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Formulation and Evaluation of Candesartan Cilexetil Sustained Release Bilayer Tablets

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ABSTRACT: The aim of the present work is to develop sustained release bilayer tablets of oral antihypertensive drug i.e. candesartan cilexetil. The formulation was developed by using direct compression method. API was mixed with various excipients like sodium alginate, HPMC in various proportions. Nine formulations was prepared by using various proportions of excipients and preformulation parameters was performed for bulk mixture.Evaluation tests for all the formulations was performed like weight variation, friability, hardness, disintegration and dissolution studies and were found to be within the limits. Among all the formulations, it was concluded that F6 as best formulation based on dissolution profile and showed the best drug release up to 12hrs that is 98.56% when compared to others.

Keywords: candesartan, bilayer tablets, sodium alginate

I. INTRODUCTION:

Bi-layer tablets are novel medication conveyance frameworks which have been acquiring significance in the new years to treat different types of sickness or to get diverse helpful activities. These are frameworks wherein at least two medications are packed on top of one another to shape into a solid unit. The two layers are by and large made of various colorsto recognize them.At the point when at least two incompatible drugs are to be administered, forming a bilayer tablet is the most ideal alternative.A few pharma companies are at present creating bi-layer tablets, for an assortment of reasons: patent extension, treatment purpose[1, 2, & 3]etc.

History:

The set of experiences for bilayer tablets is very more established from more than 50 years and one of the early logical assessments of layered tablets was distributed by Stephenson. Gunsel et al. plans the strategy during 1970 and it made conceivable to check the heaviness of individual layers by inspecting the machine, giving in measure control to guarantee right dosing. In any case, regardless of this, a lot of skill is as yet needed to detail these tablets and to guarantee steady assembling to fulfill administrative requirements.The plans utilized forevery individual layer ought to be compressible and compactable all alone for example they should show agreeable decrease in volume and structure precisely solid, cognizant strong bodies. Under this suspicion the interface between the layers should bind together during compaction and solid grip powers should hold the layers together after tablet ejection.Confirmed perceptions previously made by Karehill et al., [4,5]i.e. that the compaction pressure used to form the first tablet layer should be kept at a minimum to provide sufficient surface roughness for nesting and particle interlocking between layers to occur. Due to the increase in surface roughness there is a larger contact area between the layers, which enhances interlayer it is also necessary to devise an experimental method that can be used on bilayer tablets to detect lamination tendencies that are not already obvious after tablet ejection, but only manifest themselves after storage and handling of the compacts[6, 7].

Oral route is the most commonly employed route ofdrug administration. Although different Route of administration are used for the delivery of drugs, oral route remain the preferred mode. The popularity of the oral route is attributed patient acceptance, ease of administration, accurate dosing, cost effective manufacturing method and generally improved shelf-life of the product. Even for sustained release systemsthe oralroute of administration has been investigated the most, because of flexibility in dosage forms design that the oral route offers. With many drugs, the basic goal of therapy is to achieve a steady-state blood level or tissue level that is therapeutically effective and non-toxicfor an extended period of time[8, 9, &10]

Advantages

1. Dosage frequency can be reduced.

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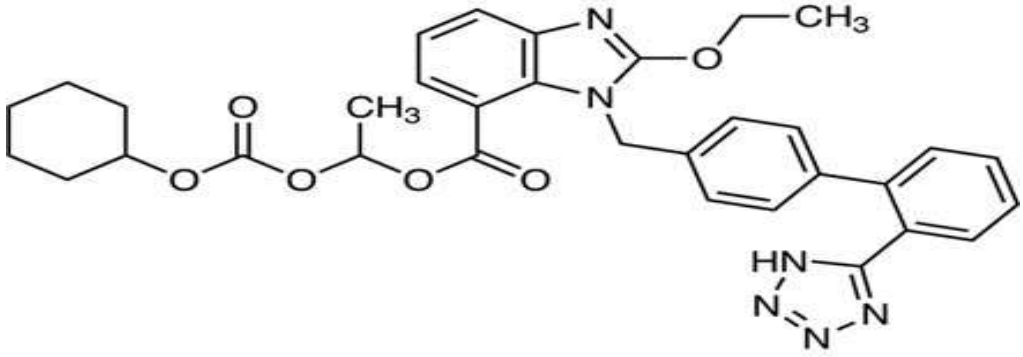
2. Patient feels better with this type of medication.

