug sample / Tapped volume

Carr's Index[14]

The Carr's index is an indication of the compressibility of a powder. It is calculated by the formula,

C=VT-VB / VT

Where, VB is the freely settled volume of a given mass of powder, and VT is the tapped density of the same mass of powder The Carr's index is frequently used as an indication of the flowability of a powder. A Carr index greater than 25% is considered to be an indication of poor flowability and below 15% of good flowability.

Table 3: Relationship between %Compressibility and Flowability

Carr's index	Type of Flow
5-15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Extremely poor

Angle of Repose[15]

The angle of repose is indicative of flowability of the substance. Funnel was adjusted in such a way that the stem of the funnel lies 2.5 cm above the horizontal surface. The sample

powder was allowed to flow from the funnel, so the height of the pile just touched the tip of the funnel. The diameter of the pile was determined by drawing a boundary along the circumference of the pile and taking the average of three diameters.

The angle of repose is calculated by,

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

Where, h is height of the pile, r is the radius of the pile

Table 4: Relationship between Angle of Repose (θ) And Flowability

Angle of Repose (θ)	Flowability
< 25	Excellent
25-30	Good
30-40	Passable
> 40	Very Poor

Hausner's ratio[16]

The Hausner's ratio is an indication of the compressibility of a powder. It is calculated by the formula,

H= Tapped density / Bulk density

The Hausner's ratio is frequently used as an indication of the flowability of a powder. A Hausner's ratio greater than 1.25 is considered to be an indication of poor flowability. The observations for the flow properties determinations were mentioned in Table 21.

Evaluation of Controlled Porosity Osmotic Pump Tablets

The tablets were evaluated for various parameters as follows and readings were recorded in Table 22 and 23.

Appearance and Shape

The general appearance of the tablet includes the morphological characteristics like size, shape, colour etc. Also tablets may have lines, break-marks and may bear a symbol or other markings.

Uniformity of Thickness and Diameter

The uniformity of the diameter and thickness was measured using vernier caliper. The average diameter and thickness of the tablet was calculated. The test passed if none of the individual diameter and thickness value deviated by ± 5% of the average.

Hardness[17]

Monsanto hardness tester was used to check the hardness of the tablet. The tablet was placed vertically between the jaws of the tester. The two jaws placed under tension by spring and screw gauge. By turning the screw, the load was increased and at collapse the applied pressure from the spring was measured in kg/cm^2.

Weight Variation

To study weight variation, 20 tablets of each formulation were weighed using an electronic balance and the test was performed according to the official method. Since the average weight of tablet is more than 265 mg, the test requirements are met if none of the individual tablet weights are less than 95% or more than 105% of the average weight.

Dissolution Studies

Effect of Various Concentrations of Chitosan and Carbopol 934P Interpolymer Complex (IPC) On Drug Release.

In order to study the effect of various concentration of IPC of chitosan and carbopol 934P on *in vitro* drug release, the IPC were added ranging from 10 mg to 70 mg. The total wt. of the tablet were kept at constant wt. of 265 mg (Table 5)

Table 5: Formulations of Varying Concentrations of Chitosan-Carbopol 934P IPC

Ingredients	**F1 (mg)**	**F2 (mg)**	**F3 (mg)**	**F4 (mg)**	**F5 (mg)**	**F6 (mg)**	**F7 (mg)**
Irbesartan	150	150	150	150	150	150	150
CS-PAA	10	20	30	40	50	60	70
Sodium Chloride	30	30	30	30	30	30	30
MCC	65	55	45	35	25	15	5
Lactose	2	2	2	2	2	2	2
Magnesium Stearate	5	5	5	5	5	5	5
Talc	3	3	3	3	3	3	3
Total weight	265	265	265	265	265	265	265

6.7.5.2 USP Dissolution Test for Products Labeled Controlled release dosage form[18]

If the product complies with this test, the labeling indicates that it meets USP Dissolution Test. The release rate of Irbesartan from CPOP was determined using USP Apparatus 2 (Paddle). The dissolution test was performed using 900 ml of dissolution medium for 10 hr at 50 rpm. The dissolution medium comparises of three media. Firstly acidic media of 0.1 N HCl, pH 1.2, then after 2 hrs. It is replaced with phosphate buffer of ph 4.8, and finally phosphate buffer of ph 7.2 is used. The temperature of the medium was maintained at 37 ± 0.5ºC. Aliquot of 5 ml were withdrawn at an interval of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 hr. The withdrawn samples were replaced with fresh dissolution medium. The samples were filtered through Whatman filter paper and analyzed spectrophotometrically at 249 nm. Dissolution profiles of all formulations were summarized in Table 10.

