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Original Article

FORMULATION AND EVALUATION OF RATE RETARDING POLYMERS IN THE PROLONGED RELEASE TABLETS OF LOVASTATIN

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ABSTRACT

The aim of the present study was to develop Lovastatin extended release tablets to maintain constant therapeutic levels of the drug for over 12hrs. Gum Acacia, Almond gum and Grewia gum were used as polymers. All the formulations were passed various physic chemical evaluation parameters such as bulk density, tapped density, cars index, hausners ratio, angle of repose , weight variation, hardness, thickness, friability and drug content. From the dissolution studies it was evident that the formulation F9 showed better and desired drug release pattern i.e., 98.82% in12 hours. It contains the Grewia gumas polymer. It followed Higuchi release kinetics mechanism.

Keywords: Lovastatin, Gum Acacia, Almond gum, Grewia gum and Extended Release Tablets.

INTRODUCTION

The oral route is the most popular route used for administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes. The terms Sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of asingledose.[1, 2]

There are several reasons for attractiveness of these dosage forms: provides increased bioavailability of drug product, reduction in the frequency of administration to prolong duration of effective blood levels, reduces the fluctuation of peak trough concentration and side effects and possibly improves the specific distribution of the drug. If one were to develop an ideal drug delivery system, two pre-requisites would be required: Firstly single dose for the duration of treatment whether for days or weeks as with infection ,diabetes or hypertension. Second it should deliver the active entity directly to the site of action minimizing the side effects.

There are certain considerations for the preparation of extended release formulations: If the active compound has along half-life, it is sustained on its own, If the pharmacological activity of the active is not directly related to its blood levels, If the absorption of the drug involves an active transport and If the active compound has very short half-life then it would require a large amount of drug to maintain a prolonged effective dose. The above factors need serious review prior to design.[3]

Extended release formulations make the drug available over extended time period after oral administration. The extended release product will optimize therapeutic effect and safety of a drug at the same time improving the patient convenience and compliance. By incorporating the dose for 24hrs into one tablet/capsule from which the drug is released slowly. This formulation helps to avoid the side effects associated with low and high concentrations. The ideal drug delivery system should show a constant zero-order release rate and maintain the constant plasma concentrations.

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It is desirable to maintain a therapeutic blood concentration in order to achieve the desirable pharmacological effects. To maintain a narrow range of therapeutic blood concentration it is desirable to have a dosage form that can deliver the drug in a more sustainable or controlled way to achieve the desired results. Extended release tablets and capsules are commonly taken once or twice daily, compared with counter part conventional forms that may have to be taken three or four times daily to achieve the same therapeutic effect. Typically, extended release products provide an immediate release of drugs that promptly produces the desired therapeutic effect, followed by gradual release of additional amount of drugs to maintain this effect over a predetermined period. The sustained plasma drug levels provided by extended release products often eliminate the need for night dosing, which benefits not only the patient but the patient but the care giver as well.[4]

Draw backs of Conventional Dosage Form.5

- ✓ Poor patient compliance, increased chances of missing the dose of a drug with short half life for which frequent administration is necessary.
- ✓ The unavoidable fluctuations of drug concentration may lead to under medication or over medication.
- ✓ Atypical peak-valley plasma concentration time profile is obtained which makes attainment of steady-state condition difficult.
- ✓ The fluctuations in drug levels may lead to precipitation of adverse effects especially of a drug with small Therapeutic Index (TI) when ever over medication occur.

AdvantagesofExtendedReleaseDeliverySystem.6

- ✓ The extended release formulations reduce dosing frequency of drugs.
- ✓ The extended release formulations may maintain therapeutic concentrations.
- ✓ Reduce the toxicity by slowing drug absorption.
- ✓ The use of these formulations avoids the high blood concentration.
- ✓ Extended release formulation shaves the potential to improve the patient compliance and convenience.
- ✓ Minimize the local and systemic side effects.
- ✓ Increasethestabilitybyprotectingthedrugfromhydrolysisorotherdegradativechangesingastrointestinaltract.
- ✓ Improvement in treatment efficacy.
- ✓ Minimize drug accumulation with chronic dosing.
- ✓ Improve the bioavailability of some drugs.
- ✓ Usage of less total drug.
- ✓ Improve the ability to provide special effects. For example, Morning relief of arthritis through bed time dosing.

