Sustained Release Quinapril HCL Tablets Preparation and Evaluation

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Abstract— **The work was designed to formulate and evaluate the quinapril Hcl Sustained release tablets which is used for management of Anti hypertensive diseases. Tablets were prepared by wet granulation method with different concentration of HPMCK4, HPMCK100 and guar gum as retard polymer to release the drug for prolonged time. The evaluated studies revealed that weight variation, hardness, friability and drug content test were within pharmacopeial limit. The drug release from formulations F1-F3 was almost 97-99% by 8hrs, F4-F6 was released 98-99% within 10hrs, F7-F9 released 99% of drug by the end of 12hrs.F8 was found to be optimized which released 96.03% of drug over 12hrs and follows zero order kinetics. The drug release was independent of concentration followed higuchi mechanism.**

INTRODUCTION

Sustained release[1,2] tablets allowing a twofold or greater reduction in frequency of administration of a drug in comparison with the frequency required by a conventional dosage form. It is designed to maintain constant levels of a drug in the patient's bloodstream by releasing the drug over an extended period. Maintaining constant blood levels of the drug in the bloodstream increases the therapeutic effectiveness of the drug.[3]

Hypertension[4], is a chronic medical condition in which the blood pressure in the arteries is elevated. This requires the heart to work harder than normal to circulate blood through the blood vessels. Quinapril HCl[5] is anti-hypertensive drug used to treat essential hypertension and congestive heart failure. It is a prodrug that belongs to the angiotensin-converting enzyme (ACE) inhibitor class of medications. It is metabolized to quinaprilat (quinapril diacid) following oral administration. Quinapril is a competitive inhibitor of ACE, the enzyme responsible for the conversion of angiotensin I to angiotensin II. ATII regulates blood pressure and is a key component of the renin-angiotensin-aldosterone system (RAAS) Quinapril hydrochloride may be used to treat essential hypertension and congestive heart failure.

MATERIALS AND METHODS

Preparation of Sustained Release tablets

Quinapril Hcl tablets were formulated by using HPMC K100 M, HPMC K 4M and guar gum as binding agent[6] with wet granulation method[7] by using starch solution as granulating agent, were Magnesuim stearate and talc are used as lubricating agent[8]. The formulation chart of tablets were showed in table- 1.

Table-1 Formulation of Quinapril HCl sustained release tablets

INGREDIANT	F1	F2	F3	F4	F5	F6	F7	F8	F9
QUINAPRIL	20	20	20	20	20	20	20	20	20
HPMC K100M	10	….	….	20	….	….	10	10	10
HPMC K4M	….	10	….	….	20	….	10	….	….
GUAR GUM	….	….	10	….	….	20	….	10	10
MAGNESIUM STEARATE	3	3	3	3	3	3	3	3	3
TALC	2	2	2	2	2	2	2	2	2
MCC	55	55	55	45	45	45	45	45	45
STARCH	10	10	10	10	10	10	10	10	10
TOTAL WEIGHT	100	100	100	100	100	100	100	100	100

Drug- Excipients Compatibility studies[9]

IR Spectroscopy

The FT-IR spectra of Quinapril HCl were recording with ABB Bomen Series spectrophotometer over the region of 400 – 4000 cm^{-1} by adopting Potassium bromide disc containing the samples (1% concentration) is prepared prior to IR analysis. IR spectroscopy was carried out to check the compatibility between drug and excipients.

PRE-COMPRESSION PARAMETERS:[10,11]

Flow Properties of Blend: The flow properties of blend (before compression) were characterized in terms of angle of repose, Carr's index and Hausner's ratio.

1. **Angle of Repose (tanθ):** This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane. The powders were allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by $\tan\theta = h/r$
2. **Bulk Density (D_b):** It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and the initial volume

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was noted. This initial volume is called the bulk volume.

$$D_b = m/V_o$$

3. **Tapped density (D_t):** The volume was measured by tapping the powder for 500 times. Then the tapping was done for 750 times and the tapped volume was noted (difference between these two volumes should be less than 2%). If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted.

$$Dt = \frac{m}{vi}$$

4. **Compressibility Index (Carr's Consolidation Index):** The flow ability of powder was done by comparing the bulk density (D_b) and tapped density (D_t) of powder and the rate at which it packed down.

$$\text{Compressibility index (\%)} = \frac{D_t - D_b}{D_t} \times 100$$

5. **Hausner's Ratio:** Hausner's Ratio is an indirect index of ease of powder flow. If the Hausner's ratio of powder is near to 1.25, indicates better powder flow.

$$\text{Hausner's Ratio} = \frac{Db}{Dt}$$

POST COMPRESSION PARAMETERS: [12,13,14,15]

1. **Weight variation:** Twenty tablets from each formulation were selected randomly and weighed individually, average weight was determined. Individual tablets were weighed and then they were compared with average weight.
2. **Tablet hardness:** The resistance of tablets to shipping or breakage under the conditions of storage, transportations and handling before usage depends on its hardness. The tablet was placed in between avil and spindle of Pfizer hardness tester, then the screw was rotated until. the tablet breaks. It was measured in terms of Kg/cm^2.
3. **Friability:** This device subjects the tablets to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Pre weighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were then de-dusted using a soft muslin cloth and reweighed.

$$\text{\% Friability} = \frac{(w1 - w2)}{w1} \times 100$$

4. **Drug content uniformity:** 20 Quinapril HCl SR tablets are taken and crushed,from this 20mg(theoretical) was transferd into 100ml volumetric flask by adding 100ml of distilled water with vigorous shaking.Take 10ml of above solution and it was diluted with 100ml of distilled water. Measure the absorbance of the resulting solution at λ max of Quinapril HCl. From absorbance calculate the drug content (Practical). Then calculate the % drug content by the following equation[16]

$$\text{Percentage drug content} = \frac{\text{i. Practical drug content}}{\text{Theoretical drug content}} \text{ X } 100$$

Limit: The percentage drug content should be 100 ± 15%

5. **In-vitro dissolution studies:** In vitro release studies were carried out using tablet USP- II dissolution test apparatus. Using 900ml of 7.4 phosphate buffer maintaining a temperature of 37°C ± 5°C with a rotation speed of 75rpm .samples was withdrawn every one hour and absorbance was taken at λ_{max} of 258nm.
6. **Data Analysis (Curve fitting analysis):** To analyze the mechanism of the drug release rate kinetics of the dosage form, the data obtained were plotted as[17].

RESULTS AND DISCUSSION

PRE-FORMULATION STUDIES

Drug-Excipients Compatibility studies: Pure drug of Quinapril HCl complies with the reference sample and the combination of API with different excipients show no deviation from pure drug. Hence there was no compatibility problem between API and excipients and it was showed in table-2 and figure-1-4.