3. Reduction in drug level fluctuation in blood

Chemical Structure of candesartan:



Chemical name: Cyclohexyl carbonate ester of (±)-1-hydroxyethyl 2-ethoxy-1-[p-(o-1H-tetrazol-5-ylphenyl) benzyl]-7-benzimidazolecarboxylate

Mechanism of action:

Candesartan blocks the vasoconstrictor andaldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland.Most of the antihypertensive effect was seen within 2 weeks of initial dosing and the full effect in 4 weeks. With once-daily dosing, blood pressure effect was maintained over 24 hours, with trough to peak ratios of blood pressure effect generally over 80%.

Materials:

Candesartan cilexetil was obtained as gift samples from mylan laboratories, Hyderabad, sodium alginate from Finar, lactose, di basic potassium phosphate, monobasic potassium dihydrogen phosphate, sodium chloride, cross carmellose sodium ,HPMC from research lab fine chemicals Mumbai, magnesium stearate from oxford laboratories thane, talc from NR chem Mumbai.

Method of preparation:

Direct compression was used for the preparation of immediate release and sustained release layer containing candesartan.Bilayer tablets were prepared by feeding 250 mg of SR powder manually into punch and compressed themwith pre compression force. Then 250 mg of IR powder were manually fed into same die cavity and applied final compression force into rotary tablet punching machine.

Table no. 1: Formulation of immediate release layer

Ingredients (mg)	IR1	IR2	IR3	IR4	IR5	IR6	IR7	IR8	IR9
candesartan	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4	4.4
Cross carmellose	8	8	8	16	16	16	-	-	-
Cross povidone	8	8	8	-	-	-	16	16	16
lactose	225	225	225	225	225	225	225	225	225
Mg stearate	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.6
talc	2	2	2	2	2	2	2	2	2

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Table no. 1.1: Formulation of sustained release layer of candesartan

	SR1(mg)	SR2(mg)	SR3(mg)	SR4(mg)	SR5(mg)	SR6(mg)	SR7(mg)	SR8(mg)	SR9(mg)
candesartan	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Sodium alginate	20	10	30	20	10	30	20	10	30
HPMC	20	30	10	20	10	30	20	10	30
MCC	192	192	192	192	192	192	192	192	192
Magnesium stearate	3	3	3	3	3	3	3	3	3
talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

Evaluation studies:

1. Evaluation of bulk powder with API:
   Bulk density, tapped density, angle of repose, compressibility index
2. Evaluation of tablets:

Weight variation, hardness, thickness, friability, dissolution.

II. RESULTS AND DISCUSSION:

All formulations were tested for physical parameters like hardness, thickness, weight variation, friability are found within the pharmacopeial limits. The results of the tests were tabulated.

