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DESIGN AND *INVITRO* EVALUATION OF PRESS COATED CORE IN CUP TABLETS FOR PULSATILE DRUG DELIVERY OF ANTI HYPERTENSIVE AGENT-ENALAPRIL

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ABSTRACT

In the present studies a model antihypertensive drug Enalapril is selected for the development of an alternative, simple, orally applicable press coated core-in-cup tablets for pulsatile drug delivery to meet the needs to treat hypertension and some types of chronic heart failures. The press coated core-in-cup tablets were prepared by direct compression method using selected swellable polymers viz., sodium alginate and sodium CMC and rupturable polymers viz., ethyl cellulose and HPMC K4M. Two core formulations were designed with hydrophilic polymers viz., PVPK90 and HPMC15cps. Four press coated core-in-cup tablets were designed with different ratios of swellable and rupturable polymers. All the batches of core tablets and core in cup tablets were evaluated for its pre compression parameters such as bulk density, tapped density, angle of repose, compressibility index etc, and post compression parameters viz., hardness, thickness, disintegration test, friability, *in vitro* dissolution studies and statistical interpretation of pharmacokinetic data with PCP Disso V3 software. All parameters were matching with specifications and well within the limits.

KEYWORDS: Enalapril, circadian rhythm, pulsatile release, swellable, rupturable, burst release.

INTRODUCTION

Among all drug delivery systems oral dosage forms are most widely used because these are safe, convenient and promising. Drug delivery on the basis of circadian rhythm i.e., Chronopharmaceutics, which is currently gaining much attention worldwide. Various ailments show circadian variation e.g. arthritis, hypertension and bronchial asthma, these demands time scheduled drug delivery for the required pharmacological action. Many epidemiological studies revealed that there is high risk of pathological conditions during 24 hr cycle. Hypertension is the most dangerous cause for the death which rises during early hours of the day or just before waking up is majorly responsible for heart attacks, or if it is severe which causes death. In order to satisfy this need novel technology is developed that is called pulsatile release.[1] Patients suffering from cardiovascular diseases like stroke, sudden cardiac death and myocardial infarction are very high in the early morning hours because blood pressure rises just before waking period. Whenever the blood pressure rises catecholamines secretion increases which further increases plasma rennin activity. So it can be well treated by chronotherapy. "Chronotherapy refers to treatment in which the availability of the drug to the body can be tailored to meet the therapeutic requirement. Earlier the development of the drug delivery system was based on the homeostatic theory, according to this theory biological functions are constant over time however chronobiological studies contradict this theory, nearly all functions of the body including those influencing pharmacokinetic parameters display significant variation. Circadian or 24 hrs rhythm exists in blood pressure, blood flow, stroke volume, peripheral resistance, gastric acid secretion".[2] In the present research work enalapril was used as a model anti hypertensive drug to design pulsatile drug delivery system. "Enalapril is an angiotensin-converting-enzyme (ACE) inhibitor used in the treatment of hypertension, diabetic nephropathy, and some types of chronic heart failure. ACE converts the peptide hormone angiotensin I to angiotensin II. Enalapril was the first member of the group known as the dicarboxylate containing ACE inhibitors. Enalapril as a treatment for high blood pressure works by modulating the renin-angiotensin-aldosterone system. Enalapril belongs to a class of medications called angiotensin converting enzyme inhibitors. Normally angiotensin I is converted to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II constricts blood vessels, increasing blood pressure. By inhibiting ACE, Enalapril decreases levels of angiotensin II leading to less vasoconstriction and decreased blood pressure. Enalapril is a pro-drug following oral administration, it is bio activated by hydrolysis of the ethyl ester to enalaprilat which is the active angiotensin converting enzyme inhibitor".[3]

Literature survey revealed that very few methods available for the preparation of pulsatile tablets with

many polymers alone, in combination with other drugs.[4,9]

MATERIALS AND METHODS

Model anti hypertensive agent Enalapril was gifted from cilpla pharmaceuticals, Mumbai: PVP K90, HPMC K4M, talc, ethyl cellulose, sodium CMC were procured from SD fine chemicals: Magnesium stearate, HPMC 15 CPS was procured from Sigma Aldrich: Galen IQ 72 as directly compressible diluents was procured from Beneo palatinit, Germany.