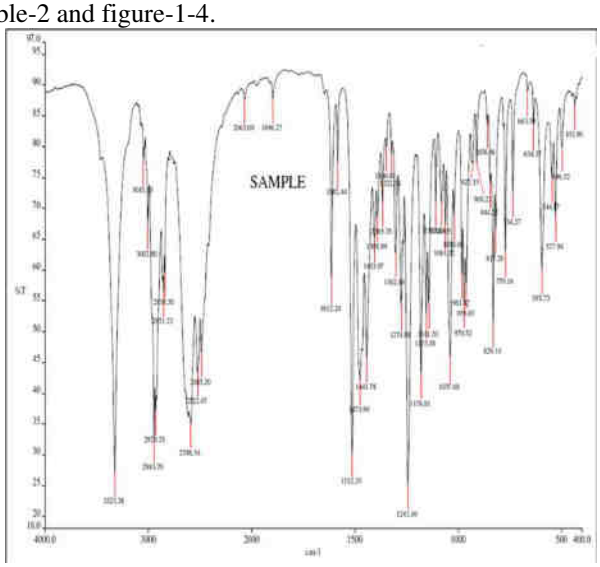


Figure-1 FTIR spectrum of Quinapril HCl

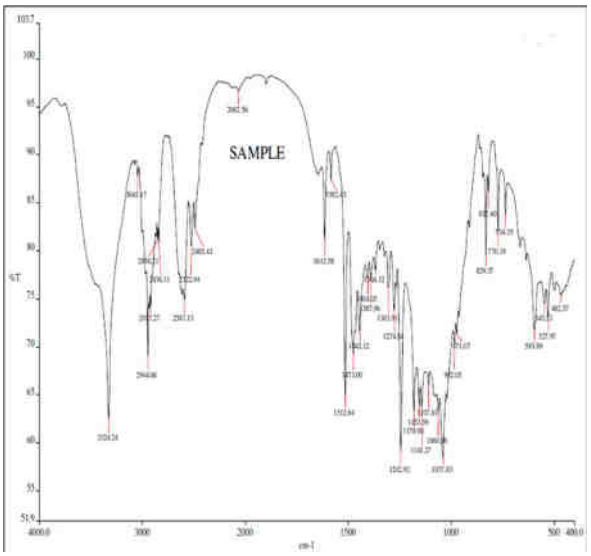


Figure-2 FTIR spectrum of Quinapril HCl with HPMC K4M and MCC

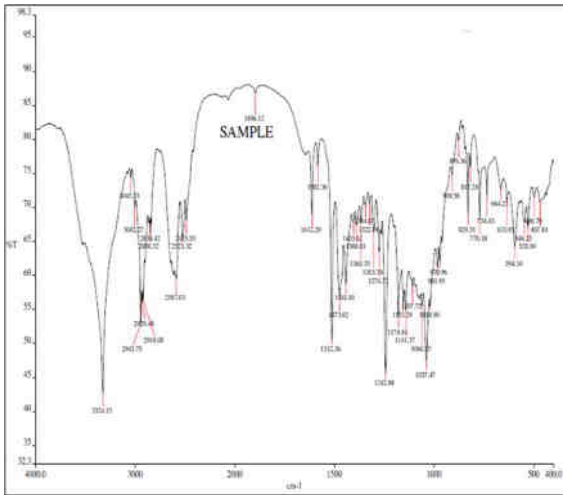


Figure-3 FTIR spectrum of Quinapril HCl with HPMC K100M and MCC

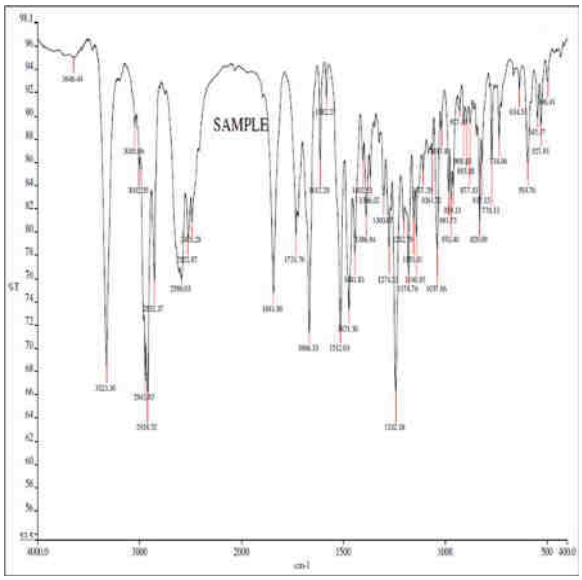


Figure-4 FTIR spectrum of Quinapril HCl with Guargum and MCC

Table-2 Drug excipients compatibility results

S.No	Drug- Excipients combination	Result
1	Quinapril HCl pure	Complies
	API+ HPMC K4M and Microcrystalline cellulose	Compatible
3	API+ HPMC K100M and Microcrystalline cellulose	Compatible
4	API+ Guargum and Microcrystalline cellulose	Compatible

PRE-COMPRESSION PARAMETERS:

The pre-compression studies performed on Quinapril Hcl tablets, to find out bulk density, tapped density, angle of repose, Carr's index and Hausner index. The results clearly indicate that the values were within the limits and the results are shown in Table 2.

Table-3 Pre compression parameters of the various batches of the Quinapril HCl tablet blend

Formulations	Angle of repose (degrees)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Haussner's ratio
F1	29.74± 0.05	0.429± 0.002	0.498±0 .003	13.89± 0.2	1.16 ±0.04
F2	28.43± 0.04	0.508± 0.003	0.653±0 .004	22.21± 0.3	1.2±0.0 2
F3	31.11 ± 0.06	0.501± 0.005	0.601± 0.006	16.6± 0.3	1.2± 0.05
F4	33.66 ± 0.03	0.469± 0.002	0.536± 0.005	12.5 ± 0.2	1.14±0. 03
F5	28.43 ± 0.04	0.487± 0.003	0.602± 0.006	16.6± 0.3	1.24± 0.05
F6	30.23 ± 0.04	0.507 ±0.008	0.512± 0.003	13.25 ±0.24	1.16 ± 0.07
F7	33.66 ± 0.03	0.469± 0.002	0.536± 0.005	12.5 ± 0.2	1.14 ± 0.03
F8	28.43 ± 0.04	0.508 ±0.003	0.653± 0.004	22.21± 0.3	1.2± 0.02
F9	28.43 ± 0.04	0.487± 0.003	0.602± 0.006	16.6± 0.3	1.24± 0.05

Angle of repose

The angle of repose of all the developed formulations F1 to F9 was found to be 28.43±0.52 to 33.66 ±0.03 C showed in Table3. It shows good flow property.