MATERIALS AND METHODS

Lovastatin Procured From Natco Pharma ltd, Hyderabad, India, Gum Acacia from Signet chemical corporation Pvt ltd, Mumbai, India, Almond gum from Merck Specialities Pvt Ltd, Mumbai, India, Grewia gum from Signet chemical corporation Pvt ltd, Mumbai, India, Lactose from Strides arco lab, Bangalore, India, Magnesium stearate from Hetero labs, Hyderabad, Talc from Merck Specialities Pvt Ltd, Mumbai, India.

METHODOLOGY

Analytical method development:

Determination of Calibration Curve:

10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1ml was pipette out into 10ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution required concentrations were prepared (shown in Table 8.1 and 8.2) and those concentrations absorbance were found out at required wavelength.

Preformulation parameters

The quality of tablet, once formulated by rule, is generally dictated by thequality of physic chemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Table: Angle of Repose values (as per USP)

Angle of Repose	Nature of Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Verypoor

Table: Carr's index value(as per USP)

Carr'sindex	Properties
5–15	Excellent
12–16	Good
18–21	FairtoPassable
2–35	Poor
33–38	VeryPoor
>40	VeryVeryPoor

Formulation development of Tablets:

All the formulations were prepared by direct compression. The compositions of different formulations are given in Table 7.3.The tablets were prepared as per the procedure given below and aim is to prolong the release of Lovastatin. Total weight of the tablet was considered as100mg.

Procedure:

1) Lovastatin and all other ingredients were individually passed through sieve no 60.

2) All the ingredients were mixed thoroughly by triturating upto15min.

3) The powder mixture was lubricated with talc.

4) The tablets were prepared by using direct compression method.

Table: Formulation composition for tablets

INGREDIENTS	FORMULATION CHART											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Lovastatin	10	10	10	10	10	10	10	10	10	10	10	10
GumAcacia	5	10	15	20	-	-	-	-	-	-	-	-
Almondgum	-	-	-	-	5	10	15	20	-	-	-	-
Grewiagum	-	-	-	-	-	-	-	-	5	10	15	20
Lactose	74	69	64	59	74	69	64	59	74	69	64	59
Magnesiumstearate	6	6	6	6	6	6	6	6	6	6	6	6
Talc	5	5	5	5	5	5	5	5	5	5	5	5
TotalWeight	100	100	100	100	100	100	100	100	100	100	100	100

EvaluationofpostcompressionparametersforpreparedTabletsTable:Pharmacopoeialspecificationsfortabletweightvariation

Average weight of tablet(mg)(I.P)	Average weight of tablet (mg)(U.S.P)	Maximum percentage difference allowed
Lessthan80	Lessthan130	10
80-250	130-324	7.5
More than	More than 324	5

In vitro drug release studies

Procedure:

900ml of 0.1 HCl was placed in vessel and the USP apparatus–II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°c + 0.5°c. Tablet was placed in the vessel and apparatus was operated for 2hours and then the media 0.1N HCl were removed and pH 6.8 phosphate buffer was Added process was continued up to 12hrs at 50rpm. At definite time intervals withdrawn 5ml of sample, filtered and again 5ml media was replaced. Suitable dilutions were done with media and analyzed by spectro photometrically at required wavelength using UV-spectrophotometer.

