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Formulation of Carbopol Capsules for Sustained Release of Losartan Potassium

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ABSTRACT

Sustained release formulations have been extensively studied for their benefits in improving various physicochemical and pharmacokinetic properties of large number of drugs. The aim of this study was to develop and evaluate sustained release capsules of losartan potassium in order to provide drug release over a long period of time. This allows the drug much time for absorption in gastrointestinal tract (GIT) and hence may increase the bioavailability of the drug. Carbopol 971 P was used as rate controlling polymer for the preparation of capsules. The capsules were evaluated for matrix integrity and drug release using USP type II dissolution apparatus. The sustained release capsules showed excellent matrix integrity and released more than 90% of the drug over a period of 12 hours. The kinetic studies showed that the drug release from the carbopol matrices followed Korsmeyer Peppas release kinetics and hence the mechanism of drug release was a combination of more than one processes i.e. diffusion and erossion. Hydration volume as well as matrix integrity were affected by the change in the amount of the polymer in the capsules. The study suggests that carbopol 971P capsules can be efficiently used to control and extend the release of losartan potassium over a long period. Thus improved absorption and bioavailability can be achieved which requires further studies in animals in future.

Keywords: Sustained release, Carbopol, Hydration volume, Capsules

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INTRODUCTION

Drug release characteristics of a dosage form are very important in determining the extent of the drug reaching the blood and the actual site of action. Depending upon the physicochemical properties of a drug, its absorption in different regions of the gastrointestinal tract varies [1]. This in many cases results in incomplete absorption and low bioavailability of the drug. A large number of approaches have been adopted to improve the physicochemical and pharmacokinetic properties of many drugs e.g. using salt form of drug increases drug solubility [2, 3] or inclusion complexes [4-6]. Also, a prodrug may be more permeable via biological membranes than the actual drug e.g. levodopa (prodrug) is more permeable than the original drug (dopamine) [7]. After crossing the blood brain barrier levodopa gets converted to dopamine which is the actual drug that shows action. Similarly, solid dispersions [8, 9] and nano drug delivery systems are used to improve solubility and bioavailability of many drugs [10, 11].

Another approach that is used to increase the absorption and bioavailability of the drugs is the development of sustained release dosage forms [12-14]. Sustained release dosage forms provide drug release at relatively slower rate than conventional dosage forms. The drug is released in smaller amounts giving enough time to the drug to absorb. This is beneficial in case of drugs that are absorbed by saturable mechanism in which case the release of large amounts of drug near the absorption site saturates absorption mechanism [15, 16]. Drugs that are highly soluble are released in large amounts and hence saturate the pathway involved in drug absorption. While low solubility drugs are inherently sustained release in nature, release of highly soluble drugs are required to be controlled. This can provide enough time for the drug to absorb.

Carbopol polymers have been extensively used in sustained release formulations [17-19]. The polymeric chains in carbopol are chemically crosslinked that provide the rate controlling properties to the polymer. The polymer is available in number of grades (Carbopol 974P, 934P, 940P, 70G etc.) differing in the extent of crosslinking. The polymer undergoes rapid hydration when placed in an aqueous medium. Upon hydration the polymer chains form gel like structures that cause enormous swelling of the polymer. The chemical crosslinking between the polymeric chains imparts the mechanical strength to the capsules and more

importantly is key in retarding the rate of drug release from the capsules. Carbopol 971 P has been used to develop sustained release products of a number of drugs.

Losartan potassium is an angiotensin II receptor blocker that is used primarily for the treatment of hypertension [20]. The oral dose of losartan potassium for the treatment of hypertension is 25, 50 and 100 mg. Due to extensive first pass metabolism the oral bioavailability of the drug is only 25-33% [21]. It is suggested that the use of sustained release formulations of losartan potassium may increase the bioavailability of the drug.