METHODS

Preparation of core tablet

Core tablet formulation viz., batch-1 was prepared by direct compression method. Calculated quantities of selected drug and polymers and manufacturing additives were mixed in a polybag for 10min to achieve uniform mixing. The mixture was subjected for direct compression using 8mm flat punch in Cadmech 10 station rotary punching machine. During compression weight variation, hardness was checked. The formulae of one core tablet comprising Enalapril, PVPK90, talc, magnesium stearate and special directly compressible vehicle Galen IQ-72 are given in table1.

Table 1: Formulae of core tablet

Drug/polymers/Ingredients	Batch-1
Enalapril	20mg
PVP K90	10 mg
Talc	1 mg
Magnesium stearate	1 mg
Galen IQ-72	38 mg
Total weight of the tablet	70 mg

Preparation of press coated tablets by direct compression method

Four batches viz., F-1, F-2, F-3 and F-4 are prepared by direct compression method. An impermeable layer consisting of mixture of rupturable polymers ethyl cellulose, HPMC K4M was filled in the die cavity of 12mm diameter then gently compact the powder bed with a flat surface spatula. The core tablet was carefully placed in the center of the powder bed then the die wall was filled with the mixture of swellable polymers sodium alginate and sodium CMC so that the surrounding surfaces of the core tablet was fully covered. The powder bed was compressed directly by using 12 mm flat punch in Cadmech 10 station rotary punching machine. The different formulae of press coated core-in-cup are given in table 2.

Table 2: Formulae of different press coated core-in-cup tablets.

Core tablet/polymer	F-1	F-2	F-3	F-4
Enalapril core tablets	70mg	70mg	70mg	70mg
HPMC K4M	50mg	75mg	50mg	75mg
Sodium alginate	50mg	25mg	----	----
Ethyl cellulose	130mg	130mg	130mg	130mg
Sodium CMC	----	----	50mg	25mg
Total weight	**300mg**	**300mg**	**300mg**	**300mg**

RESULTS

Pre compression evaluation: The prepared powder blends during the preparation of core tablets were subjected for pre compression characteristics viz., bulk density, tapped density, compressibility index, flow properties (angle of repose).[10] All studies were carried out in triplicate and mean values were reported and the results are given in tables 3 and 4.

Table 3: Pre compression evaluation data for core tablet powder blend.

Parameters	Bulk density	Tapped density	Carr's index	Hausner's ratio	Angle of repose
Batch 1	0.401 ± 0.003	0.491 ± 0.004	8.32	1.22	25'23˚

Table 4: Pre compression evaluation data for core-in-cup materials.

Parameters	Bulk density	Tapped density	Carr's index	Hausner's ratio	Angle of repose
F1	0.579 ± 0.003	0.698 ± 0.003	14.63	1.17	27'33˚
F2	0.587 ± 0.004	0.665 ± 0.006	16.77	1.20	26'41˚
F3	0.479 ± 0.005	0.548 ± 0.035	16.51	1.19	28'22˚
F4	0.567 ± 0.004	0.626 ± 0.001	13.84	1.16	26'44˚

Post compression studies

The core tablet and core-in-cup tablets were prepared and subjected for post compression evaluation and the results are given in tables 5 & 6.