DRUG EXCIPIENT COMPATIBILTY STUDIES BY FTIR

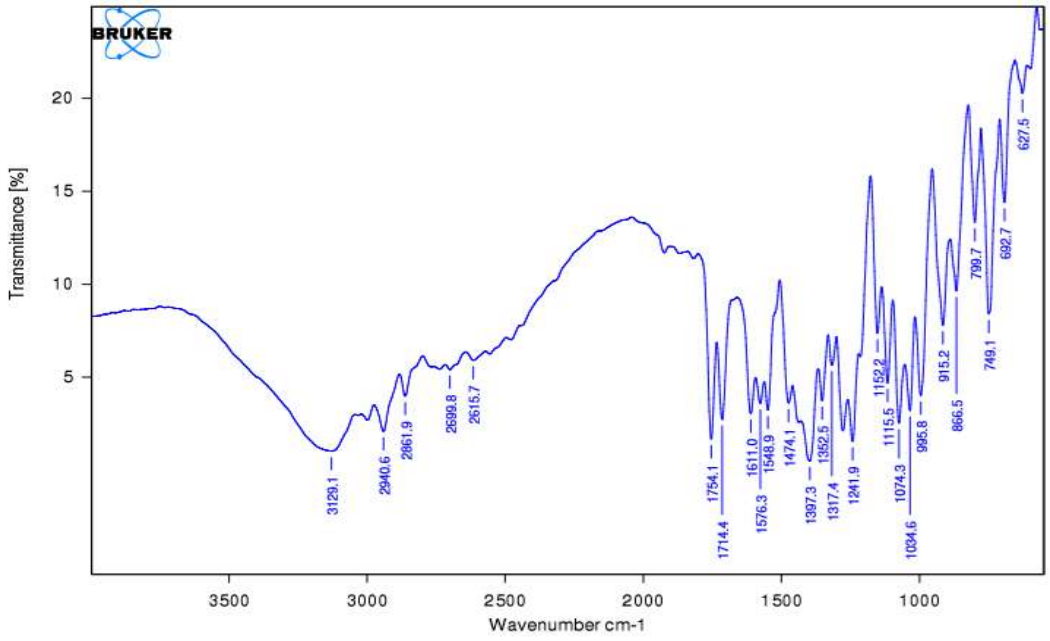

Fig no.1 candesartan drug

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Table 2: identification of drug by functional groups

Functional group	**Characteristic peaks of candesartan cilexetil observed in IR region(cm−1)**
Aromatic C-H stretching	2940.6
C=o stretching	1754.1
C-N stretching	1611.0
-c-o stretching	1241.9
O- substitution	741.9