Bulk and tapped densities

The bulk density of the formulations F1 to F9 was found to vary between 0.43± 0.001to 0.513 ± 0.0005 gm/ml as indicated in the table. Tapped density was found to be 0.511± 0.012 to 0.523 ± 0.0122gm/ml for formulations F1 to F9 as indicated in the table. Both are having low standard deviations. '

Carr's Compressibility Index

The carr's index was found to be12.52 ± 0.5 to 22.21 ± 0.3% for formulations F1 to F9 as indicated in the table.3. and having good to possible flow properties. The standard deviation was also very low.

Haussner's ratio

Hausner' ratio was found to be 1.12 ± 0.02 to1.24 ± 0.05 for the formulations F1 to F9 as indicated in the table3. These values were found to be within the pharmacopoeial limits and showing fair to good flow properties.

Evaluation of Extended release tablets of Quinapril Hcl:
POST COMPRESSION STUDIES

1. Weight Variation Test : The weight variation of tablets for all the formulations developed F1 to F9 is 101±2.6 to 99.6±1.52 mg respectively as indicated in the table.4 & figure.5 According to pharmacopeia tablets weighing between 80-250mg should not exceed a standard deviation of 7.5%. So the standard deviation of all the formulation batches did not exceed a SD of 7.5% hence the tablets comply with standard limits.

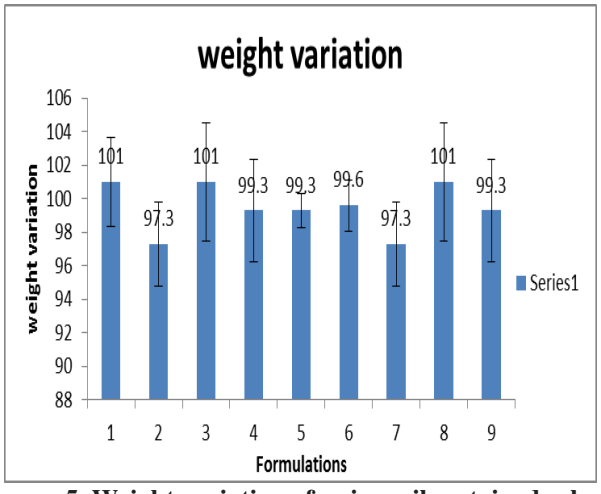
2. Friability: The friability of the tablets was found for all the developed formulations from F1 to F9 as 0.16±0.015 to 0.34±0.03% respectively as showed in the table.4& figure.7. A very low standard deviation of less than 1% was found in all the formulations.

3. Tablet hardness : The hardness of the tablets of different formulations from F1 to F9 varied between 5.5 ± 0.25 to 6.06 ± 0.37 kg/cm^2 as indicated in the table.4 & figure.6

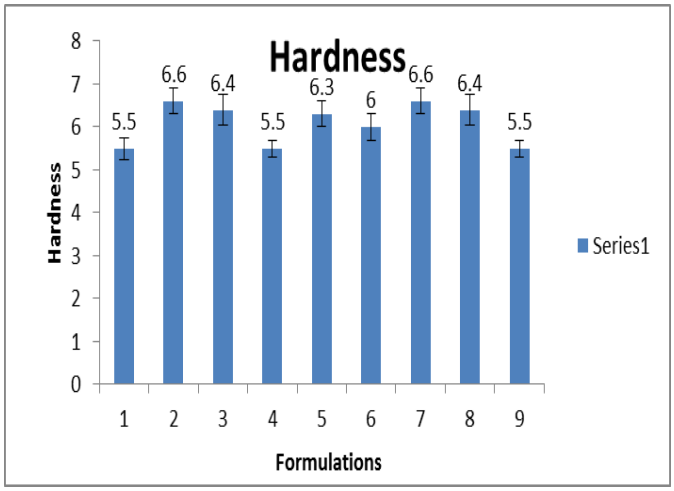
4. Drug content of Quinapril HCl Matrix tablets : The drug content was estimated in the tablets for all the formulations developed from F1 to F9. The drug content uniformity can be estimated. The drug content for the formulations F1 to F9 are 98.4±0.94 to 99.64±1.49 respectively as indicated in the table.4 & figure.7.

Table-4 Post compression parameters of the various batches of the Quinapril Hcl tablets

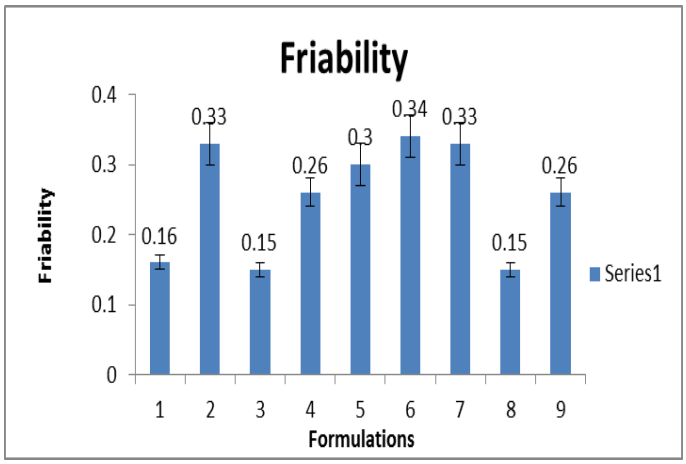
Formulation	Weight variation (mg)	Hardness (kg/cm2)	Friability (%)	Drug content (%)
F1	101± 2.64	5.5±0.25	0.16± 0.01	98.4±0.94
F2	97.3± 2.51	6.6±0.3	0.33± 0.03	95.5±2.91
F3	101± 3.51	6.4±0.35	0.15± 0.01	92.9±3.31
F4	99.3± 3.05	5.5±0.2	0.26± 0.02	100±0.88
F5	99.3± 1	6.3±0.3	0.3±0.03	97.7±0.94
F6	99.6± 1.52	6±0.3	0.34± 0.03	99.6±1.49
F7	97.3± 2.51	6.6±0.3	0.33± 0.03	95.5±2.91
F8	101± 3.51	6.4±0.35	0.15± 0.01	92.9±3.31
F9	99.3± 3.05	5.5±0.2	0.26± 0.02	100±0.88