RESULTS AND DISCUSSION

Analytical Method

Table: Observations for graph of Lovastatinin 0.1N HCl (238nm)

Conc [µg/ml]	Absorbance
0	0
5	0.148
10	0.274
15	0.386
20	0.511
25	0.647

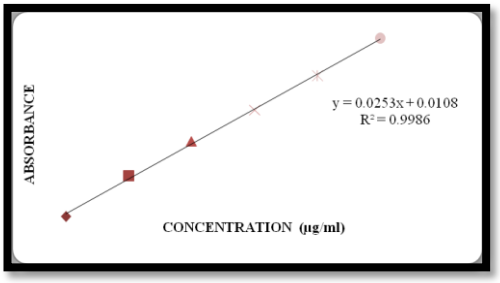

Figure: Standard graph of Lovastatin in 0.1N HCl

Table: Observations for graph of Lovastatinin pH 6.8 phosphate buffer (242nm)

Concentration [µg/ml]	Absorbance
0	0
5	0.128
10	0.254
15	0.372
20	0.482
25	0.597

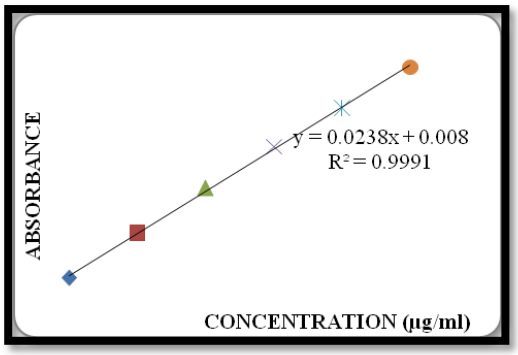

Figure: Standard graph of Lovastatin pH 6.8 phosphate buffer (242nm) Pre-formulation parameters of powder blend

Table: Pre-formulation parameters of Core blend

Formulation Code	Angle of Repose	Bulk density(gm/ml)	Tapped density(gm/ml)	Carr's index(%)	Hausner's Ratio
F1	35.24±0.07	0.525±0.11	0.619±0.02	15.32±0.09	1.197±0.07
F2	36.27±0.06	0.522±0.34	0.621±0.04	14.87±0.35	1.185±0.06
F3	34.65±0.08	0.526±0.65	0.614±0.01	15.62±0.72	1.187±0.13
F4	33.54±0.04	0.522±0.25	0.615±0.04	15.64±0.26	1.175±0.02
F5	32.21±0.01	0.516±0.24	0.622±0.05	14.96±0.15	1.186±0.03
F6	39.23±0.01	0.527±0.45	0.618±0.01	16.53±1.6	1.198±0.21
F7	31.10±0.02	0.522±0.36	0.623±0.02	14.56±0.20	1.170±0.01
F8	32.19±0.02	0.525±0.99	0.611±0.01	14.91±0.33	1.175±0.03
F9	33.28±0.01	0.517±1.05	0.617±0.03	15.66±0.10	1.185±0.15
F10	30.86±0.03	0.518±0.25	0.613±0.02	15.35±0.3	1.18±0.01
F11	31.24±0.04	0.523±0.45	0.612±0.01	14.95±0.66	1.17±0.02
F12	30.48±0.02	0.515±1.47	0.610±0.01	15.57±1.4	1.18±0.01

In-vitro quality control parameters for tablets

Formulation codes	Average Weight(mg)	Hardness (kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content(%)
F1	98.12	4.2	0.19	2.36	98.15
F2	97.64	4.9	0.24	2.64	97.36
F3	100.0	4.6	0.72	2.19	99.12
F4	99.86	4.3	0.48	2.85	96.49
F5	95.69	4.8	0.34	2.41	99.86
F6	98.34	4.1	0.52	2.75	99.0
F7	99.28	4.6	0.64	2.39	95.98
F8	97.99	4.9	0.38	2.54	98.34
F9	98.67	4.2	0.28	2.84	97.22
F10	99.33	4.7	0.35	2.16	99.64
F11	97.21	4.6	0.46	2.57	97.85
F12	99.36	4.8	0.61	2.79	98.14