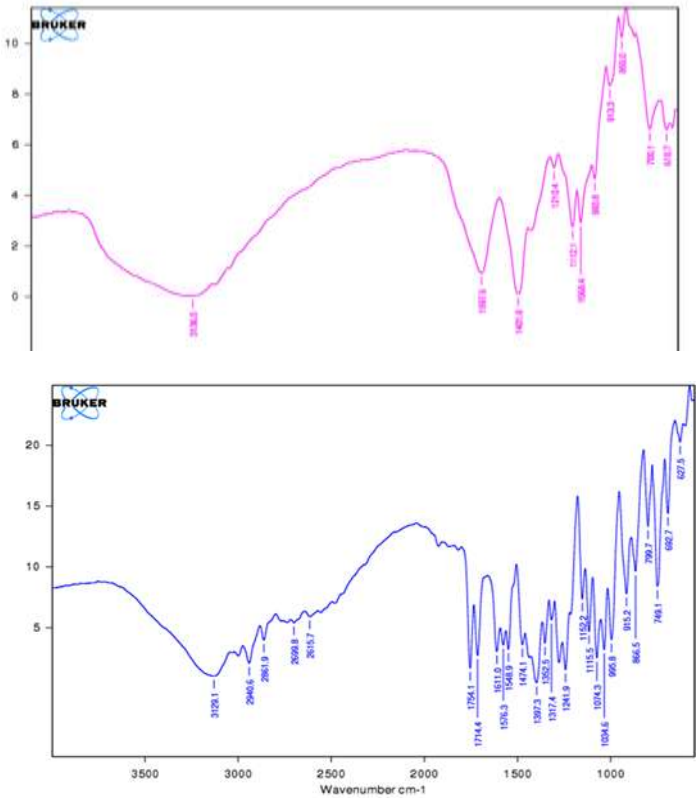

Fig no.2 Drug + cross carmellose

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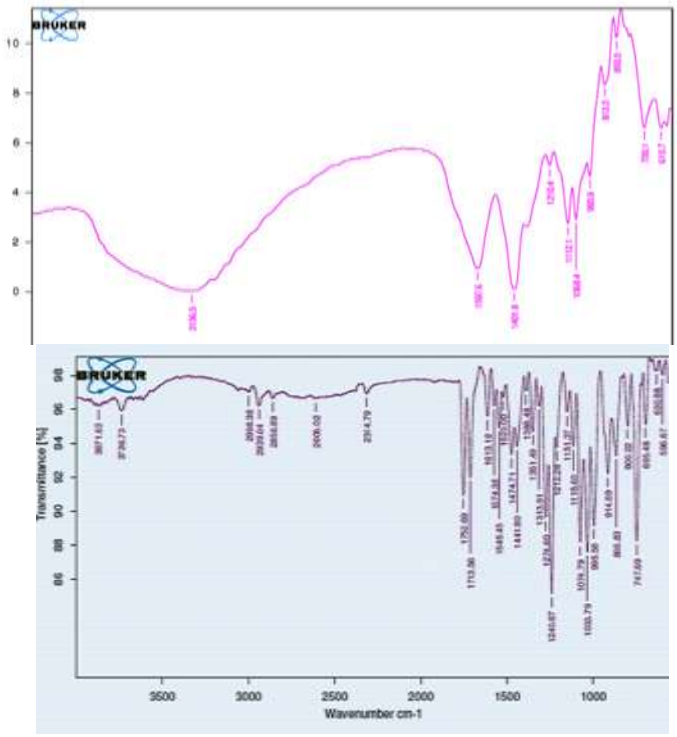

Fig no.3 Drug + cross povidone

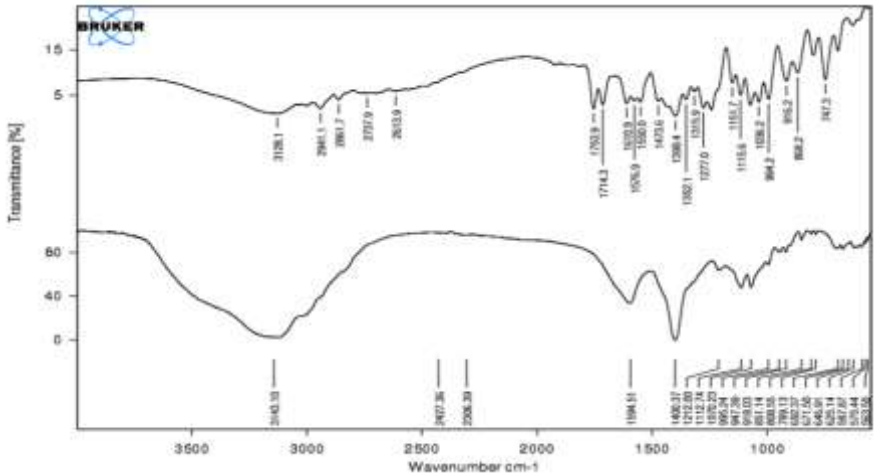

Fig no 4: drug + HPMC

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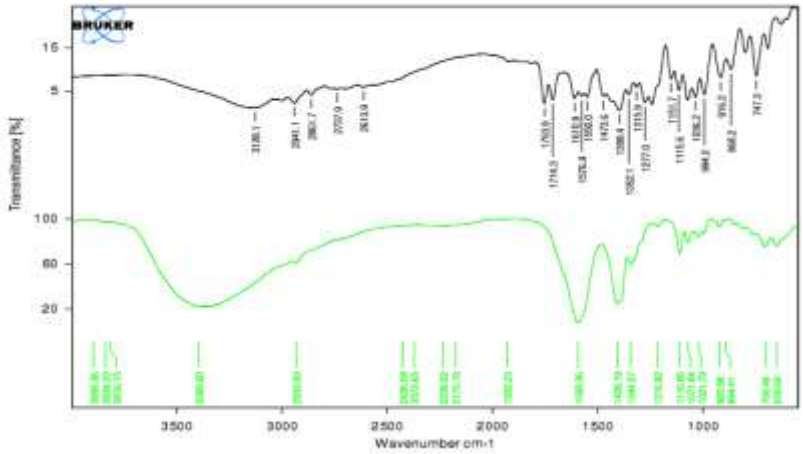

Fig no. 5 DRUG + SODIUMALGINATE

Table no3. Standard graph table

S.No	Concentration (µg/ml)	Absorbance
1	0	0
2	2	0.339
3	4	0.406
4	6	0.486
5	8	0.542
6	10	0.626
7	12	0.715

