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FORMULATION AND INVITRO EVALUATION OF HYDROCODONE ORAL SUSTAINED RELEASE TABLETS

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Abstract:

The aim of the present study was to develop an sustained release formulation of Hydrocodone to maintain constant therapeutic levels of the drug for over 8 hrs. Various grades of eudragit and HPMC were employed as polymers. Hydrocodone dose was fixed as 4 mg. Total weight of the tablet was considered as 100 mg. Polymers were used in the concentration of 10mg and 20mg concentration. All the formulations were passed various physicochemical evaluation parameters and they were found to be within limits. Whereas from the dissolution studies it was evident that the formulation (F3) showed better and desired drug release pattern i.e.,98.43 % in 12 hours. It followed zero order release kinetics mechanism.

Keywords: *Hydocodone, Eudragit, HPMC, Sustained release tablets.*

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INTRODUCTION:

Sustained release dosage forms are designed to release a drug at a predetermined rate in order to maintain a constant drug concentration for a specific period of time with minimum side effects [1-3].

Hydrocodone is a narcotic analgesic related to codeine, but more potent and more addicting by weight. It is used also as cough suppressant.To reduce the number of doses and to increase patient compliance it was formulated as sustained release tablets.

MATERIALS AND METHODS:

Hydrocodone, HPMC K4M, HPMC K15M, HPMC K100M, Eudragit L 100, Eudragit S 100, Eudragit RSPO, MCC pH 102, Magnesium stearate, PVP K30Cellulose chemicals were Laboratory grade made of SD Fine chemicals Pvt Ltd

Formulation of Hydrocodone Dispersible Tablet by Direct- Compression:

Composition of preliminary trials for Hydrocodone Dispersible Tablet by direct compression is shown in table 3.5. All the ingredients were weighed. Required quantity of drug and excipient mixed thoroughly in a polybag. The blend is compressed using rotary tablet machine-8 station with 6mm flat punch, B tooling. Each tablet contains 2.5 mg Hydrocodone and other pharmaceutical ingredients.

Table 1: Formulation of Hydrocodone sutained release matrix tablets

INGREDIENT	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F10	F11	F12
Hydrocodone	10	10	10	10	10	10	10	10	10	10	10	10
HPMC K4M	10	20	-	-	-	-	-	-	-	-	-	-
HPMC K15M	-	-	10	20	-	-	-	-	-	-	-	-
HPMC K100M	-	-	-	-	10	20	-	-	-	-	-	-
Eudragit L-100	-	-	-	-	-	-	10	20	-	-	-	-
Eudragit S 100	-	-	-	-	-	-	-	-	10	20	-	-
Eudragit RSPO	-	-	-	-	-	-	-	-	-	-	10	20
PVP K30	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium Stearate	2	2	2	2	2	2	2	2	2	2	2	2
MCC	73	63	73	63	73	63	73	63	73	63	73	63

NOTE: All ingredients are expressed in mg only for a total weight of 100mg

Evaluation of prepared tablets

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability, *In-vitro* release and drug content.

RESULTS AND DISCUSSION:

Standard Calibration curve of Hydrocodone:

Table 2: Concentration and absorbance obtained for calibration curve of Hydrocodone in 0.1 N hydrochloric acid buffer (pH 1.2)

S. No.	Concentration (µg/ml)	Absorbance* (at 230 nm)
0	0	0
1	5	0.227
2	10	0.406
3	15	0.621
4	20	0.824
5	25	0.957
Correlation Coefficient = 0.998 **Absorbance y = 0.04x +0.012**		

It was found that the estimation of Hydrocodone by UV spectrophotometric method at λ_{max} 230.0 nm in 0.1N Hydrochloric acid had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 5- 25µg/ml. The regression equation generated was y = 0.04x +0.012.