In-Vitro Drug Release Studies

TIME (hr)	CUMULATIVE PERCENT DRUG RELEASE											
	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	7.23	8.13	9.65	8.98	9.21	9.28	9.22	9.54	22.82	12.66	10.30	15.54
1	15.61	15.81	19.76	13.57	15.98	13.40	17.97	13.28	33.69	17.28	18.93	24.28
2	19.59	21.32	26.32	19.58	18.98	19.75	28.22	24.26	37.36	25.15	22.66	32.47
3	28.12	25.61	38.76	26.57	29.85	26.05	37.35	36.62	42.74	30.55	38.31	38.59
4	38.45	34.15	46.83	38.69	40.51	30.58	44.10	42.72	48.55	39.47	42.69	47.26
5	50.61	39.29	57.24	45.97	52.28	36.57	53.34	50.73	56.78	52.82	55.74	54.12
6	56.18	52.84	68.12	57.62	59.84	40.04	62.23	62.48	63.12	58.83	59.98	59.63
7	68.92	63.26	71.25	65.48	68.87	47.96	68.76	68.29	67.81	66.02	65.82	66.81
8	73.29	74.82	75.91	68.74	73.11	58.45	73.38	73.68	72.68	72.52	74.21	72.27
9	82.72	79.81	81.96	71.38	81.29	66.11	79.45	82.30	78.35	76.91	78.84	78.44
10	86.24	84.96	83.29	75.35	87.74	72.74	84.56	87.74	81.43	83.11	81.23	83.11
11	90.17	88.21	97.13	79.42	91.66	80.04	88.15	90.19	88.97	89.24	86.52	88.75
12	95.54	91.55		85.75	94.56	84.74	90.12	97.56	98.82	94.23	91.76	90.81

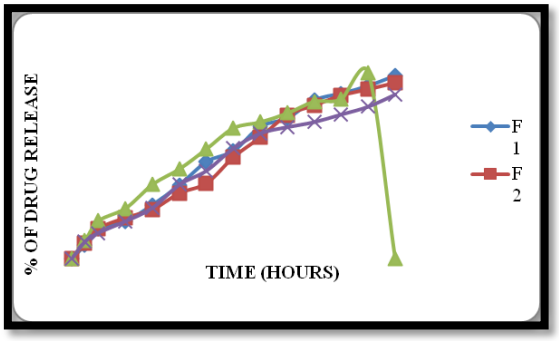

Fig: Dissolution profile of Lovastatin (F1, F2, F3, F4 formulations)

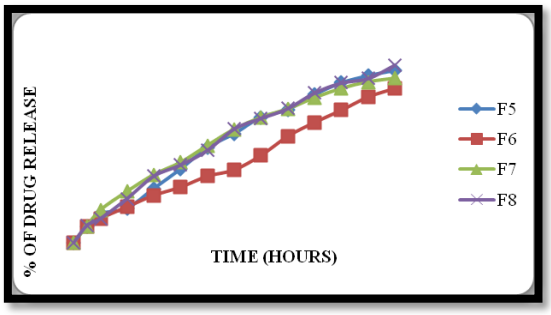

Fig: Dissolution profile of Lovastatin (F5 , F6, F7, F8 formulations)

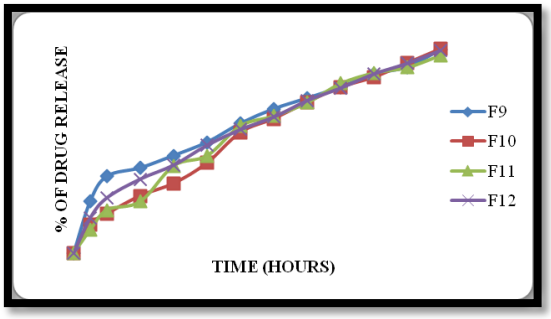

Fig: Dissolution profile of Lovastatin (F9, F10, F11, F12 formulations)

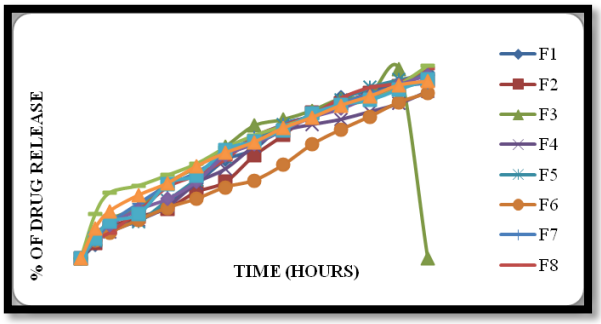

Fig: Dissolution profile of Lovastatin (F1-F12 formulations)