Table 5: Post compression evaluation data for core tablets

Parameters	F1
weight variation(mg)	69.96± 0.20
Thickness(mm)	2.91 ± 0. 26
Diameter(mm)	8.03 ± 0.017
Hardness(kg/cm^2)	4.36 ± 0.057
Friability(Percentage)	0.318±0 .025
Drug content(Percentage)	99.42 ± 0.831
Disintegration time(sec)	20.6 ± 0.577

Table 6: Post compression evaluation data for core-in-cup tablets

Parameters	F1	F2	F3	F4
Weight variation	300.07 ± 0.02	299.91 ±0.002	300.1 ±0.015	299.95 ± 0.03
Thickness(mm)	5.91 ± 0.02	5.04 ± 0.04	5.05 ± 0.011	5.12 ± 0.02
Diameter(mm)	12.03 ± 0.057	12.13 ± 0.061	12.06 ± 0.19	12.14 ± 0.068
Hardness(kg/cm^2)	4.06 ± 0.067	5.93 ± 0.058	5.96 ± 0.115	4.07 ± 0.057
Friability(Percentage)	0.488±0 .025	0.42 ± 0.0011	0.123 ± 0.0012	0.43 ± 0.0005

Dissolution studies

In vitro dissolution of designed core tablet and core-in-cup tablets were studied using USP apparatus-2 paddle method. The dissolution profiles, dissolution data and model fitting values were presented in tables 7-11 and figures 1-9.

Table 7: *In vitro* dissolution data of core tablet

Time in minutes	Cumulative percent drug released *±SD
5	13.39 ± 0.67
10	18.86 ± 0.25
15	26.24 ± 0.51
30	38.49 ± 0.67
45	48.25 ± 0.92
60	56.85 ± 0.68
75	64.13 ± 0.44
90	75.54 ± 0.51
120	86.96 ± 0.25
150	90.15 ± 0.68
180	96.98 ± 0.44

*Average of three determinations, n=3.

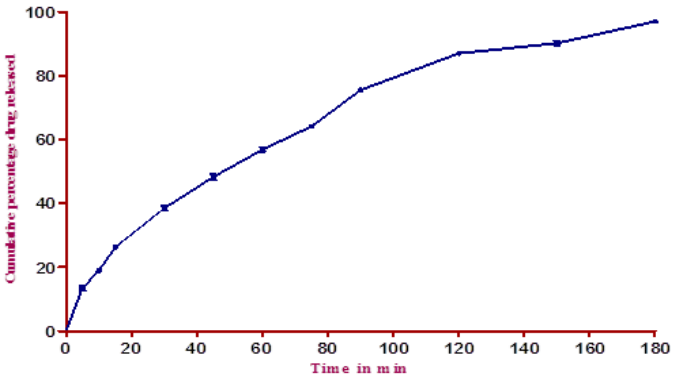

Figure 1: Dissolution profile of core tablet.

Table 8: *In vitro* dissolution data of F1 and F2 core-in-cup tablets

Time in hours	Cumulative percent drug released* ±SD	
	F1	F2
0.25	2.35 ± 0.44	1.47 ± 0.44
0.5	6.92 ± 0.67	2.94 ± 0.67

0.75	8.40 ± 0.25	4.56 ± 0.44
1	10.62 ± 0.51	6.04 ± 0.92
1.5	12.69 ± 0.67	8.26 ± 0.67
2	15.35 ± 0.92	10.48 ± 0.68
2.5	18.02 ± 0.68	12.70 ± 0.68
3	28.94 ± 0.44	16.98 ± 0.44
4	47.82 ± 0.51	27.01 ± 0.25
5	66.28 ± 0.25	64.00 ± 0.67
6	83.14 ± 0.68	74.97 ± 0.44
8	90.59 ± 0.44	84.92 ± 0.68
10	94.52 ± 0.68	87.43 ± 0.92
12	97.87 ± 0.44	93.65 ± 0.67

*Average of three determinations, n=3.

