ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research

Vol. 17, Issue, 01, pp.31538-31543, January, 2025
DOI: https://doi.org/10.24941/ijcr.48357.01.2025

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

RESEARCH ARTICLE

FORMULATION DEVELOPMENT AND IN VITRO CHARACTERIZATION OF DOLUTEGRAVIR SUSTAINED RELEASE MATRIX TABLETS

Munija Pancheddula[1], Kavvam Nikitha[2], KarankotLakshmi Durga[3] and Sandya Rani Deekonda*

*Assistant Professor, Department of Pharmaceutics, Vision College of Pharmaceutical Sciences and Research, Boduppal, Hyderabad; [1]Vice Principal, Vision College of Pharmaceutical Sciences and Research, Boduppal, Hyderabad; [2,3]Student, Pharm D IV Year, Vision College of Pharmaceutical Sciences and Research, Boduppal, Hyderabad

ARTICLE INFO

Article History:
Received 20th October, 2024
Received in revised form
17th November, 2024
Accepted 24th December, 2024
Published online 31st January, 2025

Key Words:

Dolutegravir, Natural Polymers, Direct Compression, Tragacanth, Acacia Gum, Xanthan Gum and Sustained Release tablets.

***Corresponding author:* Dr. Subbiah, M.**

ABSTRACT

Sustained-release tablets are designed to release their active ingredients gradually over an extended period, providing a prolonged therapeutic effect. They are formulated to control the rate and duration of drug release, often resulting in less frequent dosing compared to immediate-release tablets.In the present work, of the drug Dolutegravir by using natural polymers Tragacanth, Acacia gum, Xanthan gum as retarding an attempt has been made to develop Sustained release tablets polymers.All the formulations which are discussed were prepared by direct compression method. The blend of all the formulations have shown good flow properties like angle of repose, bulk density, tapped density.The prepared tablets have shown good post compression parameters and passed all the quality control evaluation parameters as per I.P limits. Among all the formulations F2 formulation showed maximum % drug release i.e., 99.19% in 12 hours hence it is considered as optimized formulation F2 which contains Tragacanth (100 mg). Optimized formulation F2 was Higuchi release kinetics mechanism[1].

Citation: Dr. Subbiah, M. 2025. "Formulation development and in vitro characterization of dolutegravir sustained release matrix tablets*". International Journal of Current Research*, 17, (02), 31538-31543.

INTRODUCTION

Sustained-release tablets are designed to release their active ingredients gradually over an extended period, providing a prolonged therapeutic effect. They are formulated to control the rate and duration of drug release, often resulting in less frequent dosing compared to immediate-release tablets. The extended-release nature of sustained-release tablets allows for less frequent dosing, contributing to improved patient adherence to the prescribed medication regimen. This not only enhances convenience but also helps maintain a more consistent therapeutic effect, contributing to better overall treatment outcomes.The primary objectives in designing sustained-release delivery systems include reducing dosing frequency, enhancing drug effectiveness through targeted localization, minimizing required doses, and achieving uniform drug delivery[5].

A sustained-release dosage form is designed to release one or more drugs continuously in a predetermined pattern over a fixed period, either systemically throughout the body or specifically to a targeted organ or site of action. Dolutegravir is an antiretroviral medication used in the treatment of HIV infection. It belongs to the class of integrase strand transfer inhibitors (INSTIs). Dolutegravir works by inhibiting the integrase enzyme, preventing the integration of the HIV virus into the DNA of human cells. It is often included in combination therapy with other antiretroviral drugs to effectively manage HIV and reduce the viral load in the body. The drug was first developed by ViiV Healthcare and FDA approved it on August 12,2013. The combination of Dolutegravir and Rilpivirine was approved on November 21 ,2017 for the treatment of HIV 1 in adults.

MATERIALS AND METHODOLOGY

Materials: Dolutegravir, Tragacanth, Acacia gum, Xanthan gum, PVP-K 30,Aerosil, Magnesium Stearate, Lactose (source - Provided by SURA LABS, Dilsukhnagar, Hyderabad,S.D. Fine Chemicals, India. Arvind Remedies (AR), Chennai, India).

