International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2020): 7.803

Formulation and Evaluation of Vaginal Disintegrating Tablet for HIV of Dolutegravir

Bhopale. P. R [1*], Patil. P. B[2], Bachav. R. S[3]

[1*]Department of Pharmaceutics, R. G. Sapkal College of Pharmacy, Anjaneri, Nashik - 422213, Maharashtra, India.

[2]Department of Pharmaceutics, R. G. Sapkal College of Pharmacy, Anjaneri, Nashik - 422213, Maharashtra, India.

[3]Department of Pharmacology, R. G. Sapkal College of Pharmacy, Anjaneri, Nashik - 422213, Maharashtra, India.

E- Mail Id: *pragatibhopale18[at]gmail.com*

Abstract: ***Intra - vaginal route of administration is a route of administration where the dosage form is applied vaginally for the convenient release of the dosage form and for better therapeutic action of the medicament, it is usually used in HIV patients. Vaginal route is been used as a traditional delivery system used for the conventional delivery of several locally acting drugs like antimicrobial agents. The various types of formulations as well as the dosage forms are available for intra - vaginal drug delivery system such as tablets gels vaginal rings etc. the disease's such as HIV or other diseases caused into the vaginal area due to causative agents like bacteria fungi etc. For efficient vaginal delivery of drugs, the delivery system should reside at the site of infection for a prolonged period of time. dolutegravir vaginal tablets were evaluated for various parameters like thickness (mm), Hardness (kg/cm2), Average weight (mg), % Drug Content,, % Friability, Effect on pH of medium, disintegration study, in - vitro release study and data treatment thereof. All the physical parameters were found to be satisfactory within the specified limits.***

1. Introduction

- The vagina is an important application site for drug delivery, especially for local therapy of different diseases, such as bacterial, fungal and protozoa infections, for HIV prevention. Although the vaginal tissue is referred to as mucosal, the vagina does not have secretory glands. However, a mixture of fluids originating from a number of different sources comprises a moist film coating the vaginal surface. In order to maintain high patient compliance and adherence to therapy, the dosage forms or delivery systems should also be easy to administer and not cause discomfort or irritation. It should provide high efficiency based on an even distribution and long retention time of the drug in the vagina. . Different types of conventional dosage form, such as creams, gels, ointments and tablets, have been investigated for vaginal drug delivery.
- Solid formulations have the advantage of high dose accuracy and long term stability, as compared to semi - solid systems. The main aim of these study was to prepare and evaluate the the solid dosage form in the form of tablets as the the disintegrating tablet for the vaginal route for treating the desease called HIV.
- Infection of HIV is an incurable disease. The higest rate of chances of HIV infection is through the vaginal route during the sexual intercourse.
- At present the use of antiretroviral treatment reduces the rate of mortality and morbidity too.
- In contrast the scientific knowledge regarding the possibilities of drug delivery via the vagina is limited. To date, there are only a limited number of vaginal dosage forms available, although various possibilities are presently being explored.
- The conventional drug delivery systems (e. g. pessaries, foams, creams, gels and tablets) have some limitations such as leakage, messiness and low residence time, which contribute to poor subject or patient compliance. Considerable progress has been made over the last ten years in investigating and developing novel vaginal drug delivery systems with desirable distribution, bioadhesion, retention and release characteristics. Attempts are being made to develop novel vaginal drug delivery systems that can meet the clinical as well as the patient's requirements

2. Material and Method

Material

S.No	Ingradients	Category
1	DOLUTIGRAVIR	Active Pharmaceutical Ingredients
2	Sodium Starch Glycolte	Super Disintegrant
3	Crosscarmellose Sodium	Super Disintegrant
4	Lactose Monohydrate	Binder
5	Magnesium Stearate	Lubricant
6	Talc	Binder

Preparation of Benzydamine Bioadhesive Vaginal Tablets
Preparation of Benzydamine Bioadhesive Vaginal Tablets

Preparation of Benzydamine Bioadhesive Vaginal Tablets
Preparation of Benzydamine Bioadhesive Vaginal Tablets

Preparation methods of dolutegravir tablets

Preparation of Powder Blend

Powder blend were prepared for the preparation of matrix tablet by direct compression method. All the ingredients were weighed accurately and mixed by passing through 60# sieve. Mixing was again done by spatulation & tumbling in glass morter and pestle. Each tablet contains 50mg DOLUTEGRAVIR and has an approximate weight of 150 mg.