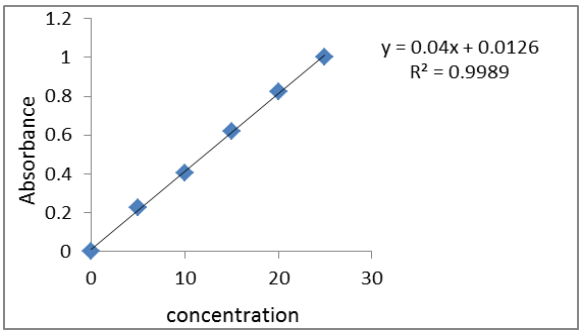

Fig 1: standard graph of Hydrocodone in 0.1 N HCl

Table 3: Observations for graph of Hydrocodone in pH 6.8 phosphate buffer (234nm)

Conc [µg/l]	Abs
0	0
2	0.125
4	0.267
6	0.367
8	0.456
10	0.571
12	0.701

It was found that the estimation of Hydrocodone by UV spectrophotometric method at λ_{max} 234.0 nm in 0.1N Hydrochloric acid had good reproducibility and this method was used in the study. The correlation coefficient for the standard curve was found to be closer to 1, at the concentration range, 0- 12µg/ml. The regression equation generated was y = 0.056x +0.014.

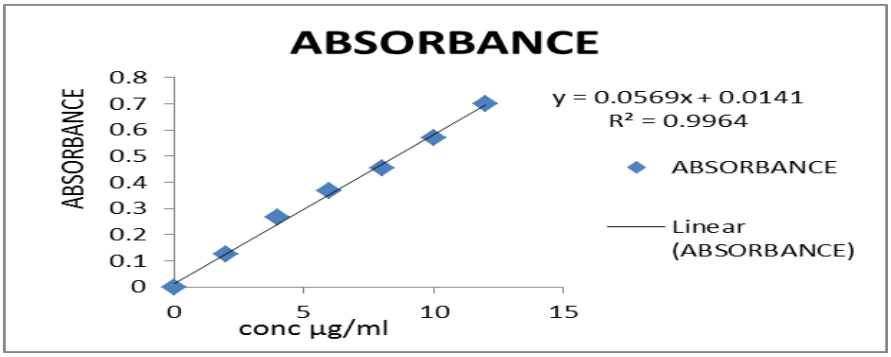

Fig 2: Standard graph of Hydrocodone pH 6.8 phosphate buffer (234nm)

Evaluation Parameters for Sustained release Tablets of Hydrocodone:
Pre-compression parameters:

Table 4 Pre-compression parameters

Formulations	Bulk Density **(gm/cm^3)**	Tap Density **(gm/cm^3)**	Carr's Index **(%)**	Hausner ratio	Angle Of Repose(Θ)
F_1	0.45	0.55	18.18	1.22	27.91
F_2	0.47	0.55	14.54	1.17	28.23
F_3	0.5	0.58	13.79	1.16	29.34
F_4	0.46	0.55	16.36	1.19	26.71
F_5	0.5	0.58	13.79	1.16	29.34
F_6	0.47	0.55	14.54	1.17	28.23
F_7	0.5	0.58	13.79	1.16	29.34
F_8	0.41	0.5	18	1.21	26.78
F_9	0.41	0.5	18	1.21	26.78
F10	0.42	0.51	18.24	1.2	26.68
F11	0.48	0.56	18.12	1.21	26.7
F12	0.41	0.54	18.11	1.22	26.71

Post-compression parameters:

Table 5: Post-compression parameters

Formulations	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Assay (%)
F_1	105	4.5	3.59	0.43	97.23
F_2	104	4.6	3.64	0.34	98.55
F_3	110	4.5	3.59	0.49	98.16
F_4	109	4.6	3.58	0.47	99.34
F_5	99.4	4.3	3.59	0.49	98.16
F_6	102	4.7	3.64	0.34	98.55
F_7	101	4.5	3.59	0.49	98.16
F_8	107	4.6	3.56	0.34	99.25
F_9	102	4.5	3.56	0.34	99.25
F10	103	4.4	3.55	0.43	98.6
F11	102.4	4.8	3.45	0.54	98.7
F12	98.5	4.5	3.54	0.43	98.5

Both the pre and post compression parameters were found to be with in the limits

***Invitro* Dissolution studies[6]:**

Invitro dissolution studies were carried out by using 900ml of 0.1 N HCl in USP dissolution apparatuss 2 hrs after that using 6.8ph phosphate buffer by using paddle method. The dissolution studies were carried out for about 12hr.