Table 9: *In vitro* model fitting values for core in cup tablets F1 and F2

Batch code	Zero order	1st order	Matrix	Hixon Crow	Peppas	n	K	Best fit model
F1	0.9648	0.9544	0.8983	0.9738	0.9807	**0.9753**	9.8710	**Peppas**
F2	0.9574	0.9601	0.8709	0.9656	0.9818	**1.1776**	6.0545	**Peppas**

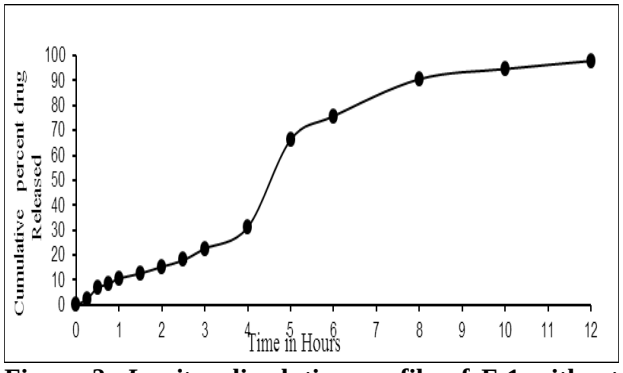

Figure 2: *In vitro* dissolution profile of F-1 without model fit curve.

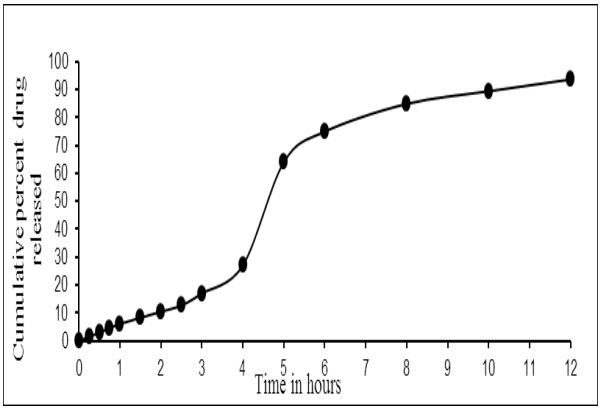

Figure 4: *In vitro* dissolution profile of F-2 without model fit curve.

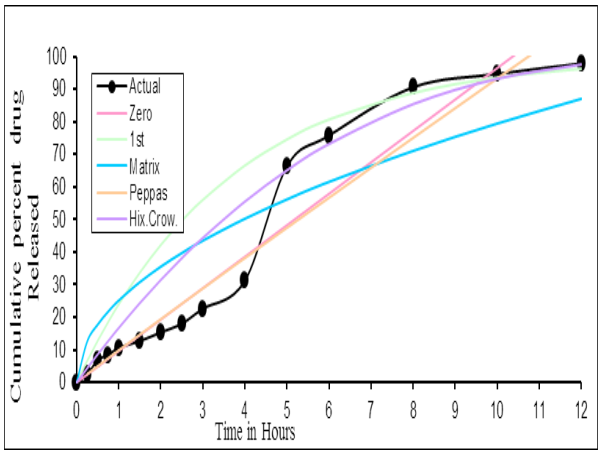

Figure 3: *In vitro* dissolution profile of F-1 with model fit curve.

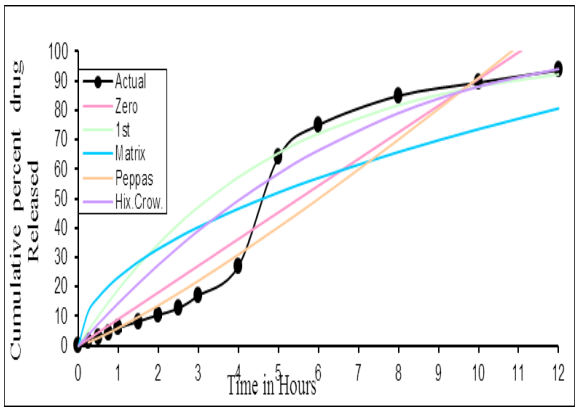

Figure 5: *In vitro* dissolution profile of F-2 with model fit curve.