Drug–excipient compatibility studies

Fourier transform infrared (FTIR) spectroscopy: The compatibility between the pure drug and excipients was detected by FTIR spectra obtained on Bruker FTIR Germany(Alpha T).The solid powder sample directly place on yellow crystal which was made up of Zn-Se. The spectra were recorded over the wave number of 4000 cm^{-1} to 400c.

Determination of λ max: 100 mg of the drug was weighed and dissolved in 10 ml of methanol. This becomes the primary stock solution (1000 µg/ml). From this stock solution, pipette out 1ml solution and transferred into a 100 ml volumetric flask and made up the volume up to 10 ml with the media (Secondary stock solution–100µg/ml). From this secondary stock solution, 1ml was taken into another volumetric flask and made it up to 10ml with media (working solution - 10µg/ml). The working solution was taken for determining the wavelength.

Determination of calibration curve: 100 mg of the drug was weighed and dissolved in 10 ml of methanol. This becomes the primary stock solution (1000 µg/ml). From this stock solution, pipette out 10 ml solution and transferred into a 100 ml volumetric flask and made up the volume up to 10 ml with the

media (Secondary stock solution–100µg/ml). From this secondary stock solution, required concentrations were prepared and their absorbance were found out at required wavelength.

Formulation development of Tablets: The tablets were all formulated by using a direct compression method. The compositions of different formulations were listed in the given table. The total weight of the tablets was considered as 300 mg.

Procedure

- Dolutegravir and all other ingredients were individually passed through sieve no ≠ 60.
- All the ingredients were mixed thoroughly by triturating up to 15 min.
- The powder mixture was lubricated with talc.
- The tablets were prepared by using a direct compression method.

Evaluation parameters

Preformulation parameters[12]:

Angle of repose: The frictional force in a loose powder can be measured by using angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane.

Tan θ = h / r

Tan θ = Angle of repose
h=height of the cone
r=radius of the base

Bulk density: Density is defined as weight per unit volume. Bulk density, is defined as themass of the powder divided by the bulk volume and is expressed as gm/cm^3.

The bulk density was calculated using the formula:

Bulk Density = M / V_o
Where, M = weight of sample

V_o = apparent volume of powder

Tapped density: After carrying out the procedure given in the measurement of bulk densitythe cylinder which contains the sample was tapped using a suitable mechanical tapped density tester that can provide 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit. The tapped density was calculated, in gm per L, using the formula:

Tap= M / V

Where,Tap= Tapped Density
M = Weight of sample
V= Tapped volume of powder

Measures of powder compressibility: The Compressibility Index (Carr's Index) is the measure of the propensity of a powder to be compressed. It can be determined from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

Carr's Index = [(tap - b) / tap] × 100
Where, b = Bulk Density
Tap = Tapped Density

Postformulation parameters[13]: The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight variation test: The weight variation test is a pharmaceutical quality control test performed to ensure the uniformity of dosage units, such as tablets or capsules, within a batch. It is a critical test to verify that each individual dosage unit contains the specified amount of active pharmaceutical ingredient (API) or drug substance.

% Deviation = (Individual weight – Average weight / Average weight) × 100

Hardness: Tablet hardness, also known as tablet crushing strength or tablet compression strength, is a critical parameter in pharmaceutical manufacturing. It measures the ability of a tablet to withstand mechanical stress or pressure. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

Thickness: Tablet thickness is an important parameter in pharmaceutical manufacturing, as it directly affects the size, appearance, and ease of handling of the tablets. The thickness of a tablet is measured as the distance between the two opposing faces or surfaces of the tablet.