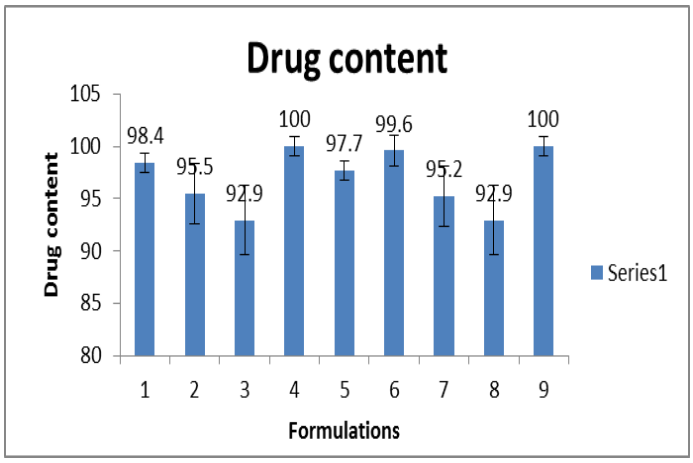
Figure–5 Weight variation of quinapril sustained release tablets



Figure–6 Hardness of quinapril sustained release tablets



Figure–7 Friability of quinapril sustained release tablets



Figure–8 Drug content of quinapril sustained release tablets

***IN-VITRO* DISSOLUTION STUDIES:**

The dissolution profile of the formulations F1 to F9 were analyzed and release pattern of drug was found. Formulations F1 to F3 containing drug released almost 97 to 99% of the drug by 8 hrs. Formulation F4 to F6 released 98 to 99% of the drug within 10 hrs. F7 to F9 formulations released almost 99% of the drug by the end of 12 hrs which was showed in table.5 and figure9-13.

Table.5 In-Vitro drug release of formulations F1-F9

Time (hours)	F1 (%)	F2 (%)	F3 (%)	F4 (%)	F5 (%)	F6 (%)	F7 (%)	F8 (%)	F9 (%)
1	15.59	13.58	17.09	10.56	11.56	17.09	9.55	6.03	13.57
2	29.66	31.17	39.22	28.66	24.64	33.69	17.59	14.58	27.15
4	51.79	62.85	64.86	52.29	56.31	49.78	25.64	28.15	44.75
6	79.44	78.94	79.94	75.92	78.94	67.37	48.76	42.73	62.85
8	97.54	95.03	99.55	86.98	82.96	79.44	67.37	63.85	73.40
10	97.54	95.03	99.55	98.54	98.04	100.05	83.96	73.91	85.97
12	97.54	95.03	99.55	98.54	98.04	100.05	97.53	96.03	99.55