MATERIALS AND METHODS

Losartan potassium was obtained Eaton Laboratories, Srinagar J&K, as a gift sample. Carbopol 971 P was a generous gift from Lubrizol. All the other chemicals were of analytical grade.

Preparation of Sustained Release Capsules

Sustained release capsules of losartan potassium were prepared by simply mixing all the ingredients and then manually filling the mixture into hard gelatin capsules in proper amounts. Carbopol and losartan potassium were mixed in different ratios in order to evaluate the effect of carbopol on drug release. The mixing was carried out for 10-15 min. The amount of carbopol was tuned to get the maximum amount of drug release over the period of 12 hours without losing the matrix integrity. The composition of various formulations prepared is shown in table 1.

Table 1: Composition of various sustained release carbopol formulations

Formulation	Polymer	Drug	Capsule wt.
F1	200	50	250
F2	175	50	225
F3	150	50	200
F4	125	50	175
F5	100	50	150
F6	75	50	125
F7	50	50	100

Weight Variation

Weight variation of the capsules was determined by calculating the average weight of 20 capsules using an electronic balance and then determining the average deviation of each capsule from the average.

Content Uniformity

Contents of 10 capsules were dissolved in 0.1 N HCl and the solution obtained was filtered through Whatman filter paper. Drug content in the filtered solution was detected by measuring the absorbance of the filtrate by UV spectrophotometer at λ_{max} 254 nm [22].

Polymer Hydration

Hydration and swelling studies were done to determine the amount of water intake by the carbopol capsules upon immersion into an aqueous medium. The experiment was carried out in USP type II dissolution apparatus. The capsules were placed in 900 ml of 0.1 N HCl for 12 hours and taken at regular time intervals for measuring the dimensions of the capsules using a Vernier caliper.

Drug Release Studies

Drug release studies were carried out in USP type II dissolution apparatus. The drug containing capsules were placed in the dissolution flasks containing 900 ml of 0.1 N HCl as dissolution medium maintained at a temperature of 37± 0.5 ºC. The dissolution medium was stirred a constant speed of 100 rpm throughout the experiment. The duration of the experiment was 12 hours. 5ml samples were taken after every hour and after proper dilution absorbance of each sample was measured using at λ_{max} 254 nm UV spectrophotometer. From the values of absorbances the percentage drug release at different time intervals was calculated.

RESULTS AND DISCUSSION

Preliminary Studies

In order to choose a suitable polymer for developing sustained release capsules of losartan potassium various polymers were thoroughly screened. The screening was done on the basis of matrix integrity and the drug release from the capsules. On the basis of this evaluation Carbopol 971 P was showed positive results and was hence chosen for thee further studies.

Hydration Behaviour of Carbopol 971P Capsules

Carbopol capsules were placed for 12 hours in 0.1 N HCl and examined for change in their volume. The capsules were taken out regularly and using a Vernier calliper the dimensions of the capsules were measured. It was observed that the volume of the carbopol capsules increased as the capsules spent more and more time in the dissolution medium (0.1N HCl). After 12 hours the capsules volume was almost double the initial volume of the capsules. Carbopol is a hydrophilic polymer that undergoes extensive hydration when placed in an aqueous medium [23]. As the capsules are placed inside the dissolution medium the water penetrates into the bulk of the capsules and the individual polymeric chains get surrounded by tremendous amount water. The hydrated polymer chains form gel like structures increasing the bulk of each polymer chain. When hundreds of such polymer chains get hydrated it increases the overall volume of hydration of the capsules [24].

Effect of Drug on Hydration Behaviour of Carbopol Capsules

The addition of the drug had some effect on the hydration properties of the capsules. It was observed that the incorporation of the drug decreased the swelling behaviour of the capsules. Figure 1 shows the effect of addition of drug on the hydration behaviour of carbopol capsules. It was found that as the amount of the in the capsules increases the hydration volume decreases. This may be because of replacement of some amount of polymer by the drug leading to less gelation and hence decreased swelling. Also, since losartan potassium is a hydrophilic drug, as the water enters the capsule the drug gets dissolved and is released into the

medium decreasing the total content of the capsule and hence decreasing the hydration volume [23].