Friability %: It is a quality control that measures the tendency of tablets to crumble or break during handling, transportation, and packaging. The friability test helps assess the mechanical strength and durability of tablets. Roche friabilator was used to determine the friability by following procedure. Pre weighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as
% Friability = [(W1-W2) / W] × 100

Where, W1 = Initial weight of three tablets
W2 = Weight of the three tablets after testing

Determination of drug content: Tablets were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of drug were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to volume with media. The solution was suitably diluted and the absorption was determined by UV–Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

***In vitro* drug release studies**

Dissolution parameters: Apparatus--USP-II, Paddle Method
Dissolution Medium -- 0.1 N HCl, p H 6.8 Phosphate buffer
RPM --50

Sampling intervals (hrs.)--0.5,1,2,3,4,5,6,7,8,9,10,11,12
Temperature--37°C $\pm$ 0.5°C

Procedure: 900ml 0f 0.1 H Cl was placed in the vessel and the USP apparatus–II (Paddle Method) was assembled. The medium was allowed to equilibrate to temperature of 37°c $\pm$ 0.5°c. Tablet was placed in the vessel and apparatus was operated for 2 hours and then the media 0.1 N HCl were removed and pH 6.8 phosphate buffer was added. The process was continued up to 12 hours at 50 rpm. At definite time intervals withdrawn 5 ml of

sample, filtered and again 5ml media was replaced. Suitable dilutions were done with media and analyzed spectrophotometrically at required wavelength using UV-spectrophotometer at 262.

RESULTS AND DISCUSSION

Drug – Excipient compatibility studies

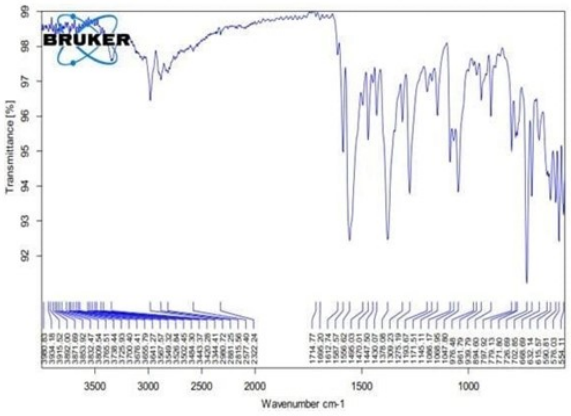


Figure 1. FT-IR Spectrum of Dolutegravir pure drug

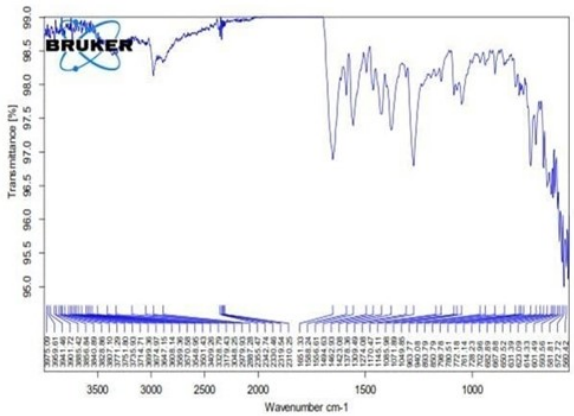
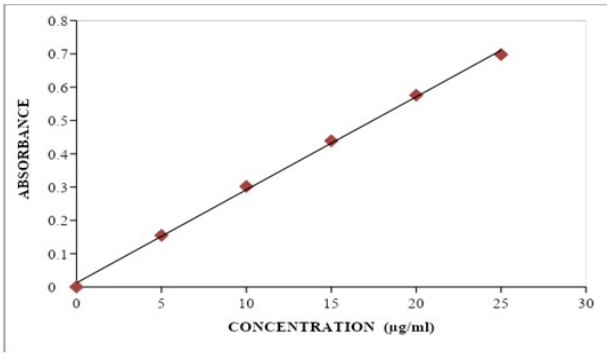
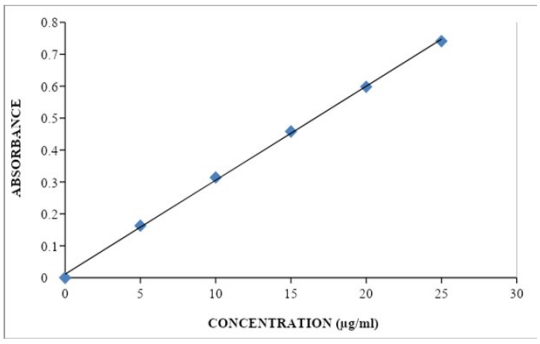