Table 10: *In vitro* dissolution data of F3 and F4 core in cup tablets

Time in hours	Cumulative percent drug released *±SD	
	F3	F4
0.25	1.91 ± 0.44	1.47 ± 0.44
0.5	3.54 ± 0.26	3.24 ± 0.44
0.75	4.27 ± 0.67	4.56 ± 0.44
1	6.04 ± 0.26	6.34 ± 0.44

1.5	8.26 ± 0.67	8.99 ± 0.44
2	9.76 ± 0.68	10.04 ± 0.67
2.5	12.55 ± 0.44	11.98 ± 0.51
3	14.04 ± 0.26	14.18 ± 0.51
4	39.23 ± 0.25	18.45 ± 0.26
5	69.17 ± 0.44	64.23 ± 0.44
6	78.23 ± 0.67	72.16 ± 0.25
8	87.59 ± 0.68	81.52 ± 0.67
10	91.37 ± 0.92	86.61 ±0.44
12	94.86 ± 0.51	92.01 ± 0.88

*Average of three determinations, n=3.

Table 11: *In vitro* model fitting values for core in cup tablets F3 and F4

Batch code	Zero order	1st order	Matrix	Hixon Crow	Peppas	n	K	Best fit model
F3	0.9587	0.9562	0.8694	0.9645	0.9787	**1.1345**	6.5009	**Peppas**
F4	0.9506	0.9563	0.8586	0.9595	0.9739	**1.1419**	6.0159	**Peppas**

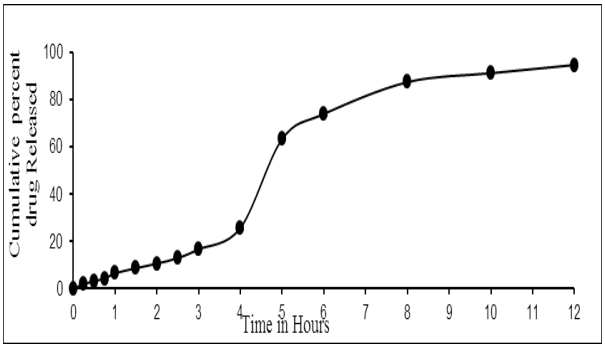

Figure 6: *In vitro* dissolution profile of F-3 without model fit curve.

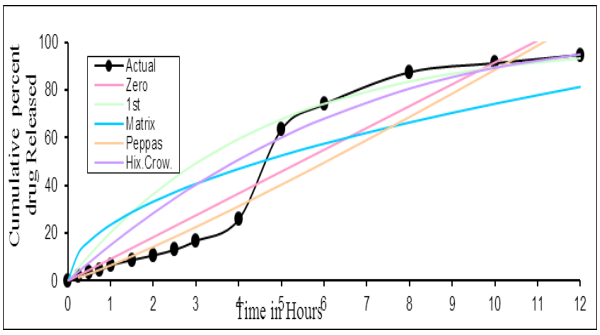

Figure 7: *In vitro* dissolution profile of F-3 with model fit curve.

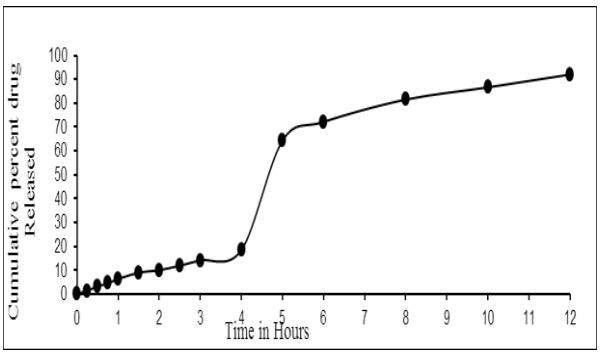

Figure 8: *In vitro* dissolution profile of F-4 without model fit curve.