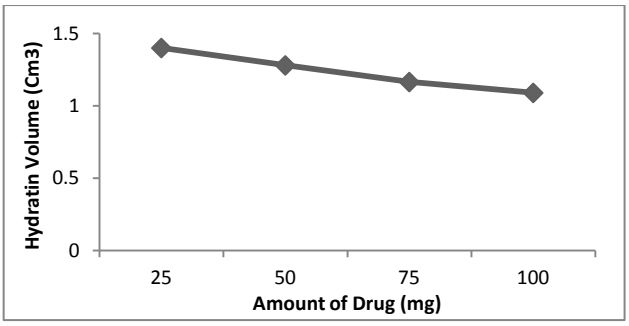

Figure 1: Effect of Amount of drug on hydration behaviour of Carbopol 971P capsules. The hydration volume of the capsules decreases as the amount of the in the capsules increases

Effect of Polymer:Drug Ratio Matrix Integrity of Capsules

The capsules were placed in 900 ml of 0.1N HCl for 12 hours with at temperature 37± 0.5 ºC and stirred at 100 rpm and the time from which the capsules started showing the signs of erosion was noted.

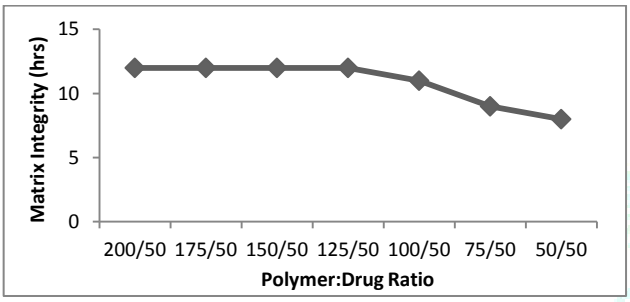

Figure 2 Effect of Carbopol 971P: Drug ratio on matrix integrity of capsules.

The capsules were placed in 0.1N HCl for 12 hours with stirred at 100 rpm and temperature 37± 0.5 ºC and the matrix integrity was noted in terms of the time for which the capsules withstood the hydrodynamic force of the medium.

Matrix integrity was reported in terms of the time for which the capsules withstood the hydrodynamic force of the medium. It was found that polymer from the capsules did not erode upto a certain limit of polymer:drug ratio, beyond which the capsules could not withstand the hydrodynamic force of the medium and the polymer started eroding faster as the polymer:drug ratio decreased (figure 2).

Drug Release Studies

As mentioned earlier, drug release studies were carried out in USP type II dissolution apparatus containing 900mll of 0.1N HCl maintained at temperature 37± 0.5 ºC and stirred at a rate of 100 rpm. The carbopol matrices provided sustained drug release over the period of 12 hours. Formulations F1, F2, F3, F4 and F5 showed good matrix integrity while formulation F6 and F7 showed polymer abrasion from the surface of the capsules. This may be due to the fact that since the drug:polymer ratio was 1:1, the drug release from the capsules might have left large voids within the polymer matrix, hence loosening the gel structure and causing erosion [23, 25]. Table 2 gives the 12 hour drug release data from the carbopol capsules. Carbopol capsules successfully retarded the drug release from its matrices and it was observed that as the proportion of the carbopol in the capsules was increased the amount of the drug release decreased as shown in figure 3. This may be attributed to the fact that polymeric chains in carbopol are tightly crosslinked that decreased the drug penetration into the carbopol matrix and hence not allowing drug release in large amounts [24, 26].