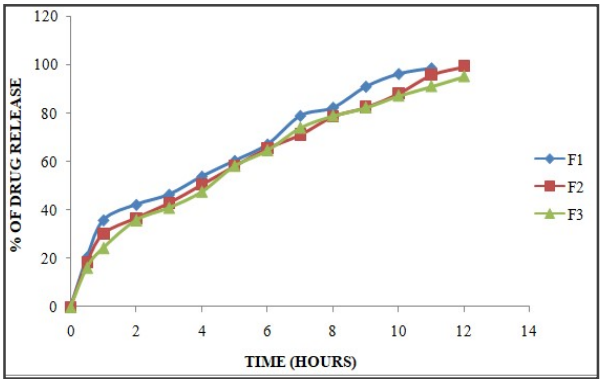
Figure 2. FT-IR Spectrum of Optimized Formulation



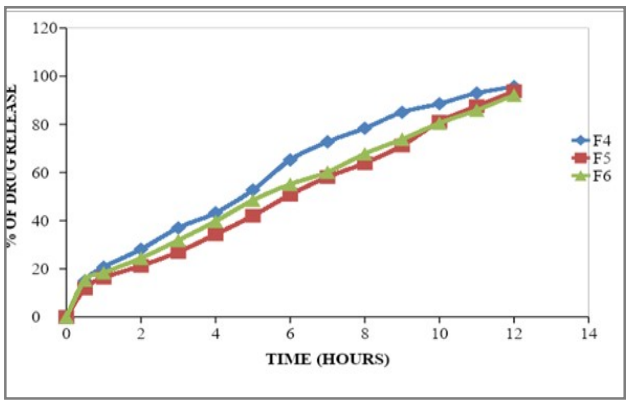
Graph 1. Standard curve of Dolutegravir



Graph 2. Standard curve of Dolutegravir



Graph 3. Dissolution profile of Dolutegravir (F1, F2 and F3 formulations)



Graph 4. Dissolution profile of Dolutegravir (F4, F5 and F6 formulations)

that the drug and excipients does not have any interactions. Hence, they were compatible.

Analytical method: Graphs of Dolutegravir were taken in 0.1N HCL and in pH 6.8 phosphate buffer at 259 nm and 263 nm respectively.

Preformulation parameters of powder blend: The compressibility index of all the formulations was found to be 10.11 to 11.34 which show that the powder has good flow properties.All the formulations have shown the Hausner ratio 1.11 to 1.14 indicating the powder has good flow properties.

Quality control parameters for tablets: Tablet quality control tests such as weight variation, hardness, friability, thickness, and drug release studies in different media were performed on the compression tablet.

Weight variation test: Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet. The average weight of the tablet is approximately in the range of 296.50 to 300.05 mg, so the permissible limit is ±7.5% (>300 mg). The results of the test showed that the tablet weights were within the limit.

Hardness test: Hardness of the five tablets of each batch was checked by using Pfizer hardness tester and the data were shown in Table. The results showed that the hardness of the tablets is in the range of 5.0 to 6.3 kg/cm^2,which was within IP li

Thickness: Thickness of five tablets of each batch was checked by using a Micrometer and data shown in Table. The result showed that the thickness of the tablet is ranging from 3.11 to 3.98 mm.