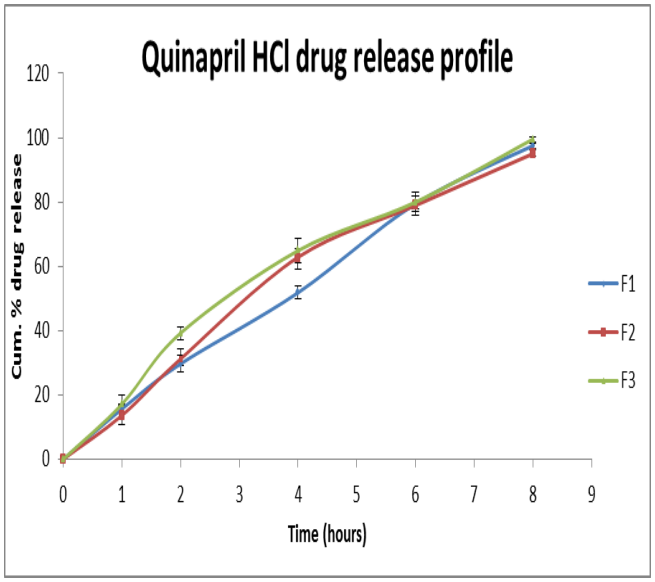


Figure-9 *In-vitro* drug release study of F1, F2 and F3 formulations

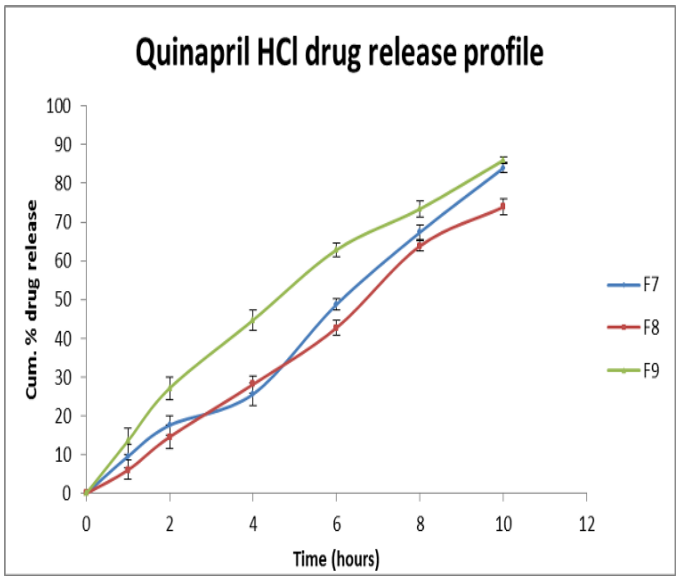


Figure-11 *In-vitro* drug release study of F7, F8 and F9 formulations

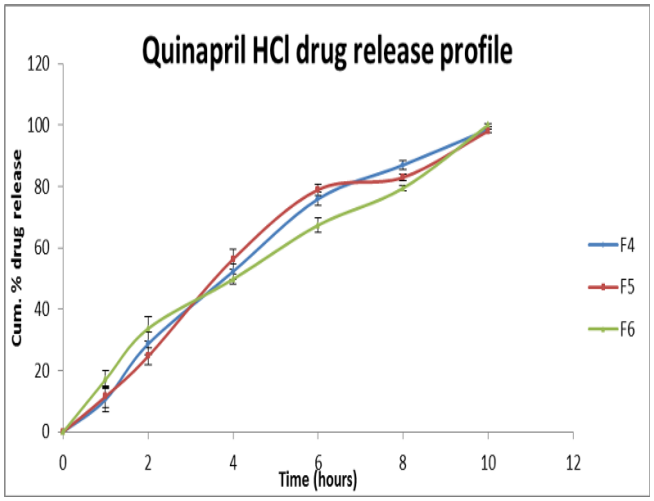


Figure-10 *In-vitro* drug release study of F4, F5 and F6 formulations

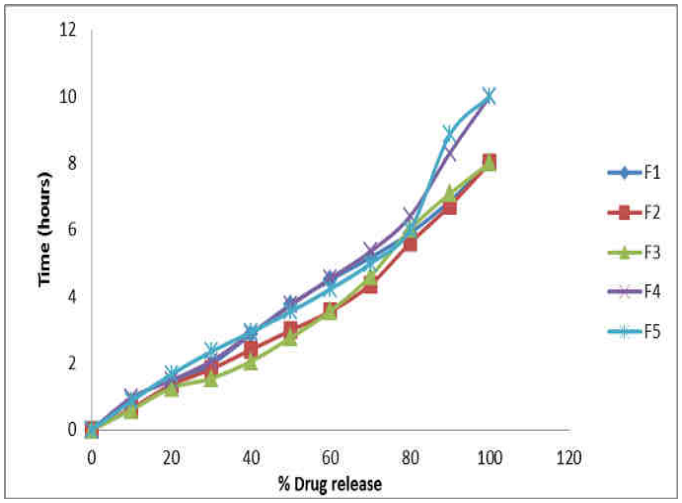


Figure-12 In-Vitro Dissolution efficiency for F1, F2, F3, F4 and F5 formulations

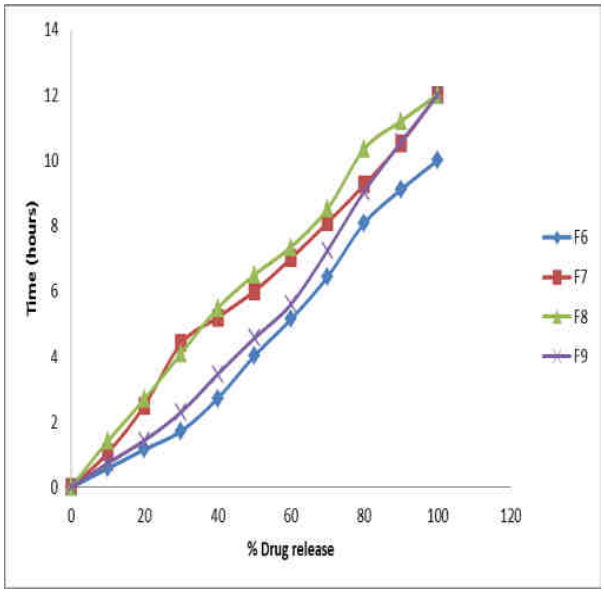


Figure-13 In-Vitro Dissolution efficiency for F6, F7, F8 and F9 formulations

***In-vitro* drug release kinetic studies**

The data obtained from dissolution studies were fitted into various kinetics models to know the mechanism of drug release and order of kinetics which was showed in table-6 and figure.14-28. dissolution studies were performed for all the formulations developed from F1 to F9.

F8 Formulation was shown best in-vitro drug release profile (96.03% in 12hrs) compare to other formulations. The drug release kinetics explains the release pattern of all the formulations developed. The best formulation F8 follows Zero order kinetic and follows Higuchi mechanism.

Table-6 *In-Vitro* Drug Release Kinetic Studies of F1-F9 Formulations

Model	Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Zero-order	K_0(h^{-1})	2.94	4.51	7.47	5.41	5.76	8.09	-0.58	-1.18	7.68
	R^2	0.995	0.975	0.970	0.970	0.955	0.979	0.993	0.995	0.980
First-order	K_1(h^{-1})	2.17	2.10	2.25	2.17	2.14	2.18	2.18	2.15	2.18
	R^2	0.864	0.942	0.788	0.883	0.887	0.767	0.819	0.795	0.795
Higuchi	K_h(% $h^{-0.5}$)	-11.45	-10.71	-8.53	-11.94	-11.69	-8.08	-15.90	-16.27	-9.79
	R^2	0.939	0.951	0.968	0.957	0.950	0.971	0.906	0.099	0.974
Korsmeyer-peppas	n	0.88	0.94	0.82	0.96	0.94	0.73	0.91	1.10	0.81
	K_k (h^{-n})	1.19	1.18	1.28	1.10	1.105	1.26	0.958	0.797	1.16
	R^2	0.998	0.982	0.976	0.973	0.976	0.991	0972	0.996	0.993
Hixson-crowell	Kc (h^{-1})	1.384	1.398	1.527	1.508	1.512	1.661	1.377	1.259	1.698
	R^2	0.755	0.742	0.704	0.741	0.737	0.690	0.810	0.833	0.709