Table 2: Percentage Cumulative drug release from sustained release carbopol capsules

Time (hrs)	F1	F2	F3	F4	F5
1	11.53	12.87	15.45	17.88	19.59
2	18.67	20.43	22.83	23.13	25.76
3	22.96	23.69	26.97	27.87	33.23
4	28.78	31.98	33.18	35.77	39.49
5	34.11	37.54	39.07	41.24	47.64
6	40.23	42.12	45.24	49.33	52.19
7	46.55	48.32	52.56	56.12	59.38
8	51.26	55.79	58.59	61.59	67.27
9	58.79	60.11	64.36	67.09	76.54
10	65.85	66.04	70.71	75.05	83.02
11	69.19	73.68	77.52	82.48	88.13
12	73.06	77.11	84.05	86.83	93.44

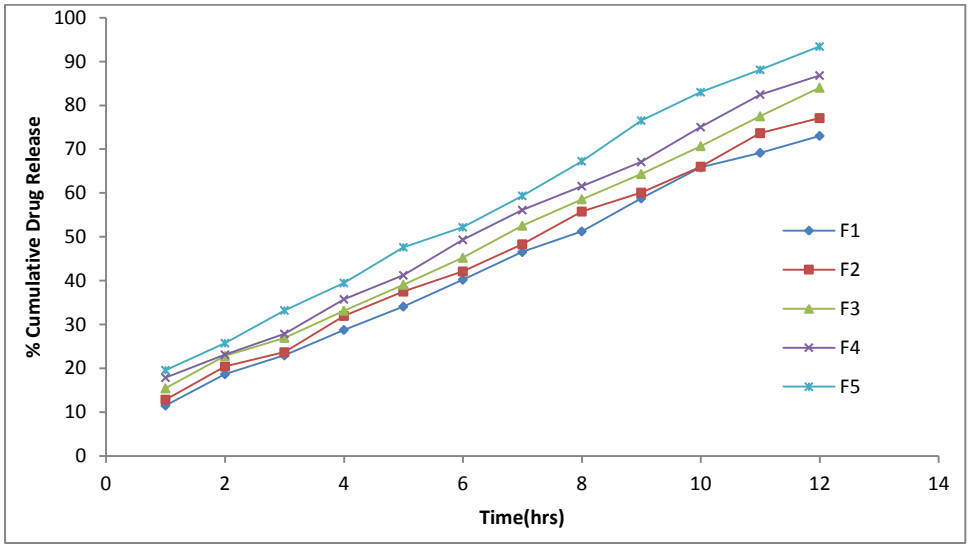

Figure 3: Comparison of drug release from different Carbopol 971P sustained release capsules containing different amounts of Carbopol 971P at different time points upto 12 hours. The drug release was evaluated using USP type II dissolution apparatus.

Effect of Carbopol 971P on drug release from sustained release capsules

Formulations containing different amounts of carbopol 971P were prepared and drug release studies were carried out in 0.1 N HCl in USP type II dissolution apparatus. It was found that with increase in the amount of carbopol 971P in the capsules the amount of drug released at different time points over the period of 12 hours, decreased. Carbopol 971P is a chemically crosslinked polymer that undergoes rapid hydration in water to give rise to a 3D gelatinous structure.

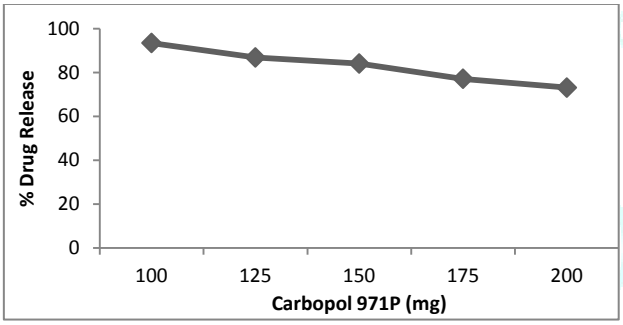

Figure 4: Effect of varying amounts of Carbopol 971P on drug release from the sustained release capsules. The graph shows the total amount of the drug released after 12 hours from capsules with different amounts of Carbopol971P.