Table 1. Formulation composition for tablets

INGREDIENTS (MG)	FORMULATION								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Dolutegravir	50	50	50	50	50	50	50	50	50
Tragacanth	50	100	150	-	-	-	-	-	-
Acacia gum	-	-	-	50	100	150	-	-	-
Xanthan gum	-	-	-	-	-	-	50	100	150
PVP-K 30	10	10	10	10	10	10	10	10	10
Aerosil	5	5	5	5	5	5	5	5	5
Magnesium Stearate	4	4	4	4	4	4	4	4	4
Lactose	181	131	81	181	131	81	181	131	81
Total Weight	300	300	300	300	300	300	300	300	300

Table 2.Angle of repose values

Angle of Repose	Nature of Flow
<25	**Excellent**
25-30	Good
30-40	Passable
>40	Very poor

Table 3. Carr's index value (as per USP)

Carr's index	Properties
5 – 15	Excellent
12 – 16	Good
18 – 21	Fair to Passable
2 – 35	Poor
33 – 38	Very Poor
>40	Very Very Poor

Table 4. Pharmacopeial specifications for tablet weight variation

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

Table 5. Observations for graph of Dolutegravir in 0.1N HCL

Concentration (µg/ml)	Absorbance
0	0
5	0.155
10	0.302
15	0.439
20	0.576
25	0.698

Table 6. Standard graph values of Dolutegravir at 263 nm in pH 6.8 phosphate buffer

Concentration (µg/ml)	Absorbance
0	0
5	0.163
10	0.314
15	0.458
20	0.598
25	0.741

Table 7. Preformulation parameters of Core blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	25.56±0.3	0.57±0.01	0.61±0.01	10.11±0.8	1.13±0.02
F2	24.67±0.3	0.53±0.01	0.68±0.03	10.23±0.5	1.12±0.03
F3	25.56±0.2	0.52±0.06	0.64±0.03	10.34±1.0	1.14±0.06
F4	23.30±0.1	0.50±0.21	0.66±0.12	10.23±0.5	1.12±0.06
F5	22.56±0.1	0.65±0.02	0.59±0.02	11.23±0.8	1.11±0.05
F6	23.89±0.2	0.50±0.04	0.68±0.04	11.34±0.6	1.14±0.03
F7	26.54±0.1	0.59±0.04	0.64±0.05	10.12±0.7	1.13±0.09
F8	23.67±0.3	0.58±0.12	0.58±0.04	10.23±1.0	1.11±0.07
F9	24.34±0.4	0.56±0.02	0.54±0.01	10.23±0.8	1.13±0.02

All the values represent n=3

Table 8. Quality control parameters for tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (% loss)	Thickness (mm)	Drug content (%)
F1	299.85	5.1	0.58	3.21	98.12
F2	300.05	5.6	0.42	3.69	99.27
F3	297.61	5.8	0.36	3.47	100.00
F4	298.47	6.1	0.34	3.22	95.34
F5	299.83	5.0	0.29	3.98	96.87
F6	300.02	6.3	0.20	3.45	99.31
F7	299.87	5.0	0.41	3.28	97.24
F8	296.50	5.2	0.52	3.11	98.62
F9	299.75	5.8	0.44	3.72	95.40

Table 9. Dissolution data of Dolutegravir tablets F1-F9

Time (H)	% OF DRUG RELEASE								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	20.62	18.38	16.23	14.97	11.82	15.31	11.22	13.49	9.07
1	35.81	30.14	24.38	20.65	16.31	18.38	17.38	15.21	13.31
2	42.20	36.63	35.79	28.16	21.23	24.43	22.45	19.07	21.03
3	46.39	42.82	40.88	36.98	26.96	31.86	29.59	26.17	24.12
4	53.85	50.40	47.54	43.29	34.35	39.75	37.83	35.56	31.13
5	60.34	58.09	58.17	52.73	42.02	48.46	43.26	42.58	39.09
6	67.13	65.46	64.62	65.22	50.75	55.13	53.15	51.27	48.17
7	78.91	71.02	73.93	72.73	58.13	60.16	61.29	59.68	55.24
8	82.28	78.59	78.87	78.40	63.84	67.77	66.76	67.37	64.36
9	90.96	82.36	82.26	85.01	71.22	73.85	73.27	71.77	68.81
10	96.21	88.11	87.15	88.58	81.09	80.49	78.19	77.42	75.63
11	98.56	95.78	91.02	92.96	87.56	85.88	84.64	82.12	79.43