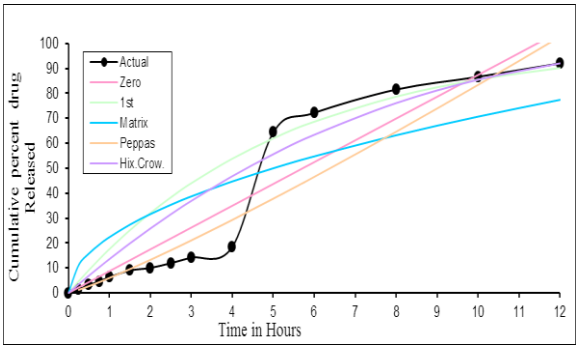

Figure 9: *In vitro* dissolution profile of F-4 with model fit curve.

DISCUSSION

Enalapril as model drug belonging to antihypertensive class was selected for the formulation of pulsatile tablets. In the present studies one core tablet formula viz., batch-1 was fabricated and same was used to prepare different core-in-cup tablets using swellable and rupturable polymers with varying proportions. The powder blends of all the formulations for core tablet and core in cup tablets were evaluated for precompression parameters viz., repose angle, bulk density, tapped density, Carr's index and Hauser's ratio. The powder blend of all the formulations for core tablet and core in cup tablets were subjected for direct compression into desired tablets using 12 mm flat faced punches in 10 station rotary punching machine. These fabricated tablets were evaluated for post compression evaluation parameters viz., thickness, diameter, weight variation, drug content uniformity, hardness, friability, *in vitro* disintegration time and *in vitro* dissolution.

Precompression evaluation of core formulation

The bulk density was found to be 0.401±0.003 g/cm^3; tapped density 0.491±0.004 g/cm^3; compressibility index 6.09 and Hauser's value 1.22 for Batch-1 indicates a powder with good flow properties. Batch-1 formulation showing that the blend of powder in core formulation having good flowability. The angle of repose was found

to be 25'23˚ for Batch-1 formulation indicates blend was free flowing and can be used for direct compression.

Precompression evaluation of core in cup formulation
The bulk density was found to be in the range of 0.479±0.003 to 0.587±0.004g/cm^3; tapped density 0.548±0.035 to 0.698±0.003g/cm^3; compressibility index value 13.84 to 16.77 and Hauser's value 1.16 to 1.20 for F1 to F4 respectively indicates a powder with good flow properties. F1 to F4 formulations showing that the blend of powder in all formulations having good flowability. The angle of repose was found to be in the range of 26'41˚ to 28'22˚ for F-1 to F-4 formulations showing that the blend of powder were free flowing and can be used for direct compression.

Post compression evaluation of core tablet
Thickness of the core tablet was found to be 2.91±0.26mm and 8.03±0.017mm for Batch-1 formulation. The results are within the limits and are in accordance with pharmacopoeial standards. The hardness of the tablets was about 4.36±0.057 kg/cm^2 and friability was 0.318±0.025% which was below 1% indicating the sufficient mechanical integrity and strength of the prepared tablets. The hardness and friability data indicates good mechanical strength/resistance to the tablets.

The weight variation results revealed that average percentage deviation for 20 tablets of core tablet formulation was less than ±10%, which provide good uniformity of the tablets and were found to be within acceptable limits as per the pharmacopoeial specifications where as the percentage drug content was found to be in the range of 99.42 ± 0.831 for Batch-1 formulation. The low SD values indicate the drug content was uniform in all the formulated tablets. The disintegration test was performed and it was found to be 20.6 ± 0.577 min for Batch-1 indicating well within the standards.

Post compression evaluation of core in cup tablet
Post compression evaluation tests were done for core in cup tablets, the Thickness of the core in cup tablets was found to be in the range of 5.04±0.04 to 5.91±0.02 mm and diameter was found to be in the range of 12.03±0.057 to 12.14±0.068 mm for F-1 to F-4 formulations. The results are within the limits and are in accordance with pharmacopoeial standards.