6.7.6 Kinetics of Drug Release

The dissolution profile of all the formulations were fitted to zero order kinetics, first order kinetics, Higuchi, Korsmeyer and Peppas to ascertain the kinetic modeling of drug release and

the model with the higher correlation coefficient was considered to be the best model. The observations were summarized in the Table 11.

The value of n i.e. release exponent was found in the range of to which shoes release of drug from system by anomalous transport. Korsmeyer et.al, is used to describe drug release from polymeric systems

$$M_t/M_x=kt^n$$

Where, M_t/M_x is the fractional release of drug, t is the release time (expressed in hours), k is a constant that incorporates structural and geometric characteristics of the release device and n is the release exponent which indicates the kinetics of the release.

Pappas and Sahlin proposed a heuristic model and derived an equation which is very useful for quantifying the approximate amount of drug released by Fickian and polymer relaxation.

$$M_t/M_x= k_1t^{1/2} + k_2t$$

Where, the first term of the right hand side represents the fickian contribution, and the second term is the case II relaxational contribution, k_1 and k_2 corresponding to the release rates of case` I and case II mechanism respectively. The n value is used to interpret the release mechanism as shown in Table 25.

The n values were found to be between to indicating non-fickian diffusion or anomalous transport. The n ($0.5<n<1$) value also revealed the drug release mechanism via diffusion coupled with erosion.

Fickian diffusional release occurs by the usual molecular diffusion of the drug due to a chemical potential gradient. Case II relaxational release is the drug transport mechanism associated with stress and state transition hydrophilic glassy polymers, which swells in water or biological fluids. This term also includes polymer disentanglement and erosion.

RESULTS AND DISCUSSION

Optimization of Sodium Chloride in Core Tablet

A preliminary trial with 10 mg sodium chloride into the core tablet revealed a slow drug release rate at from the system.

The results revealed that incorporating sodium chloride at a concentration of 30 mg/tablet gives desired drug release rate from 15 mg/hr during a period of 6hr. (Table 6 and fig 1). Further study with a higher concentration of sodium chloride in the core tablet resulted into bursting of tablet (40 mg NaCl). The 30 mg/tablet concentration of sodium chloride was selected as an optimized concentration of osmogen for further study.

Table 6. Effect of Sodium Chloride on Drug Release

Formulation Code	% CR
S1	52.97 %
S2	54.69 %
S3	61.78 %
S4	65.43 %
S5	72.61%
S6	**76.93 %**

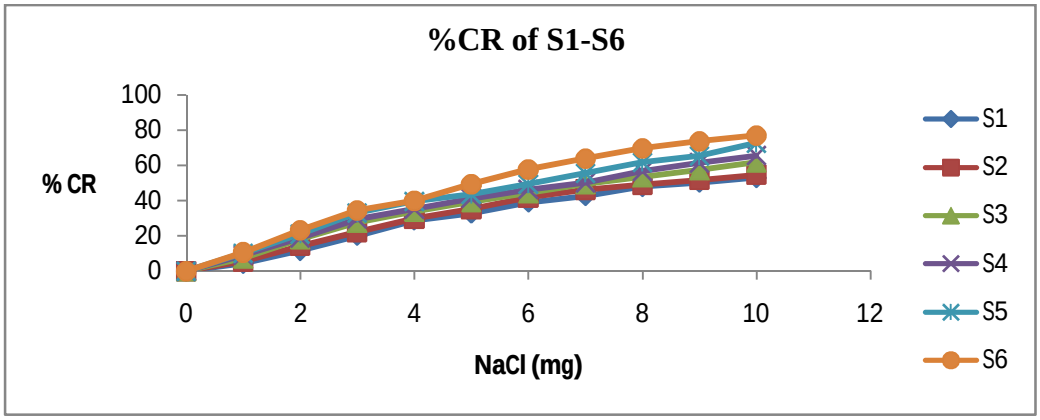

Figure 1. Effect of Sodium Chloride On Drug Release

7.6 Precompression studies

Many different properties have been employed to assess flowability, of these; angle of repose is the most relevant. Repose angle of the powder was investigated. The value of Angle of

repose (θ) decreased after the addition of lubricant. Angle of repose (θ) is an indicative parameter of powder flowability from hopper to die cavity.