Table 10. Release kinetics

Cumulative (%) release q	Time (t)	root (t)	log (%) release	log (t)	log (%) remain	release rate (cumulative % release / t)	1/cum% release	Peppas log q/100	% drug remaining	Q01/3	Qt1/3	Q01/3-qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
18.38	0.5	0.707	1.264	-0.301	1.912	36.760	0.0544	-0.736	81.62	4.642	4.338	0.304
30.14	1	1.000	1.479	0.000	1.844	30.140	0.0332	-0.521	69.86	4.642	4.119	0.523
36.63	2	1.414	1.564	0.301	1.802	18.315	0.0273	-0.436	63.37	4.642	3.987	0.655
42.82	3	1.732	1.632	0.477	1.757	14.273	0.0234	-0.368	57.18	4.642	3.853	0.789
50.4	4	2.000	1.702	0.602	1.695	12.600	0.0198	-0.298	49.6	4.642	3.674	0.967
58.09	5	2.236	1.764	0.699	1.622	11.618	0.0172	-0.236	41.91	4.642	3.474	1.168
65.46	6	2.449	1.816	0.778	1.538	10.910	0.0153	-0.184	34.54	4.642	3.257	1.385
71.02	7	2.646	1.851	0.845	1.462	10.146	0.0141	-0.149	28.98	4.642	3.072	1.570
78.59	8	2.828	1.895	0.903	1.331	9.824	0.0127	-0.105	21.41	4.642	2.777	1.865
82.36	9	3.000	1.916	0.954	1.246	9.151	0.0121	-0.084	17.64	4.642	2.603	2.038
88.11	10	3.162	1.945	1.000	1.075	8.811	0.0113	-0.055	11.89	4.642	2.282	2.359
95.78	11	3.317	1.981	1.041	0.625	8.707	0.0104	-0.019	4.22	4.642	1.616	3.026
99.19	12	3.464	1.996	1.079	-0.092	8.266	0.0101	-0.004	0.81	4.642	0.932	3.709

Friability: Tablets of each batch were evaluated for percentage friability and the data were shown in the Table. 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 above studies it was found that there was no shifting in the major peaks which indicated that there were no significant interactions occurred between the Dolutegravir and excipients used in the preparation of different Dolutegravir Sustained release formulations. Therefore, the drug and excipients are compatible to form stable. Formulations under study, The FTIR spectra of Dolutegravir and physical mixture used for optimized formulation were obtained and these are depicted in above figures. From the FTIR data it was evident

Drug content: Drug content studies were performed for the prepared formulations. From the drug content studies it was concluded that all the formulations were showing the % drug content values within 95.40 – 100.00 %. All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits

***IN VITRO* DRUG RELEASE STUDIES**

Different formulations (F1-F9) were prepared using different polymers like Tragacanth, Acacia gum and Xanthan gum alone at different ratios. Formulations F1-I3 were prepared using Tragacanth at the ratio of 1:1, 1:2 and 1:3 which showed the drug release about 98.56% at 11h, 99.19% at 12h and 95.14 at 12h %. Formulations F4-F6 were prepared using Acacia gum at the ratio of 1:1, 1:2 and 1:3 with the drug release of 95.63%, 93.75 and 92.16 % and the formulations F7-F9 were prepared by using Xanthan gum polymer at the ratio of 1:1, 1:2 and 1:3 Showed the drug release of 95.49 %, 89.28 % and 87.19 % at the end of 12 h. Among all these formulations F2 was selected as the best ideal formulation which exhibited 99.19 % of drug release in 12 h. Finally Concluded that F2 formulation was considered as optimized formulation.