The hardness of the tablets was found to be in the range of 4.06±0.067 to 5.96±0.115 kg/cm^2 for F-1 to F-4 formulations. The friability was found to be in the range of 0.123±0.0012 to 0.488±0.025% for F-1 to F-4 formulations which were below 1% indicating the sufficient mechanical integrity and strength of the prepared tablets. The hardness and friability data indicates good mechanical strength/resistance to the tablets.

The weight variation results revealed that average percentage deviation for 20 tablets of core in cup tablet formulations was less than ±7.5%, which provide good uniformity of the tablets and were found to be within acceptable limits as per the pharmacopoeial specifications. The low SD values indicate the drug content was uniform in all the formulated tablets. All parameters were found to be within specified limits as per IP/USP. The results are within the limits and are in accordance with pharmacopoeial standards.

In vitro drug release studies were carried out for core tablet and core-in-cup tablet in 900 ml of 0.1 N HCl using USP XXII dissolution apparatus type II.

CONCLUSIONS

The press coated core-in-cup pulsatile system developed in the present study consist of three components, the central core tablet made up pure drug enalapril and different concentrations of PVP K90, Galen IQ72, talc and magnesium stearate, the impermeable surrounding (lateral) consist of ethyl cellulose and the top layer consist of swellable polymer sodium alginate. Both the external layers are intended to regulate the function of the system and modify the release of drug. The polymer materials present in the core tablet regulate drug release in controlled manner. This type of tablet could be described as a hybrid system in which the top cover layer consists of a swellable polymer layer and the inner part of a conventional core tablet prepared with hydrophilic polymer acting as a drug reservoir. The first trail F-1 was designed with an active core using the various ratios of HPMC K4M: Sodium alginate at 1:1, F2 with 3:1 ratio by using same polymers used in F2; F3 with HPMC K4M: Sodium CMC at 1:1 and F4 with 3:1 ratio using same polymers used in F3; and hydrophobic cup with ethyl cellulose kept constant in all the four formulations.

The initial burst release was found to be of 10.62%, 6.04%, 6.04% and 6.34% for F-1, F-2, F-3 and F-4 formulations respectively at the end of 1hr. The lag time for F-1, F-2, F-3 and F-4 formulations were found to be 2.5 hr, 3 hr, 3 hr and 4 hr respectively. The F-1 formulation prepared with 1:1 ration of HPMCK4M: sodium alginate clearly indicates the lag period was less because of rapid swelling of sodium alginate but in F-2 formulation prepared with 3:1 ration of HPMCK4M: sodium alginate indicates as the concentration of sodium alginate decreases the lag period increases. The F-3 formulation prepared with 1:1 ration of HPMCK4M: sodium CMC and F-4 formulation prepared with 3:1 ration of HPMCK4M: sodium CMC. The results suggest that as the concentration of sodium CMC decreases the lag period increases.

In all the four formulations the lag period was found to be in the range of 2.5 hrs to 4hrs. After lag period the drug release was rapid due to influence of combination of rupturable and swellable polymers and it was extended up to 6 hrs. The cumulative amount of drug

release after 6 hrs was found to be 83.14%, 74.97%, 78.23% and 72.16% for F-1, F-2, F-3 and F-4 formulations respectively. Further, the drug release was sustained for 12 hrs. The cumulative amount of drug release after 12 hrs was found to be 97.87%, 93.65%, 94.86% and 92.01% for F-1, F-2, F-3 and F-4 formulations respectively.

The dissolution data was fitted with various kinetic models using dissolution software PCP DissoV.03. In all the four formulations the best fit model was found to be Korsemeyer peppas with exponential 'n' value ranging from 0.9753, 1.1776, 1.1345 and 1.1419 for F-1, F-2, F-3 and F-4 formulations respectively clearly indicates the drug release was bi exponential follows case II transport mechanism.

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