Compression of Powder Blend

The compression of powder blend was done by direct compression method. The compression was carried out using 8 mm flat - faced circular punches on rotary compression machine (Rimek, Minipress - 1 - Karnavati.). Various ingredients and quantities used are as shown in the Table 1

Evaluation of Dolutegravir Disintegrating Tablets

Preformulation Study of Drug:

Preformulation testing is the first stepin the rational development of dosage formsof a drug. It can be defined as an investigationof physical and chemical properties of drugsubstance, alone and when combined withexcipients. The overall objective ofpreformulation testing is to generateinformation useful to the formulator indeveloping stable and bioavailable dosageforms, which can be mass - produced

Identification Tests

a) Organoleptic Properties:

The sample of Clopidogrel was studied for organoleptic characteristics such as colour, odour and appearance.

b) Melting Point:

Melting point of Clopidogrel was determined by taking a small amount of sample in a capillary tube closed at one end and placed in melting point apparatus. The melting point was noted in triplicate and average value was noted.

c) IR Spectroscopy

The FT - IR spectrum of the obtained sample of drug was compared with the standard FT - IR spectra of the pure drug.

d) Solubility analysis:

Preformulation solubility analysis was done to select a suitable solvent system to dissolve the drug and also to test its solubility in the dissolution medium which was to be used.

e) Differential Scanning Calorimetry:

The powdered sample (3 mg) was hermetically sealed in aluminium pans and heated at a constant rate 10^0C/min, over a temperature range of 30 - 300^0C with nitrogen flow rate of 30ml/min. Thermograms of the samples were obtained using differential scanning Calorimetry (DSC - 60, Shimadzu, Japan). Thermal analysis data were recorded with Shimadzu software programs. Indian standard was to calibrate the DSC temperature and enthalpy scale.

Compatibility studies

a) *IR Spectroscopy*

Compatibility study was carried out by using Fourier Transform Infrared Spectrophotometer (BRUCKER). IR study was carried on pure drug. Physical mixture of drug and excipients were prepared and samples kept for 1 month at 40^0C. The infrared absorption spectrum of Clopidogrel and physical mixture of drug and excipient was recorded using diamond disc.

b) Preparation of Standard Calibration curve of Dolutigravir

The UV spectrum of dolutegravir was obtained by using UV (Shimadzu UV - 1800, Japan). Accurately weighed 10 mg of the drug was dissolved in sufficient quantity of methanol and volume made up to 10 ml. The stock solution was diluted to obtain a concentration of 100 µg/ml.1 ml of aliquot was withdrawn and volume was made up to 10 ml using methanol to obtain the concentration of 10 µg/ml. The resultant solution was scanned from 400 to 200 nm and the spectrum was recorded to obtain the value of maximum Wavelength in respective solvents.

Evaluation of powder

The flow properties of granules (before compression) were characterized in terms of angle of repose, tapped density, bulk density, Carr's index and Hausner's ratio

Table 1: Formulation Chart of dolutegravir vaginal disintegrating tablet for HIV

Ingredients	Formulation code								
Quantity (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Dolutigravir	50	50	50	50	50	50	50	50	50
SSG	20	30	40	20	30	40	20	30	40
Croscarmellose sodium	10	15	20	10	15	20	10	15	20
lactose	25	25	25	25	25	25	25	25	25
Magnesium stearate	25	20	10	25	20	10	25	20	10
Talc	20	10	5	20	10	5	20	10	5
Total Weight	150	150	150	150	150	150	150	150	150

***In - vitro* Disintegration Time:**

Disintegration time was determined using USP disintegration apparatus withphosphate buffer. The volume of medium was 900 ml and temperature was 37 ± 0.2^0C. The time in minutes taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured. To comply the test all tablets should disintegrate within 2 - 3 minutes.

Drug Content:

Units were selected at random and drug content was determined as specified in monograph. The tablet preparation complies with the test, only if each individual content lies between 85 to 115% of the average content.