CONCLUSION

The present study was carried out to evaluate the natural polymers for its matrix forming ability due to formation of thick gel structure, so we concluded that Tragacanth, Acacia gum and Xanthan gum formulated tablets were found to be effective in sustaining the drug release up to12 hrs. During this study, it was also found that polymer concentration influences the drug release behavior. Drug Excipient Compatibility studies revealed that there was no considerable change. FT-IR studies resulted that all peaks

corresponding to different functional groups of pure drugs were present in the drug-excipient mixture no interaction between the drug and excipients.It can be concluded that stable formulation could be developed by incorporating Tragacanth polymer in a definite proportion, so that the sustained released profile is maintained for a sustained release. Release model of sample was found to follow Higuchi release kinetics mechanism with high linearity.

ACKNOWLEDGEMENT

We express our best gratitude to the management of vision college of pharmaceutical sciences and research for the support, guidance and valuable suggestions of my research work.

Glossary of Abbreviations

1. Active Pharmaceutical Ingredient (API)
2. DNA (Deoxyribonucleic Acid)
3. FDA (Food and Drug Administration)
4. Fourier Transform Infrared (FTIR) Spectroscopy
5. HCl (Hydrochloric Acid)
6. h/r (hours per rate)
7. HIV (Human Immunodeficiency Virus)
8. IP (Indian Pharmacopoeia)
9. Mg (Milligram)
10. mm (Millimetre)
11. µg/ml (Microgram per millilitre)
12. ml (Millilitre)
13. Mg (Milligram)
14. PVP-K 30 (Polyvinylpyrrolidone K-30)
15. RPM (Revolutions per minute)
16. USP (United States Pharmacopeia)
17. % (Percentage)
18. kg/cm (Kilogram per centimetre)
19. Nm (Nanometre)
20. gm/ml (Gram per millilitre)

REFERENCES

Altaf AS, Friend DR, MASRx and COSRx. Sustained-Release Technology in Rathbone MJ, Hadgraft J, Robert MS,Modified Release Drug Delivery Technology, Marcell Dekker Inc., New York, 2003; 1: 102-117.

Reddy KR., Mutalik S, Reddy S. AAPS Pharm. Sci. Tech.2003; 4: 19. 121-125.

Mohammed AD et al. Release of propranolol hydrochloride from matrix tablets containing sodium carboxymethylcellulose and Hydroxypropyl methyl cellulose. Pharm Dev Tech.1999; 4: 313-324.

Salsa T, Veiga F. Drug Develop. Ind Pharm. 1997; 23: 931.

Jantzen GM, Robinson JR, Sustained and controlled-release drug delivery systems, inBanker GS, Rhodes CT (Eds.) Modern Pharmaceutics, 3 rd Ed, Revised and Expanded, Drugs and the Pharmaceutical Sciences., Marcel Dekker, Inc. NewYork. 1995; 72: 575-609.

Jantzen GM, Robinson JR. Sustained and Controlled- Release Drug Delivery systems Modern Pharmaceutics, 4 th ed; 2003; 121: 501-502.

Lee BJ, Ryu SG, Cui JH, Drug Dev. Ind.Pharm.1999; 25: 493-501.

Gwen MJ, Joseph RR, In Banker GS and Rhodes CT, Ed. Modern Pharmaceutics, 3 rd Ed Marcel Dekker Inc. New York. 1996; 72: 575.

Vidyadhara S, Rao PR, Prasad JA. Indian J Pharm Sci. 2004; 66: 188-192.

Bogner RH. Bioavailability and bioequivalence of extended-release oral dosage forms. US Pharmacist. 1997; 22: 3–12.

Rogers JD, Kwan KC. Pharmacokinetic requirements for controlled-release dosage forms. In: John Urquhart, ed. Controlled-release Pharmaceuticals. Academy of Pharmaceutical Sciences. American Pharmaceutical Association. 1979: 95–119.

Madan PL. Sustained-release drug delivery systems, part II: Preformulation considerations. Pharm Manu fact. 1985; 2: 41–45.

Wani MS, Controlled Release System-A Review, 2008; 6 1: 56-62.

****