The angle of repose was within the range of 29° – 30°, indicative of good flowability. Bulk density may influence compressibility, tablet porosity, dissolution and other properties and depends on the particle size, shape and tendency of particles to adhere together. The bulk density was found to be between 0.665 gm/cm^3. The value indicates good packing capacity of powder. The tapped density of powder was found to be 0.759 gm/cm^3. The bulk density and tapped density was used to calculate the percent compressibility of the powder.

The value of the Hausner's ratio was found to be 1.141 indicating good flowability. The Carr's index of was observed 12.36%, indicating good compressibility of the powder. The observations were summarized in Table 7.

Table 7. Evaluation of Tablet powder

Angle of Repose (°θ)	**Bulk Density (gm/cm^3)**	**Tapped Density (gm/cm^3)**	**Hausner's Ratio**	**Carr's index (%)**
29.70 ± 0.378	0.665 ± 0.015	0.759 ± 0.001	1.141 ±0.0008	12.36 ± 0.015

* All reading taken in triplicate, n ± SD

7.7 Evaluation of Controlled Porosity Osmotic Pump Tablet

In the present study, an attempt had been made to design a controlled porosity osmotic tablet of Irbesartan (150mg), chitosan and carbopol 934P IPC (60 mg), Sodium chloride (30 mg/tablet) was selected as osmogen and release modifier in the core tablet.

7.7.1 Evaluation of Core Tablet

All formulated core tablets were shiny white with smooth surface, circular curved faced with good texture. The thickness of the core tablet was found to be 5 mm, due to constant tablet press setting irrespective of weight variation. The hardness of the tablet was found to be in the range of 6 to 7.0 kg/cm^2. This ensured good mechanical strength. The drug content of the tablet was found to be in the range of 99 to 101% (Table 8).

Table 8. Evaluation of Core Tablet

Appearance	Friability (%)	Hardness (Kg/ cm^2)	Drug content (%)
White,11mm curved faced, 5mm thickness	0.503 ± 0.015	6.533 ± 0.288	100.51 ± 1.091

* All reading taken in triplicate, n ± SD

7.7.2 Evaluation of Formulated Formulations.

The tablets formulated were off white coloured with smooth surface, circular curved faced with good texture. The tablets were evaluated for hardness, weight variation and thickness of coat (Table 9). Hardness of tablets was found to be in the range of 6 to7 kg/cm^2; which ensures integrity of tablet throughout dissolution. Uniform thickness of the tablets throughout the formulations ensures good tablet strength. Excessive variation in the tablet thickness can result in problems with packaging as well as consumer acceptance. The thickness of the tablets was found in the range of 4.216±0.028 mm.

Table 9. Evaluation of Formulated Formulations

Appearance	Hardness Kg/cm2	Weight variation(Average Weight) (mg)	Tablet thickness (mm)
White,11mm curved faced	7.133 ± 0.288	265 ± 0.0577	4.216 ± 0.028

* All reading taken in triplicate, n ± SD

7.7.3 Dissolution Studies

Osmotic tablets were subjected to in vitro drug release studies in multimedia medium containing 0.1 N HCl, pH 1.2; phosphate buffer of pH 4.8 and 7.2 for 10 hr, the dissolution profiles of all formulations were summarized in Table 10 and fig 2&3. Hence, it was evident that increase in concentration of chitosan and carbopol 934P IPC, the drug release from the system was found to be increased. IPC produces a significant effect on release profile. The formulation F6 meets USP Dissolution Test. acceptance criteria.

Table 10. Drug Release Profiles of F1 to F7

Time (hr)	Cumulative % drug release						
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**
1	3.89	4.23	4.10	5.23	5.10	**7.67**	6.23
2	9.76	9.87	10.97	11.38	11.21	**12.34**	11.56
3	22.19	17.34	20.45	20.98	20.65	**21.21**	20.34
4	27.56	29.78	32.64	32.65	33.59	**31.24**	32.45
5	33.78	40.29	41.34	40.98	40.21	**42.04**	43.42
6	42.38	46.57	52.56	52.78	53.78	**51.34**	54.90
7	52.67	52.39	59.76	61.76	59.42	**62.87**	60.21
8	59.89	57.29	64.53	70.54	69.70	**69.73**	70.49
9	62.52	62.59	71.98	76.87	73.52	**78.19**	77.91
10	66.89	69.81	76.56	81.32	80.43	**84.97**	82.87