***In Vitro* drug release kinetics studies**

Kinetic model had described drug dissolution from solid dosage form where the dissolved amount of drug is a function of test time. In order to study the exact mechanism of drug release from the tablets, drug release data was analyzed according to zero orders, first order, Higuchi square root, korsmeyer peppas model.

3. Result and Discussion

Compatibility study by IR spectroscopy

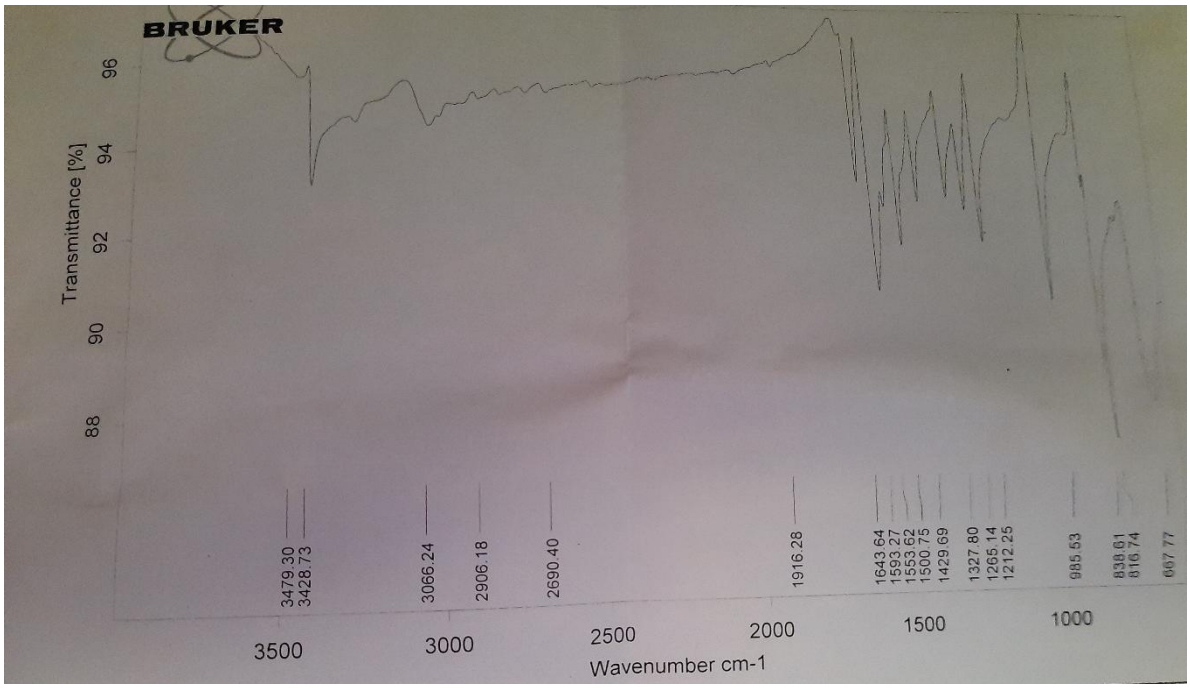

Figure 1: FTIR Spectrum of dolutegravir

The FTIR spectra of pure Clopidogrel showed the peaks at wave numbers (cm^{-1}) which correspond to the functional groups present in the structure of the drug.

Evaluation of Formulation:
The dolutigravir tablets were prepared by direct compression method. Ingredients were accurately weighed and passed through mesh. The powder blend was studied for rheological characteristics. The uniformly blend of powder was then compressed in a 10 station tablet punching machine using 8 mm flat faced punches

Before compression powder bed of all formulations were studied for various rheological characteristics bulk density, true density, compressibility index, Hausner's ratio. The results of the studies indicated that the powder bed is easily compressible, and hence can be compressed into a compact mass of tablets. The angle of repose is an indicative parameter of powder Flowability from hopper to die cavity.

A repose angle between 25^0 to 30^0 indicates excellent Flowability of powder bed. In this work, the angle of repose was found to be varying between 22.81^0 and 26.72^0 when glidants were incorporated. These studies indicated that, the powder beds of all formulations are easily flowable.

Evaluation of Pre - compressed parameters:
All formulations were studied for various rheological characteristics bulk density, true density, compressibility index, Hausner's ratio and angle of repose. The results of the studies indicated that the powder is blend is easily compressible.