Table 6: *Invitro* dissolution data

Time(hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
0.5	10.46	7.46	6.77	8.54	5.46	9.66	10.79	11.77	8.73	9.75	11.46	13.87
1	20.22	14.26	15.02	17.21	14.66	16.22	21.1	19.5	23.54	16.44	20.74	22.46
2	32.65	20.65	22.55	35.53	28.44	25.45	32.86	31.88	38.33	27.87	31.57	34.78
3	49.68	39.29	40.89	50.12	43.85	46.89	43.24	49.28	44.25	32.44	42.76	46.18
4	55.24	59.55	48.22	68.84	65.88	62.83	66.49	61.11	51.01	39.78	62.15	55.41
6	74.24	80.65	59.77	79.63	96.12	72.7	84.25	82.58	78.98	58.74	85.46	76.15
8	97.55	98.34	74.35	87.46	97.56	89.26	99.96	100.25	96.99	70.84	92.82	82.16
10	97.45	98.24	91.49	98.89	97.34	98.98	99.09	100.76	96.56	81.87	97.46	87.46
12	97.35	97.67	98.43	98.67	97.95	98.33	98.45	99.67	96.18	90.47	97.13	91.16

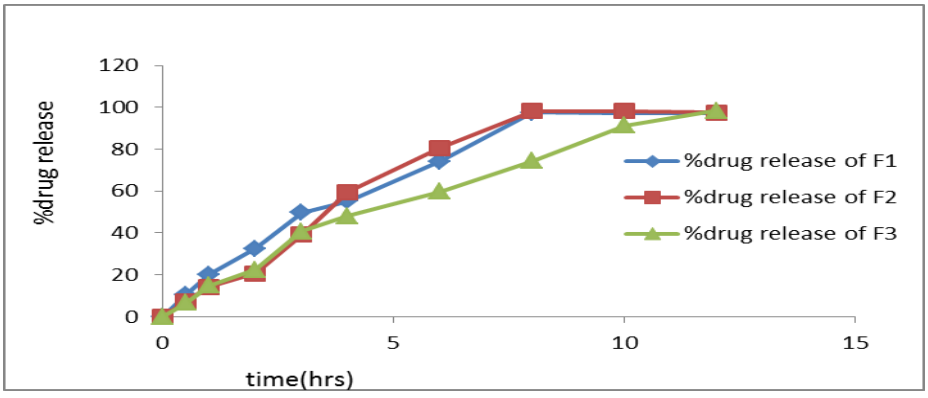

Fig 3 : Cumulative drug release of formuations(F1-F3)

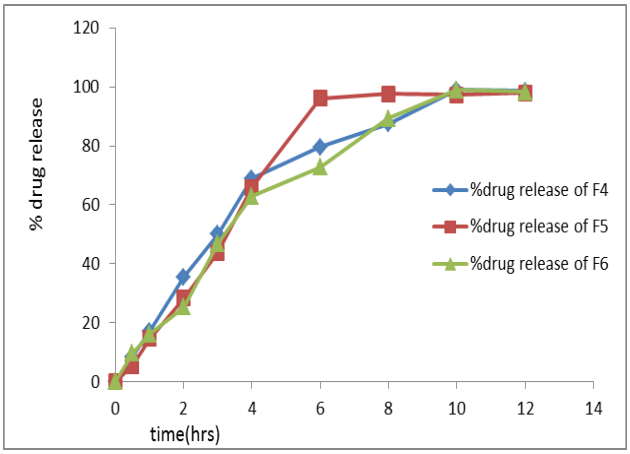

Fig 4: Cumulative drug release of formuations(F4-F6)