Table: Release kinetics data for optimized formulation

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG(%) REMAIN	RELEASERATE (CUMULATIVE %RELEASE/ t)	1/CUM %RELEASE	PEPPAS logQ/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
22.82	0.5	0.707	1.358	-0.301	1.888	45.640	0.0438	-0.642	77.18	4.642	4.258	0.384
33.69	1	1.000	1.528	0.000	1.822	33.690	0.0297	-0.472	66.31	4.642	4.048	0.594
37.36	2	1.414	1.572	0.301	1.797	18.680	0.0268	-0.428	62.64	4.642	3.971	0.670
42.74	3	1.732	1.631	0.477	1.758	14.247	0.0234	-0.369	57.26	4.642	3.854	0.787
48.55	4	2.000	1.686	0.602	1.711	12.138	0.0206	-0.314	51.45	4.642	3.719	0.922
56.78	5	2.236	1.754	0.699	1.636	11.356	0.0176	-0.246	43.22	4.642	3.509	1.132
63.12	6	2.449	1.800	0.778	1.567	10.520	0.0158	-0.200	36.88	4.642	3.329	1.313
67.81	7	2.646	1.831	0.845	1.508	9.687	0.0147	-0.169	32.19	4.642	3.181	1.461
72.68	8	2.828	1.861	0.903	1.436	9.085	0.0138	-0.139	27.32	4.642	3.012	1.630
78.35	9	3.000	1.894	0.954	1.335	8.706	0.0128	-0.106	21.65	4.642	2.787	1.854
81.43	10	3.162	1.911	1.000	1.269	8.143	0.0123	-0.089	18.57	4.642	2.648	1.993
88.97	11	3.317	1.949	1.041	1.043	8.088	FALSE	-0.051	11.03	4.642	2.226	2.416
98.82	12	3.464	1.995	1.079	0.072	8.235	FALSE	-0.005	1.18	4.642	1.057	3.585