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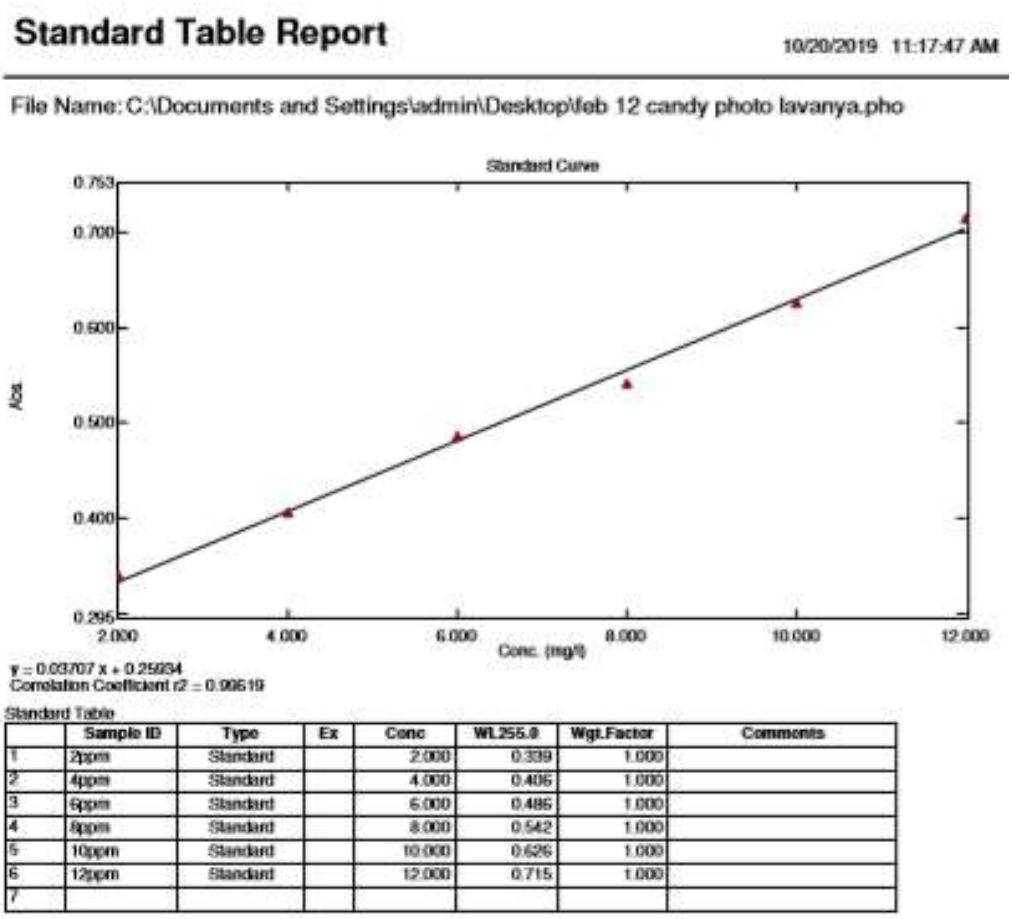

Standard Table Report

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Standard Curve

Abs

Conc. (mg/l)

y = 0.03707 x + 0.25934
Correlation Coefficient r2 = 0.99619

Standard Table

	Sample ID	Type	Ex	Conc	WL255.0	Wgt.Factor	Comments
1	2ppm	Standard		2.000	0.339	1.000	
2	4ppm	Standard		4.000	0.406	1.000	
3	6ppm	Standard		6.000	0.486	1.000	
4	8ppm	Standard		8.000	0.542	1.000	
5	10ppm	Standard		10.000	0.626	1.000	
6	12ppm	Standard		12.000	0.715	1.000	
7							