This provides high efficiency to the polymer in controlling the drug release rate from the formulation. As the amount of the polymer increases the number of gel structures formed may increase hence further decreasing the rate of drug release from the capsules [24, 26]. Figure 4 shows the effect of carbopol 971P on the drug release from sustained release capsules.

Drug Release Kinetics

In order to determine the mechanism of drug release from the carbopol matrices drug dissolution modelling was applied to the drug release. It was found that the drug release followed Korseyer-Peppas model of release kinetics. The graph based on Korsmeyer-Peppas model showed R^2 value of 0.9978 which was found to be highest. The value of "n" was found to be 0.750 which falls between 0.45 and 0.89 which demonstrates that the drug release was non-Fickian. Thus from the results it can be suggested that the drug from the carbopol 971P formulations was released by more than one mechanisms that may be a combination of diffusion and erosion mechanisms [27, 28]. Figure 5 shows the various dissolution models applied to drug release data obtained from sustained release carbopol 971P capsules. Values of various parameters of dissolution data models are shown in table 3.

Table 3: Various parameters obtained from the modelling treatment of dissolution data form the sustained release carbopol 971P capsules

Formulation	Zero Order		First Order		Higuchi		Korsmeyer-Peppas		
	K_0	R^2	K_1	R^2	K_H	R^2	K_{KP}	N	R^2
F1	6.471	0.9760	0.096	0.9753	18.531	0.8840	9.295	0.834	0.9951
F2	6.792	0.9677	0.104	0.9734	19.489	0.8953	10.351	0.807	0.9951
F3	7.271	0.9613	0.116	0.9600	20.881	0.8978	11.349	0.796	0.9923
F4	7.665	0.9537	0.126	0.9556	22.039	0.9036	12.394	0.779	0.9915
F5	8.375	0.9394	0.148	0.9451	24.134	0.9158	14.436	0.750	0.9916