* All reading taken in triplicate

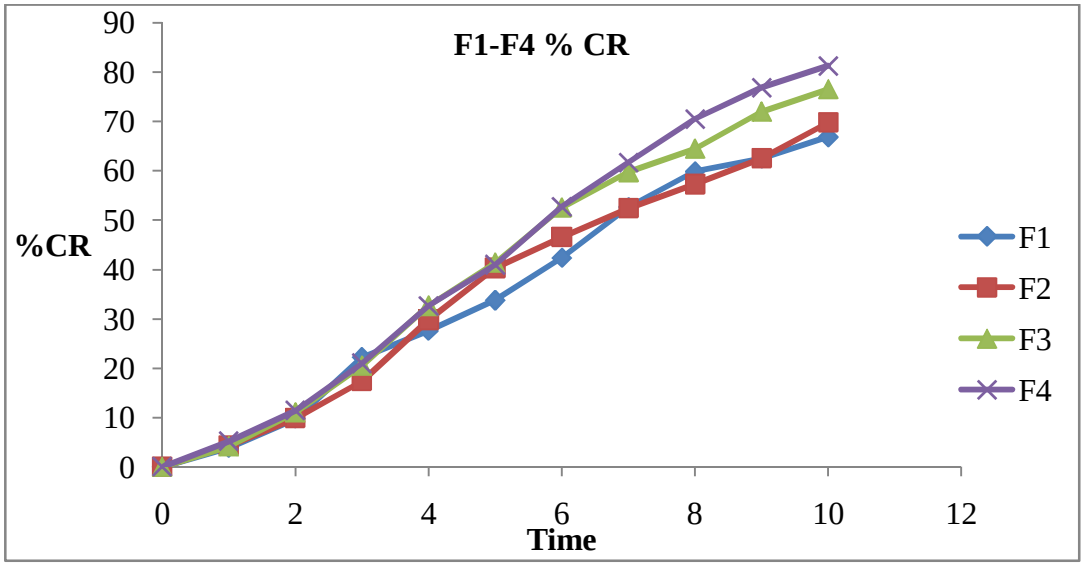

Figure 2. Effect of Different concentrations of CS-PAA IPC on drug release from CPOP

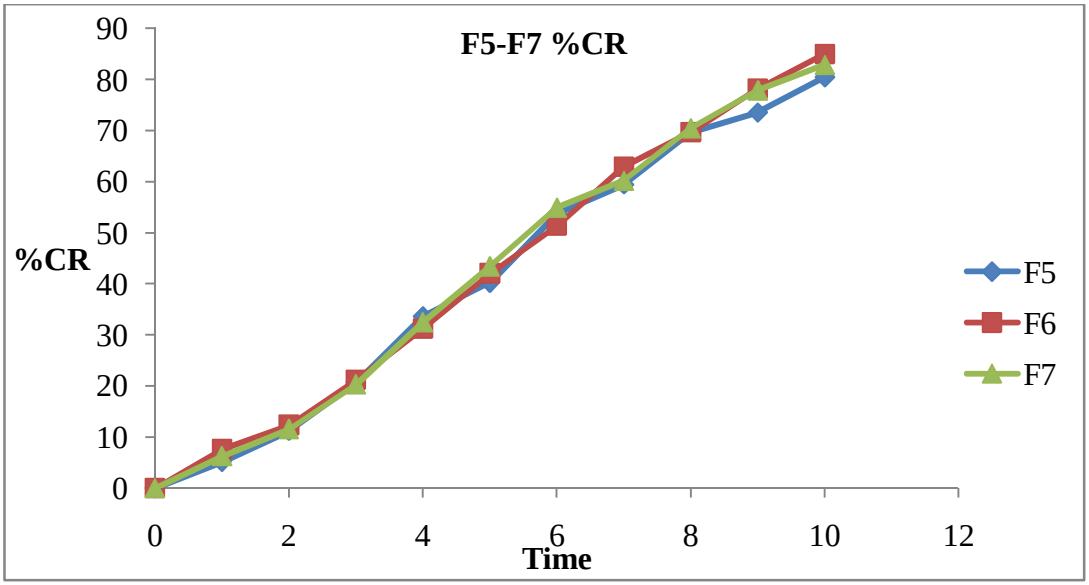

Figure 3. Effect of Different concentrations of CS-PAA IPC on drug release from CPOP

7.7.4 Kinetics of Drug Release.

In present study the dissolution were analyzed in order to study the kinetics of drug release mechanism. The results showed that nearly all of the formulations followed zero order dissolution mod. The R^2 value of all dissolution models was shown in Table 25.