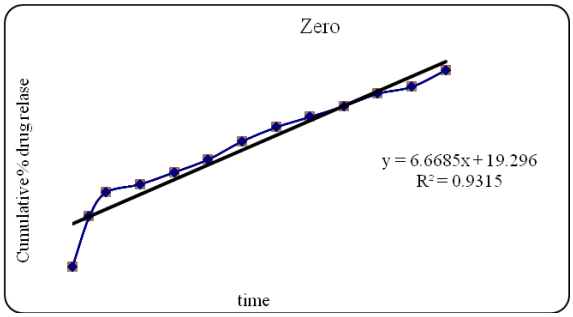

Fig: Zero order release kinetics graph

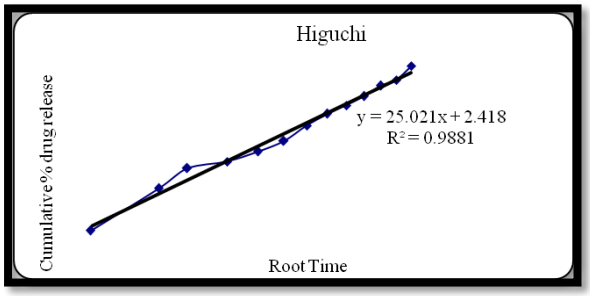

Fig: Higuchi release kinetics graph

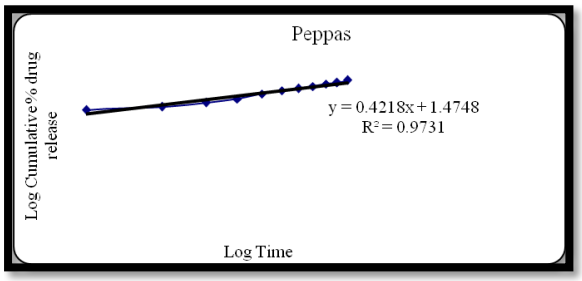

Fig: Karsmayerpeppas graph

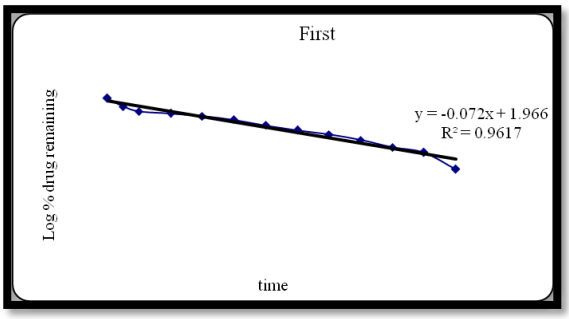

Fig: First order release kineticsgraph

Table: kinetics Correlation coefficient values

ReleaseKinetics	Correlationcoefficientvalues
Zeroorderreleasekinetics	R^2=0.931
Higuchireleasekinetics	R^2=0.988
Peppasreleasekinetics	R^2=0.973
Firstorderreleasekinetics	R^2=0.961

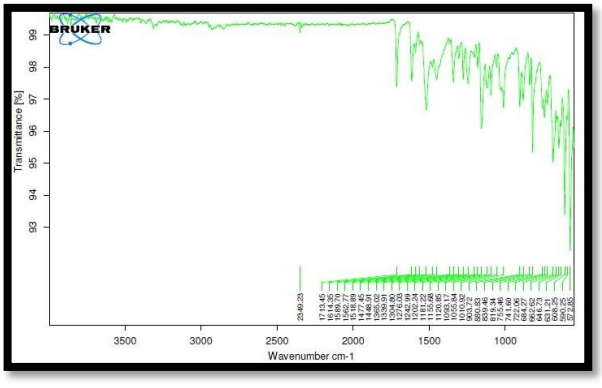

Figure: FT-TR Spectrum of Lovastatin pure drug

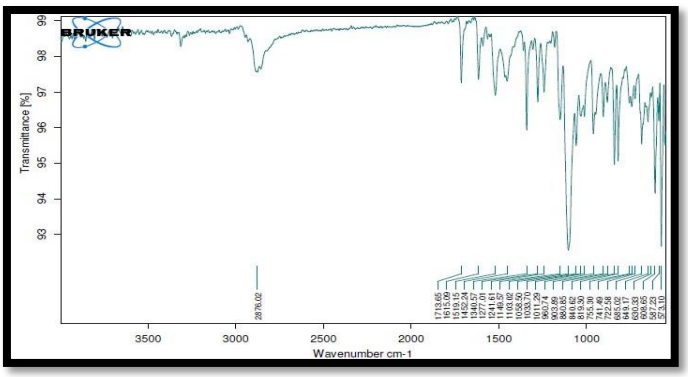

Figure: FT-IR Spectrum of Optimised Formulation

CONCLUSION

The present study was carried out on Lovastatin. It has half life about 5.3hrs. The main aim of this study is to extend the drug release up to 12 hrs. Drug wavelength and calibration curve was developed in 0.1NHCl and pH6.8 Phosphate buffer.

The drug and excipient compatibility studies were shown good compatibility between drug and excipients.Tablet powder blend was subjected to various pre-formulation parameters indicating the powder has good flow properties.

Post compression studies like Weight variation, Hardness, thickness, friability, drug content was determined. The average weight of the tablet is approximately in range of 95.69 to 100.0 mg, so the permissible limit is ± 5.0%. The results showed that the hardness of the tablets is in range of 4.1 to 4.9 kg/cm2, which was within IP limits. The result showed that thickness of the tablet is raging from 2.16 to 2.85mm. The average friability of all the formulations was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets. From the drug content studies it was concluded that all the formulations were showing the %drug content values within 95.98-99.0%.

From the dissolution data it was evident that the formulations prepared with Gum Acacia as polymer were unable to retard the drug release up to desired time period i.e.,12hours.Formulations prepared with Almond gum retarded the drug release in the concentration of 20mg (F8 Formulation) showed required release pattern i.e., retarded the drug release up to12 hours and showed maximum of 97.56% in 12hours with good retardation. Grewia gum was 5mg (F9 Formulation) showed required release pattern i.e., retarded the drug release upto 12 hours and showed maximum of 98.82% in 12hours with good retardation. Finally concluded that F9 formulation contains Grewia gum was optimized formulation.

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