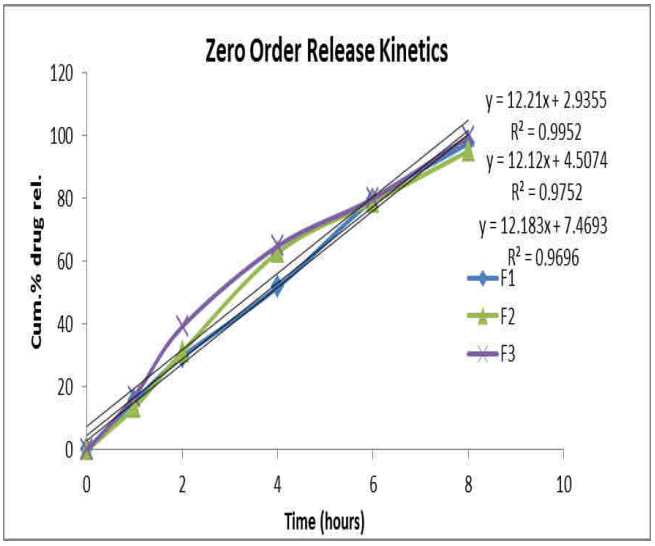


Figure-14 Zero order release kinetics of F1, F2 and F3 formulations

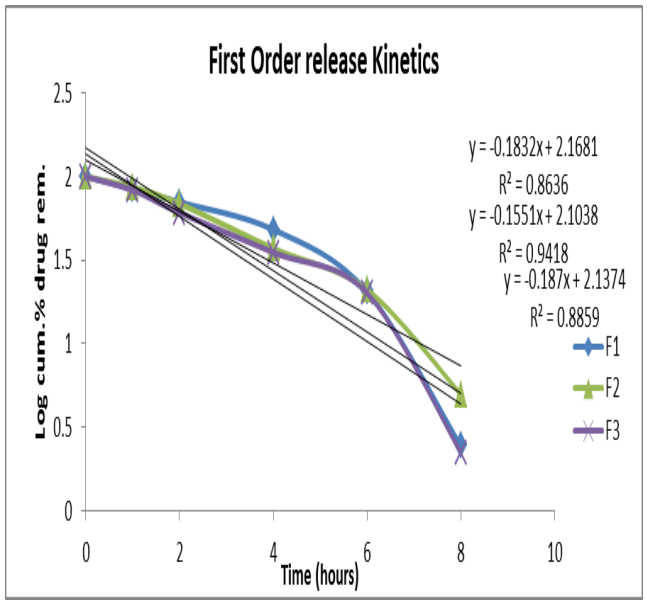


Figure-15 First order release kinetics of F1, F2 and F3 formulations

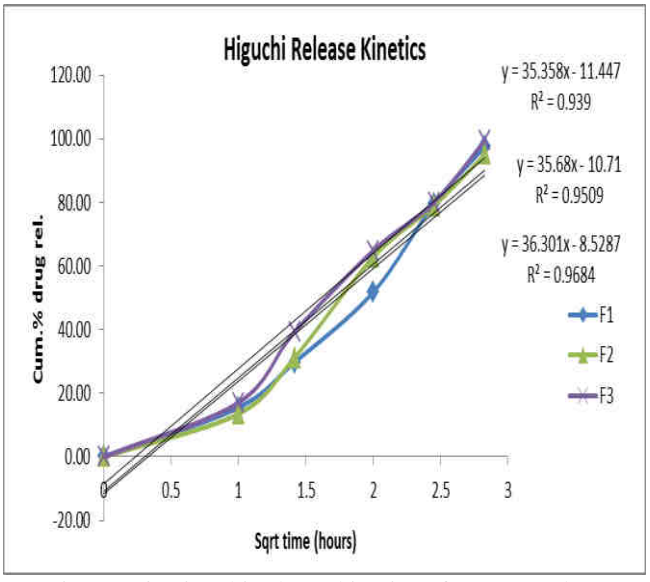


Figure-16 Higuchi release kinetics of F1, F2 and F3 formulations

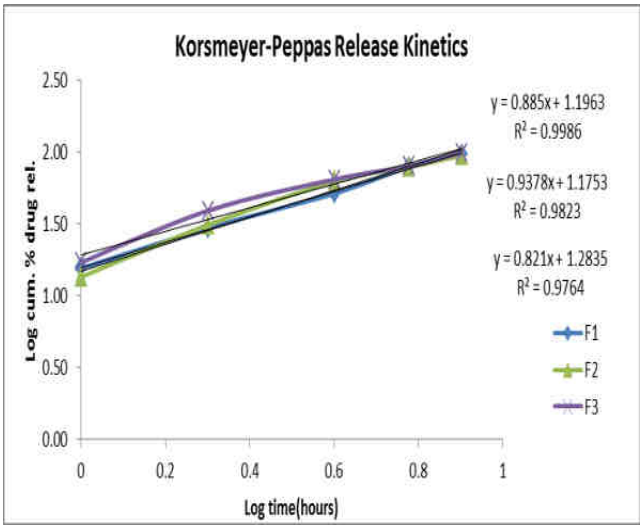


Figure-17 Korsmeyer-Peppas release kinetics of F1, F2 and F3 formulations

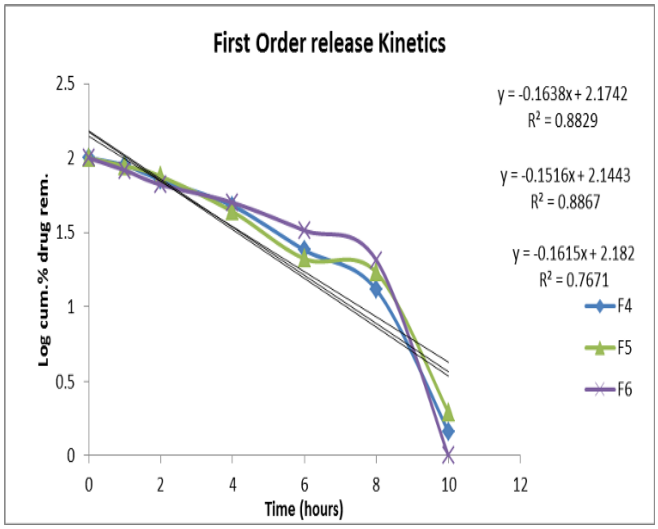


Figure-20 First order release kinetics of F4, F5 and F6 formulations

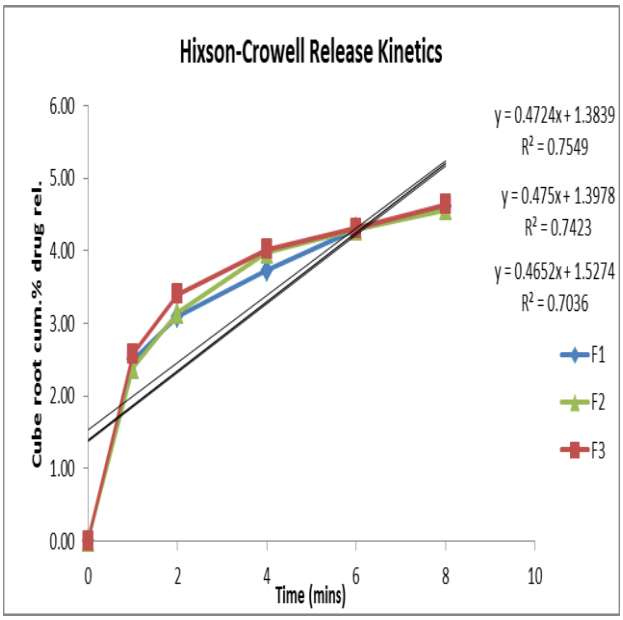


Figure-18 Hixson-crowell release kinetics of F1, F2 and F3 formulations

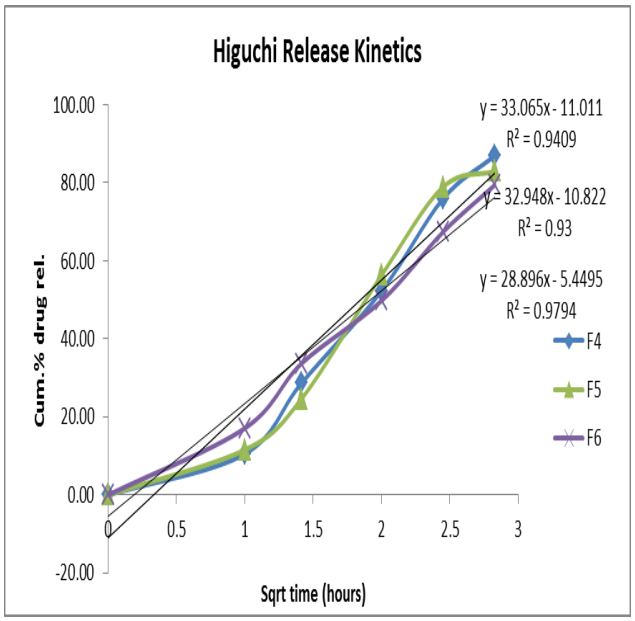


Figure-21 Higuchi release kinetics of F4, F5 and F6 formulations

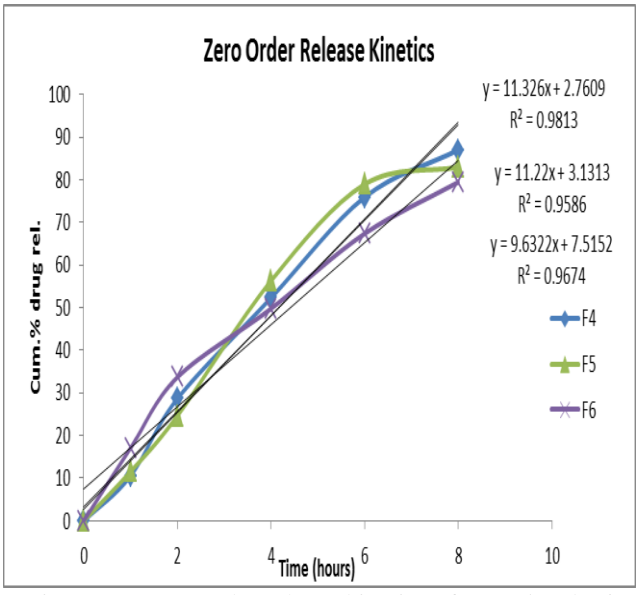


Figure-19 Zero order release kinetics of F4, F5 and F6 formulations

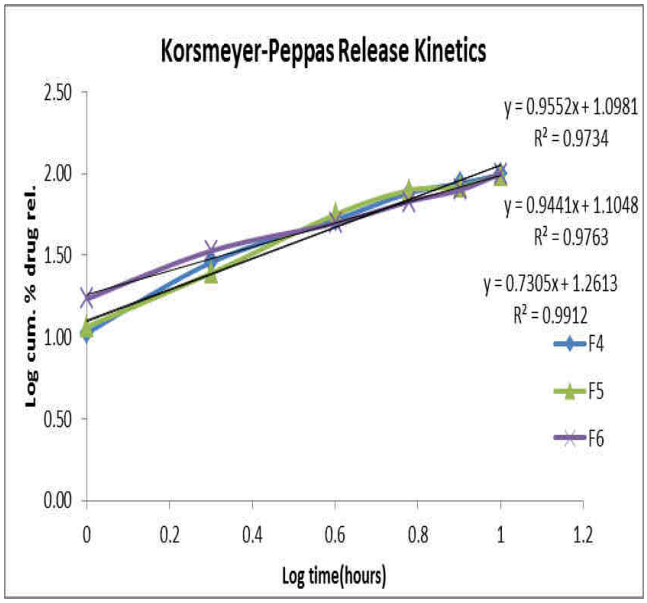


Figure-22 Korsmeyer-Peppas release kinetics of F4, F5 and F6 formulations

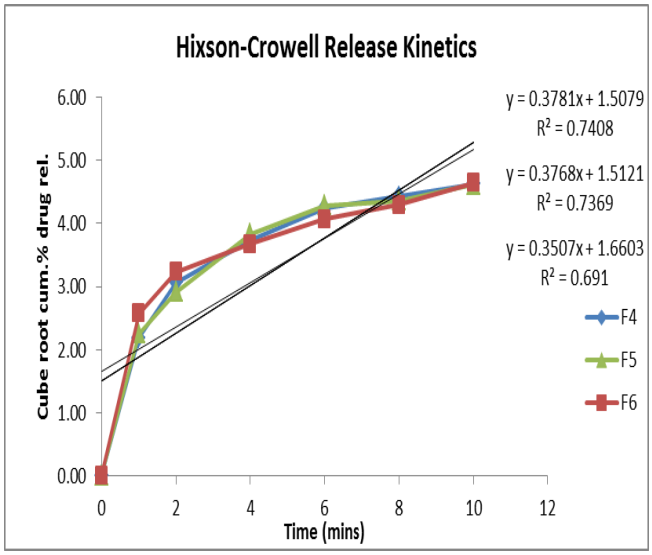


Figure-23 Hixson-crowell release kinetics of F4, F5 and F6 formulations

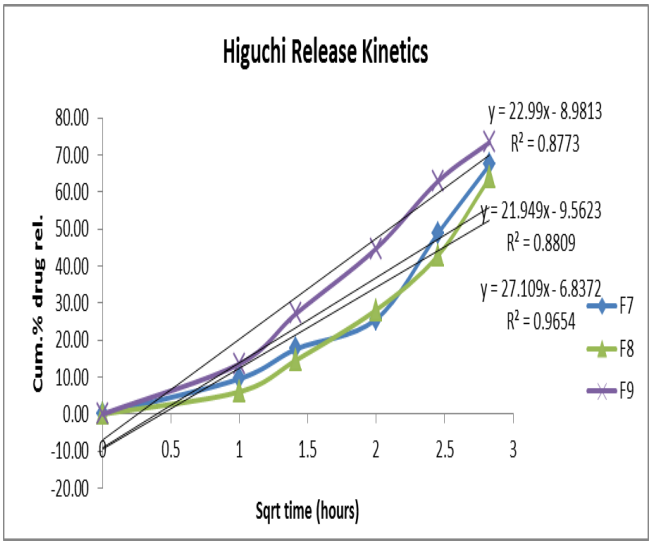


Figure-26 Higuchi release kinetics of F7, F8 and F9 formulations

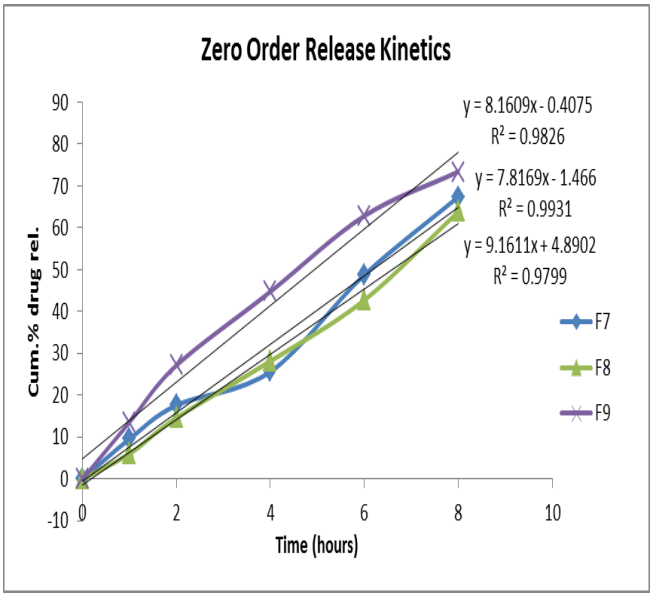


Figure-24 Zero order release kinetics of F7, F8 and F9 formulations

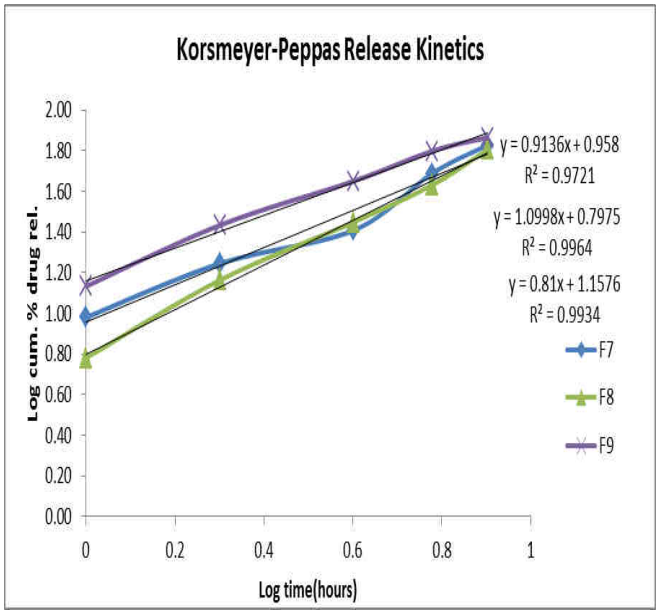


Figure-27 Korsmeyer-Peppas release kinetics of F7, F8 and F9 formulations

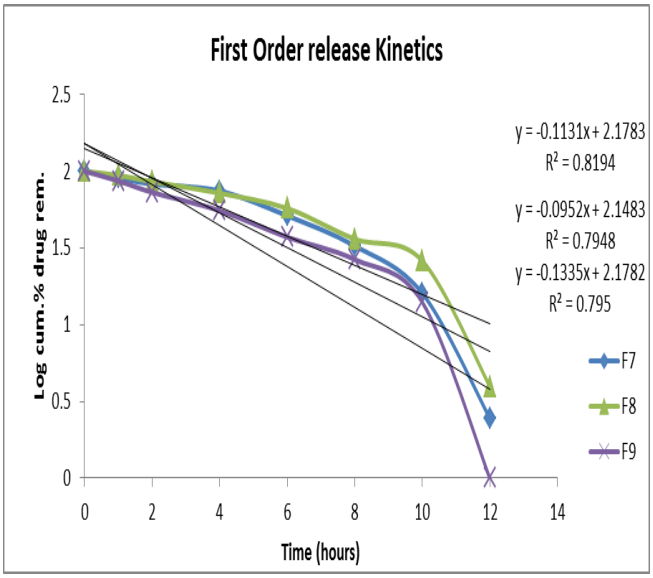


Figure-25 First order release kinetics of F7, F8 and F9 formulations

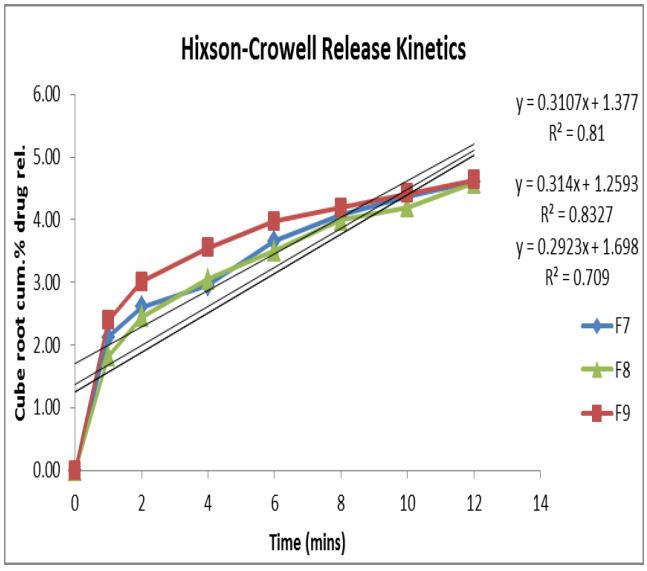


Figure-28 Hixson-crowell release kinetics of F7, F8 and F9 formulations

SUMMARY