Fig no.6 construction of calibration curve

Table no4: evaluation parameters of bi layered tablets

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Weight variation	500±0.8	499±0.3	495±0.9	500±0.7	498±0.6	499±0.1	500±0.7	498±0.6	499±0.1
Thickness(mm)	2.5±0.1	2.4±0.4	2.6±o.4	2.3±0.2	2.6±0.3	2.5±0.4	2.3±0.2	2.7±0.1	2.4±0.1
Hardness (kg/cm2)	7.8±0.8	7.4±1.2	7.6±1.6	7.2±1.3	7.3±1.6	7.2±1.5	7.9±0.9	7.3±1.6	7.2±1.6
Friability	0.17±0.25	0.23±0.3	0.19±0.2	0.13±0.7	0.18±0.5	0.10±0.4	0.15±0.8	0.19±0.7	0.17±0.28
Content uniformity	99.1±0.2	99.9±0.2	99.56±0.3	99.46±0.2	98.8±0.4	96.4±0.3	98.7±0.2	95.1±0.2	99.8±0.3

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INVITRO DISSOLUTION STUDIES:

Table no: 5 Result of dissolution profile for F1 – F9

Time in hrs	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	20.01	26	23.1	21.63	28	19.99	23.61	26.83	24.19
2	48.52	38.66	37.68	40.54	57.66	40.99	48.38	57.47	59.63
4	74.3	53.74	55.64	67.46	68.24	55.68	69.32	65.62	69.47
6	86.92	73.2	77.58	78.37	75.59	67.78	72.53	77.45	79.13
10	97.35	85.67	86.3	89.52	89.91	93	86.37	89.92	87.39
12	98.23	97.5	100	100	96.26	98.56	95.84	94.63	95.29

Comparison of drug release profiles:

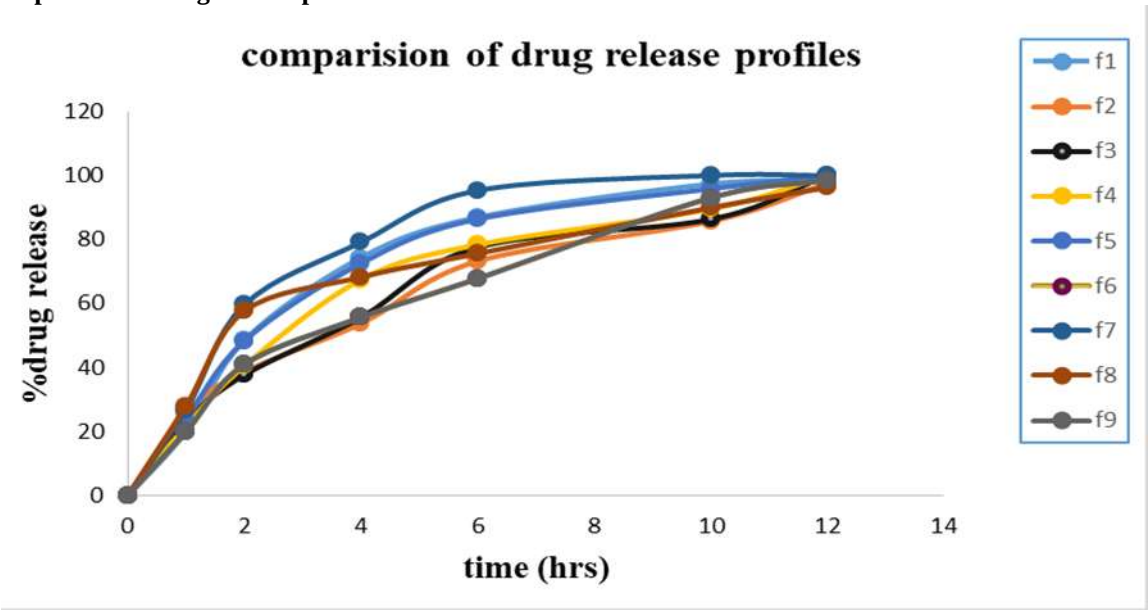

Fig no. 7 comparision of drug release profiles F1 to F9

Kinetic models:
Dissolution data was fitted in zero order, first order and higuchis equations.
Formulation F6 was found to be the optimized formulation which shows the best drug release profile.