Table 3: Pre - Compressed Evaluations

Formulation code	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of Repose (θ)	Compressibility index (%)	Hausner's ratio
F1	0.383±0.0032	0.442±0.0026	38.60±0.63	15.27±0.11	1.18±0.015
F2	0.374±0.0032	0.435±0.0026	30.90±0.57	14.01±0.10	1.16±0.005
F3	0.365±0.0035	0.412±0.0098	26.57±0.50	9.23±0.69	1.10±0.008
F4	0.352±0.0040	0.425±0.0042	30.90±0.56	11.02±0.55	1.12±0.006
F5	0.379±0.0022	0.416±0.0043	30.90±0.61	13.38±0.72	1.15±0.009
F6	0.376±0.0021	0.441±0.0049	33.47±0.54	12.03±0.24	1.13±0.003
F7	0.380±0.0036	0.442±0.0060	34.21±0.37	17.13±0.46	1.20±0.006
F8	0.361±0.0015	0.442±0.0060	30.90±0.52	14.80±0.16	1.17±0.024
F9	0.387±0.0037	0.456±0.0025	34.90±0.42	13.91±0.13	1.16±0.018

Evaluation of Post Compressed Characteristics:
The results of Hardness, Disintegration time, Drug content, Friability, all are summarized in the table given below:

Table 4: Post - Compressed Evaluations

Formulation	Hardness	Drug content (%)	(%) Friability ± S.	Thickness	Weight	Disintegration

code	(kg/cm^2) ± S. D.	± S. D.	D.	(mm)	Variation (mg)	time (sec)
F1	6.42±0.058	88.35±0.040	0.07±0.033	3.76 ±0.26	148.13± 1.7	60
F2	7.51±0.074	89.00±0.027	0.08±0.047	3.87±0.15	145±0.01	62
F3	7.54±0.077	98.42±0.018	0.07±0.081	3.98±0.21	148.07±0.01	70
F4	7.32±0.055	91.69±0.029	0.11±0.181	3.91±0.41	149.3±0.023	75
F5	7.53±0.050	90.61±0.010	0.06±0.041	3.99±0.68	148.19±1.69	60
F6	7.58±0.079	95.53±0.017	0.3±0.028	3.90±0.12	149.12±0.16	70
F7	6.56±0.085	93.22±0.023	0.11±0.026	3.90±0.49	150.8±0.018	75
F8	7.57±0.05	92.65±0.030	0.54±0.33	3.91±0.16	149 ± 0.018	60
F9	7.77±0.011	95.14±0.025	0.610±0.23	3.93±0.08	149.35±0.15	65

***In - Vitro* Disintegration time duration**

Table 5: Disintegration time

Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
Disintegration time time (sec)	60	62	70	75	60	70	75	60	65

***In - Vitro* release study**

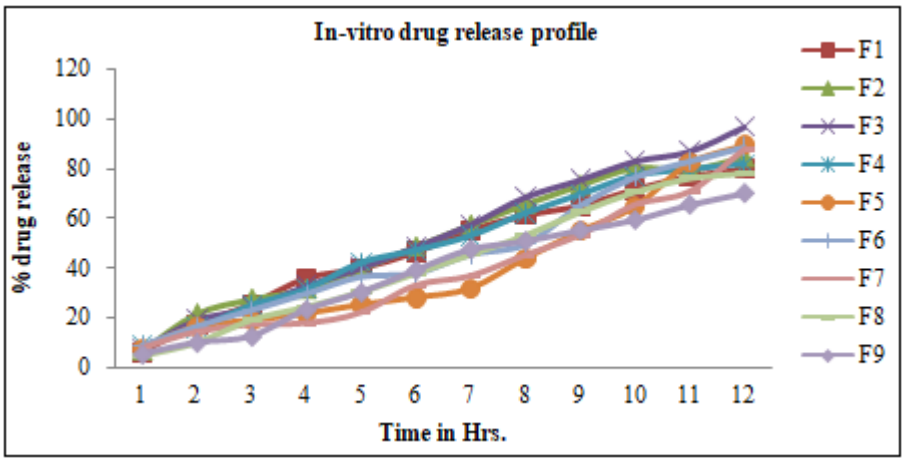

Figure 4: Dissolution Profile of Formulation Batches (F1 - F9) (Time Vs %CDR)