The objective of the present work was to design oral sustained release tablets of Quinapril for management of Anti hypertensive disease which affects all kind of individuals. As the chosen drug Quinapril HCl is soluble in water and slightly bitter in taste.

Next, preformulation studies were carried out to rule out any interactions between the drug and the polymers/excipients by Fourier transformer infrared spectroscopy. The study confirmed absence of any such interactions.

Various batches of Quinapril sustained release formulations F1 to F9 were prepared by the wet granulation method. Matrixes of Quinapril were prepared using polymers HPMC K100M, HPMC K4M and Guar gum.

It was observed that formulations F1 to F9 totally met the micromeritic properties and were within pharmacoepial limits. The thickness of the tablet formulations F1 to F9 was found to vary between 2.3 mm to 2.5 mm. A low standard deviation indicated that the method used for the formulation was reproducible and gave and hence accuracy in each tablet could be ensured.

The weight of each tablet formulation was pre-determined. The diameter of all the developed formulations F1 to F9 was found to be 3.33 to 3.56 mm. The observed results of content uniformity indicated that the drug was uniformly dispersed throughout the tablets. The percentage drug content of the examined formulations F1 to F9 varied between 92.9 to 100.3%. The hardness of the formulations F1 to F9 was found to range from 5.5 to 6.6kg/cm2.Whereas friability was found to range from 0.15 to 0.3%.