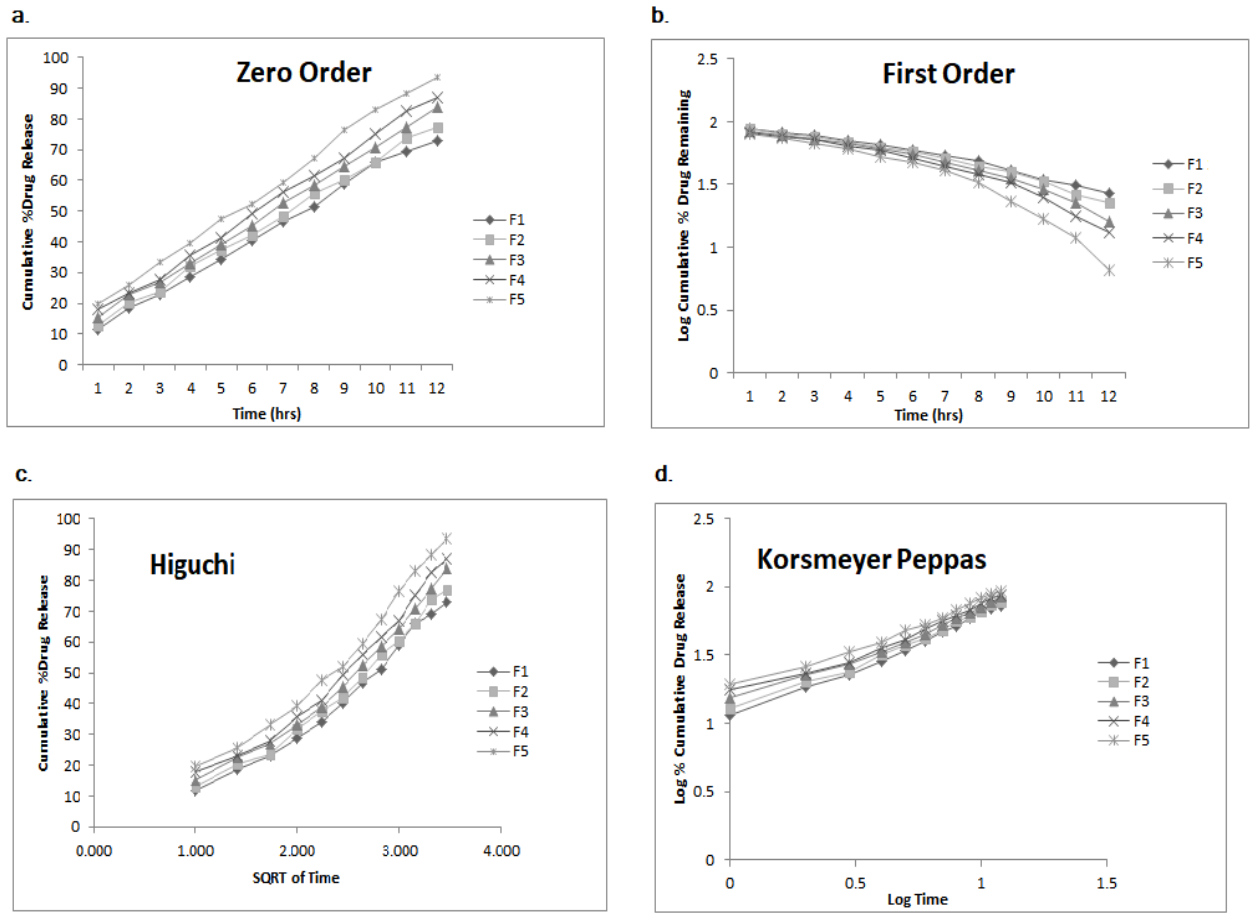

Figure 5: Kinetic modelling applied to the dissolution data or drug release data of Carbopol971P sustained release capsules. a) Zero Order Release Model; b) First Order Release Model; c) Higuchi Model; d) Korsmeyer-Peppas Model

Weight Variation

20 capsules were tested in weight variation test. All the capsules were found to pass the test. Table 4 shows the details of the weight variation test.

Table 4: Weight variation test conducted on sustained release carbopol 971P capsules

Formulation	No. of capsules	Amount of drug	Capsule wt. (Experimental)	Acceptable Wt. variation	No. of capsules passed
F1	20	250 mg	248-252 mg	±7.5%	All
F2	20	225 mg	221-229 mg	±7.5%	All
F3	20	200 mg	198-202 mg	±7.5%	All
F4	20	175 mg	172-179 mg	±7.5%	All
F5	20	150 mg	147-152 mg	±7.5%	All

Content Uniformity

10 capsules were evaluated for content uniformity. All the capsules were found to pass the test. Table 5 shows the details of the content uniformity test.

Table 5: Content uniformity test conducted on sustained release carbopol 971P capsules

Formulation	No. of capsules	Amount of drug (theoretical)	Drug amount (Experimental)	Acceptable Wt. variation	No. of capsules passed
F1	10	50 mg	48-51 mg	±15%	All
F2	10	50 mg	48-52 mg	±15%	All
F3	10	50 mg	49-51 mg	±15%	All
F4	10	50 mg	48-52 mg	±15%	All
F5	10	50 mg	47-51 mg	±15%	All

CONCLUSION

Sustained release formulations have been largely used to improve the physicochemical and pharmacokinetic properties of drugs. A number of polymers for this purpose have been used. In the present study carbopol 971P was used as rate controlling polymer in the formulation of sustained release capsules. From the above study it can be concluded that carbopol 971P capsules are efficient in providing the sustained release of losartan potassium. The hydration and swelling properties of carbopol capsules were excellent. The capsules efficiently provided drug release over a period of 12 hours with almost a constant rate. The capsules also displayed great matrix integrity over the whole period of dissolution testing. The above developed carbopol 971P capsules may prove beneficial in improving the pharmacokinetic profile of losartan potassium. The same is required to be investigated in further studies.

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