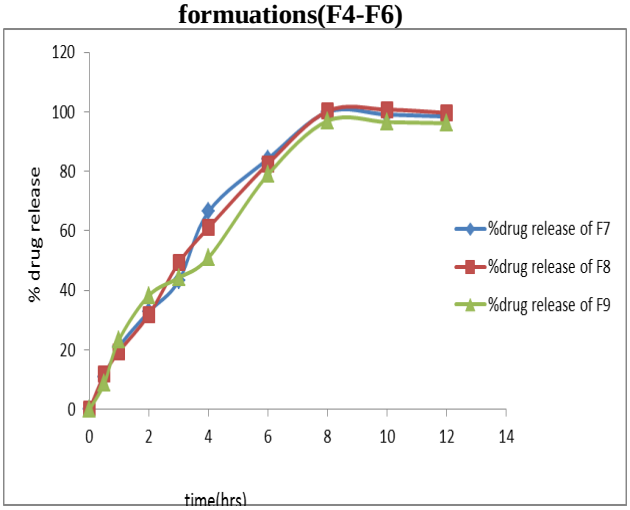

Fig 5: Cumulative drug release of formuations(F7-F9)

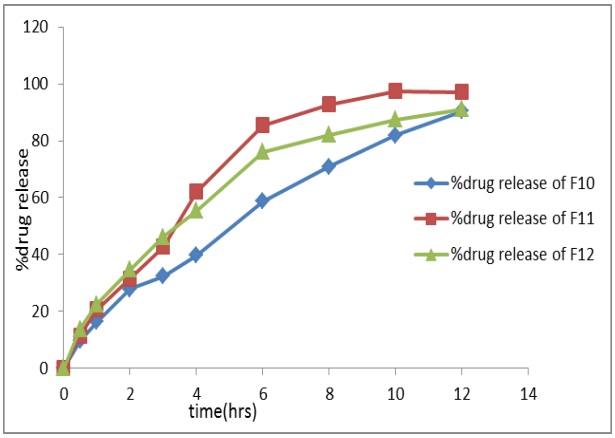

Fig 6: Cumulative drug release of formuations(F10-F12)

From this dissolution studies it was found that F3 formulation was the best formulation compared to other formulations because f3 formulation shows 98.43% at 12 hrs. This formulation was formulated by using HPMC K15M in the concentration of 10mg. other formulations also shown maximum drug release in 10 hrs like f1, f2, f5, f7, and f9. And f8 formulation 100 % drug release at 10 hrs.

These formulations (f1, f2, f5, f7, f8, f9) had shown maximum drug release in 10hrs only except F3 which has shown desired drug release in 12hrs. So it is considered as the optimised formula

Application of Release Rate Kinetics to Dissolution Data:

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

Table 7: Release kinetics data for optimised formulation (F3)

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN
0	0	0			2.000
6.77	30	5.477	0.831	1.477	1.970
15.02	60	7.746	1.177	1.778	1.929
22.55	120	10.954	1.353	2.079	1.889
40.89	180	13.416	1.612	2.255	1.772
48.22	240	15.492	1.683	2.380	1.714
59.77	360	18.974	1.776	2.556	1.605
74.35	480	21.909	1.871	2.681	1.409
91.49	600	24.495	1.961	2.778	0.930
98.43	720	26.833	1.993	2.857	0.196