The dissolution profile of the formulations F1 to F9 were analyzed and release pattern of drug was found. Formulations F1 to F3 containing drug released almost 97 to 99% of the drug by 8 hrs. Formulation F4 to F6 released 98 to 99% of the drug within 10 hrs. F7 to F9 formulations released almost 99% of the drug by the end of 12 hrs. Of all the formulations F8 was found to be the best which released 96.03% of the drug in a steady concentration according to the zero order kinetics. The F8 formulation followed zero order release as the graph was linear. The drug release is independent of concentration and it follows zero order and Higuchi mechanisam.

CONCLUSION

The present investigation was concerned with the development of the sustained release tablets, which were designed to prolong the duration of action by oral administration. Various formulations were developed by using release rate controlling and gel forming polymers like HPMC K100M, HPMC K4M & Guar gum by wet granulation method. Different proportion of HPMCK 100M and guargum mucilage was associated with decrease in the overall cumulative drug release rate. Thus, we concluded that from among all the developed formulations, F8 formulation extended the drug release longer period of time over 12 hrs when compare to other formulations. F8 was selected as the best formulation. From the result, it is evident that combination of HPMC K100M & Guargum mucilage(10% each) by forming a matrix, retards the release rate of drug and comparison with other formulations. These matrix tablets provided slow and complete release of Quinapril 12 hrs. Thus, the objective of the work was formulation of sustained release dosage form of Quinapril by using HPMC and Guar gum as release rate controlling and gel forming agents has been achieved with success. These days controlled release formulations are gaining importance.

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