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Table no.6:Drug Release kinetics data

S. No	Time (hr)	Log T	Square root of time	%CR	%Drug remaining	Log% CR	Log %drug remaining	Cube root of % drug remaining
0	0	0	0	0	100	0	2	4.6415
1	1	0	1	19.99	80.47	1.300813	1.905634	4.317291112
2	2	0.301	1.414	40.99	57.35	1.612678	1.758533	3.856362113
3	4	0.602	2	55.68	33.44	1.745699	1.524266	3.221727145
4	6	0.778	2.449	67.78	20.27	1.831102	1.306854	2.726577937
5	10	1	3.162	93	7	1.968483	0.840236	1.912931
6	12	1.079	3.464	98.56	2.47	1.993701	0.392697	1.351758112

Fig no.8 :Zero order plot for optimized formula

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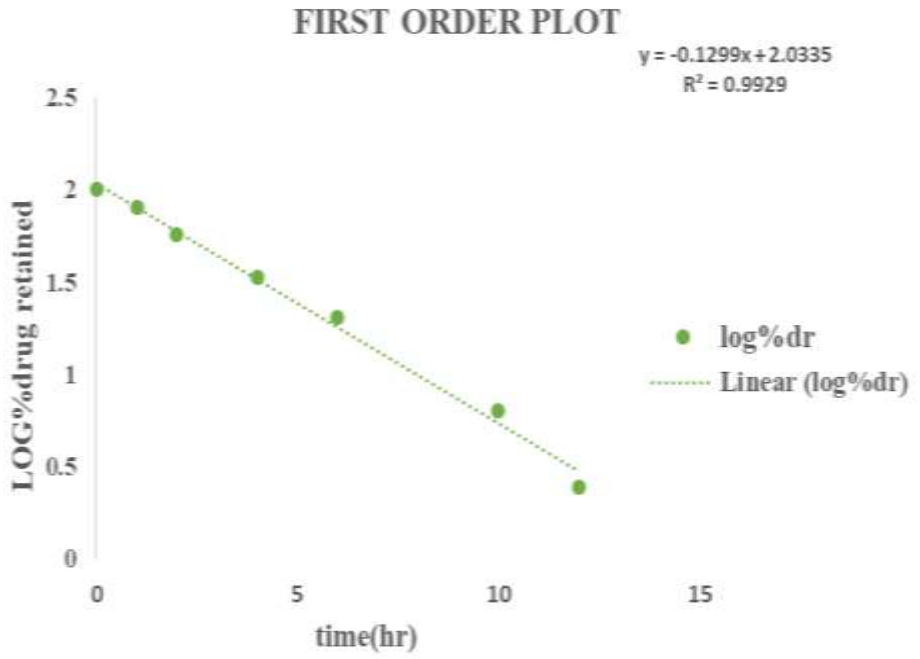