Table 11. Model Fitting of Different Formulations

Formulation code	R^2				n	K
	Zero 0rder	First order	Korsmeyer Peppas	Higuchi		
F1	0.989	0.989	0.983	0.983	0.8165	11.83
F2	0.986	**0.991**	0.985	0.985	0.8456	12.79
F3	0.988	0.990	0.986	**0.987**	0.8329	11.81
F4	0.992	0.976	**0.993**	0.981	0.8150	12.29
F5	0.990	0.978	0.991	0.982	0.9903	11.55
F6	**0.995**	0.953	0.990	0.971	0.8839	10.19
F7	0.992	0.970	0.991	0.978	0.8756	11.68

Surface Morphology Study

To investigate the change in the membrane structure, surface of coated tablets (both before and after dissolution studies) was studied using Scanning Electron microscopy microphotographs showed in (Figure 20 & 21). Figure 20 shows membrane structure before dissolution, initially the surface of coated tablets was smooth before coming into contact with aqueous environment and coats appeared to be free of pores. A microporous structure of the membrane after dissolution was observed from (Figure 21), which shows SEM of membrane after dissolution. This significant porosity has resulted due to leaching of pore forming additive i.e. PEG 400 during dissolution through which drug release takes place.

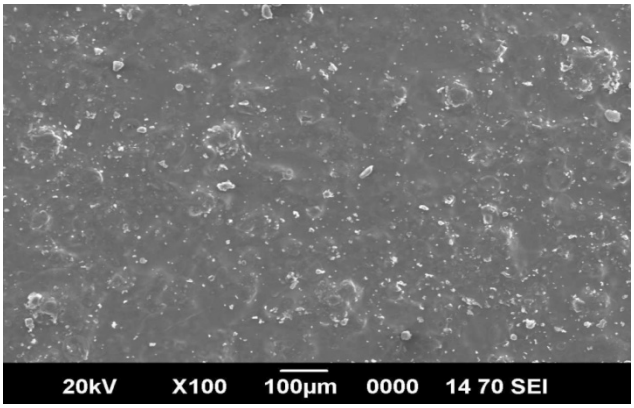

Figure 20. SEM Microphotograph (At 100X Magnification) of Irbesartan CPOP Tablet before Dissolution

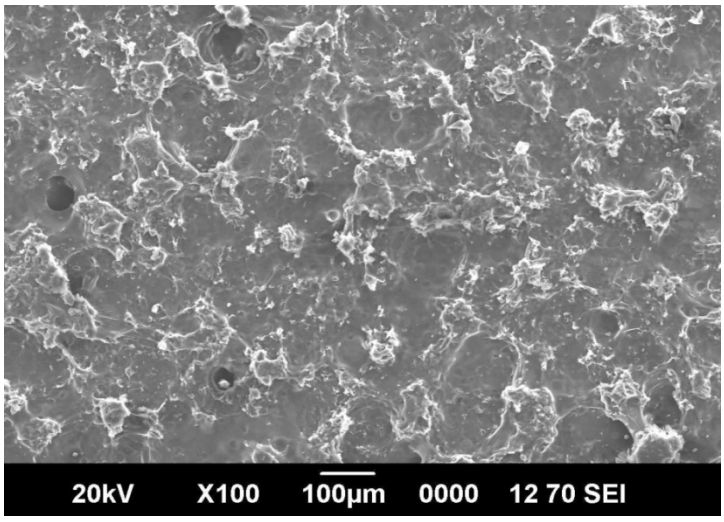

Figure 21. SEM Microphotograph (At 100X Magnification) of Irbesartan CPOP Tablet after Dissolution

Conclusion:

The desired release of Irbesartan from the CPOP was achieved through careful monitoring of the selected formulation variables. The effect of chitosan and carbopol 934 P in different concentrations evaluated in the study which reveals that the chitosan and carbopol 934 P IPC in concentration of 60 mg gives good and desired release as per USP acceptance criteria. It was evident that increase in concentration of IPC the drug release from the system was found to be increased. From the studies it was revealed that the F6 is optimized formulation which was used for further studies and evaluation. The optimized formulation (F6) delivered Irbesartan independent of pH and was found to be stable. Overall, a controlled release CPOP system for Irbesartan has been successfully developed by selecting proper optimized concentrations of osmogen and IPC of chitosan and carbopol 934 P. Finally, it is concluded that release of Irbesartan is significantly controlled from the controlled porosity osmotic delivery system and thus it is a promising approach for the treatment for hypertension.

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