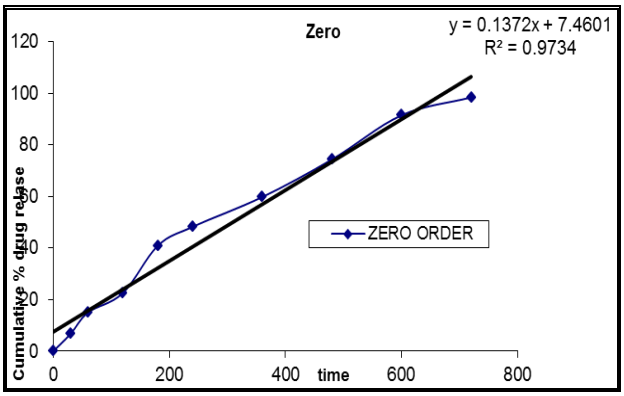

Fig 7 : Zero order release kinetics graph

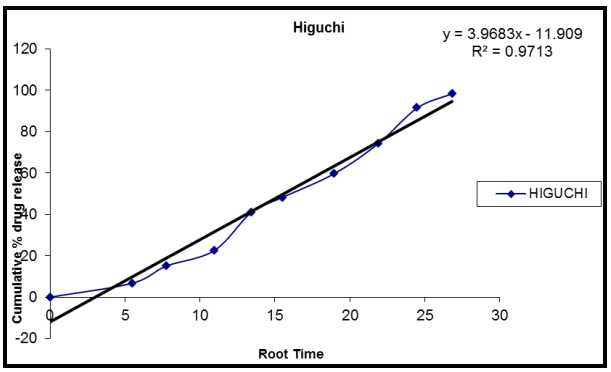

Fig 8 : Higuchi release kinetics graph

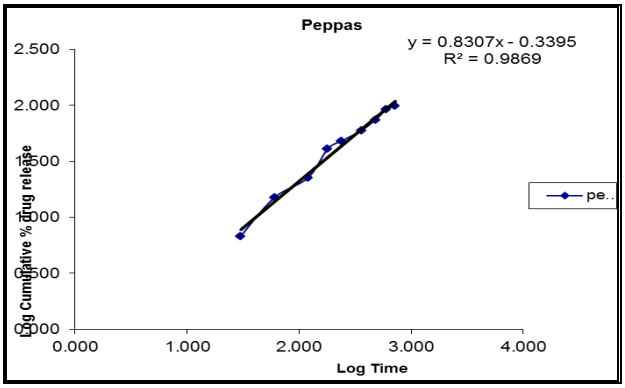

Fig 9: Kars Mayer peppas graph

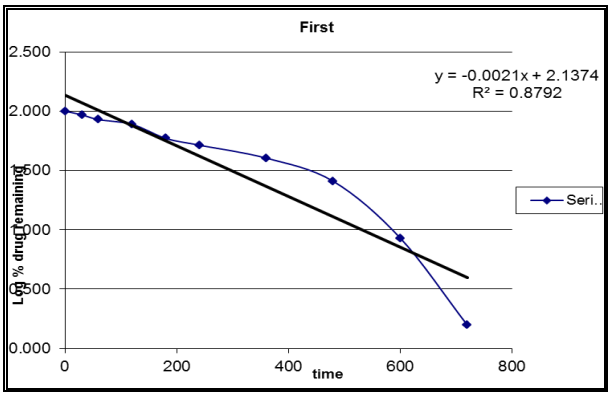

Fig 10: First order release kinetics graph

From the above graphs it was evident that the formulation F3 was followed peppas order release kinetics.

CONCLUSION:

In the present work, an attempt has been made to develop sustained release matrix tablets of Hydrocodone. Different gradess of hydroxy propyle methyl cellulose and different grades of eudragit polymers used. All the formulations were prepared by direct compression method using 6mm punch on 8 station rotary tablet punching machine. The blend of all the formulations showed good flow properties such as angle of repose, bulk density, tapped density. The prepared tablets were shown good post compression parameters and they passed all the quality control evaluation parameters as per I.P limits.Among all the formulations F3 formulation showed maximum % drug release i.e., 98.43 % in 12 hrs hence it is considered as optimized formulation. The f3 formulation contains HPMC K15M in the concentration of 10 mg.

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