Fig no.9: First order plot for optimized formulation

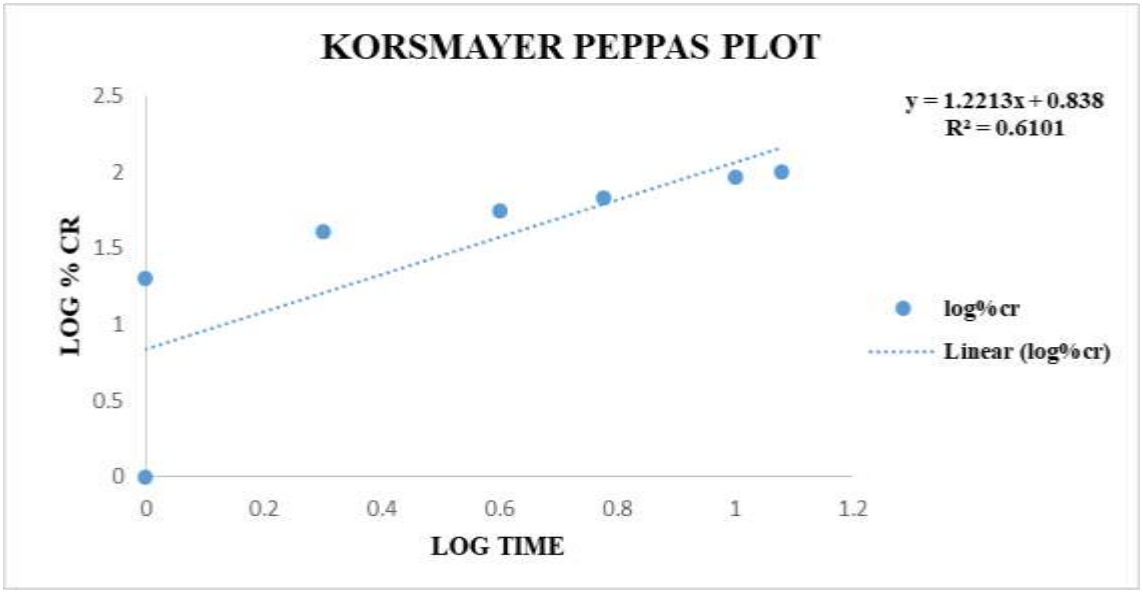

Fig no.10:Korsemeyar's peppas plot for optimized formulation

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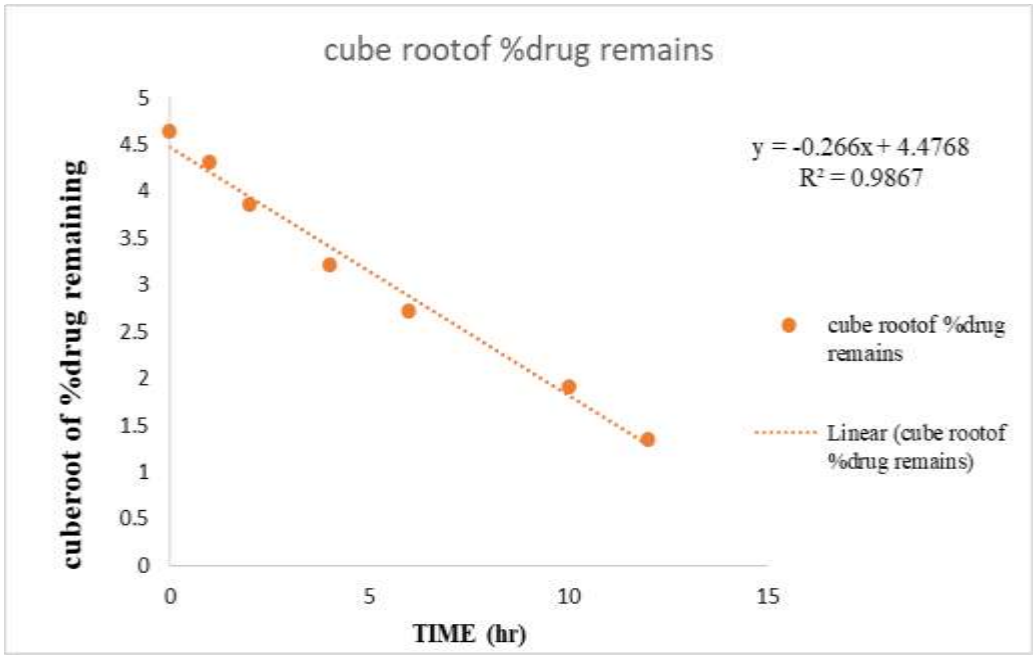

Fig no.11: HixsonCrowell's plot for optimized formulation

III. CONCLUSION:

Formulations was prepared using different concentration of rate releasing polymers like HPMC , sodium alginate for extending the drug release up to 12hrs.preformulation studies was performed and all the formulations gave good results.

Formulated tablets satisfactory results for tablet evaluation parameters and was found to be within the limits.

It was concluded that among all the formulations (F1-F9), it was observed that F6 has shown best dissolution profile.

Analysis of kinetic release data indicated that the drug release follows first order kinetics, the correlation coefficient (r2) was higher in first order model.

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