A) Surface Response Plots:

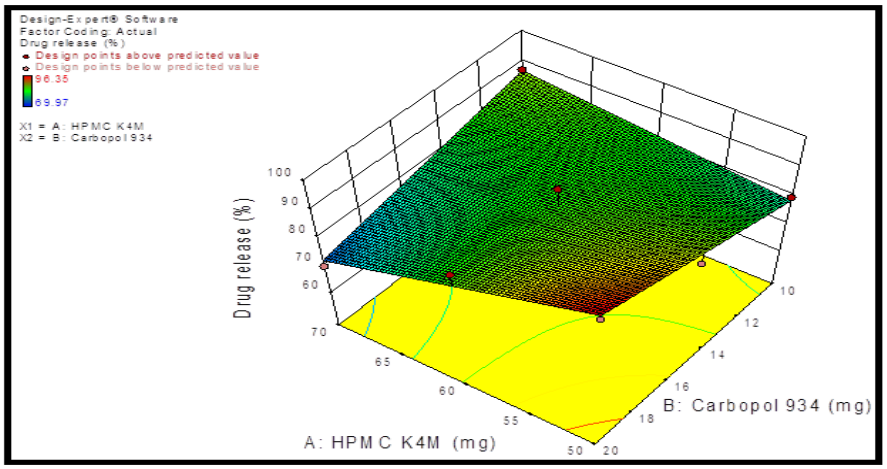

Figure 5: Surface Response plot showing effect of Carbopol 934 and HPMC K4M on drug release

B) Contour plot:

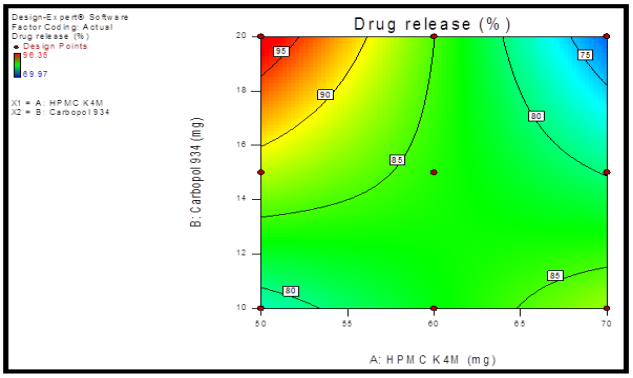

Figure 8: Contour plot showing effect of Carbopol 934 and HPMC K4M on drug release.

Drug release kinetics

In the present study, the drug release was analysed to study the kinetic of drug release mechanism. The results showed that the factorial design batches followed zero order and first order model kinetics, Higuchi and Connor's model kinetics and kosemeyer's peppas model kinetics

Zero - order comparative evaluation model kinetics:

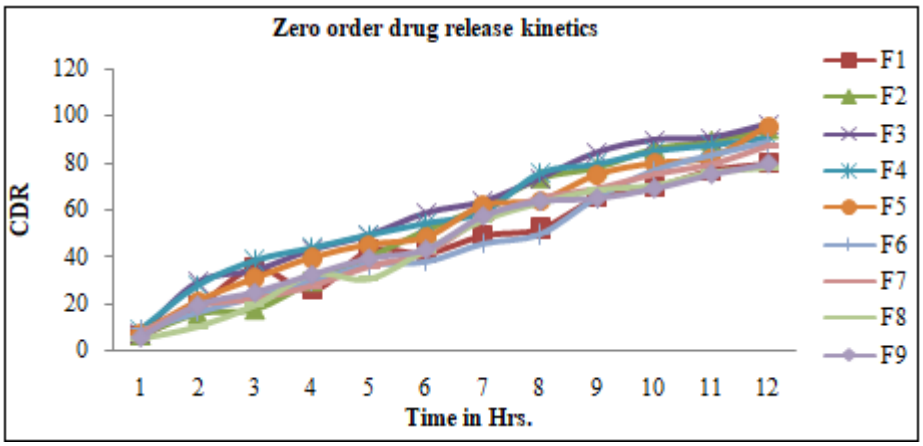

Figure 14: Model graph for comparative evaluation of zero order release kinetics

First - order comparative evaluation model kinetics:

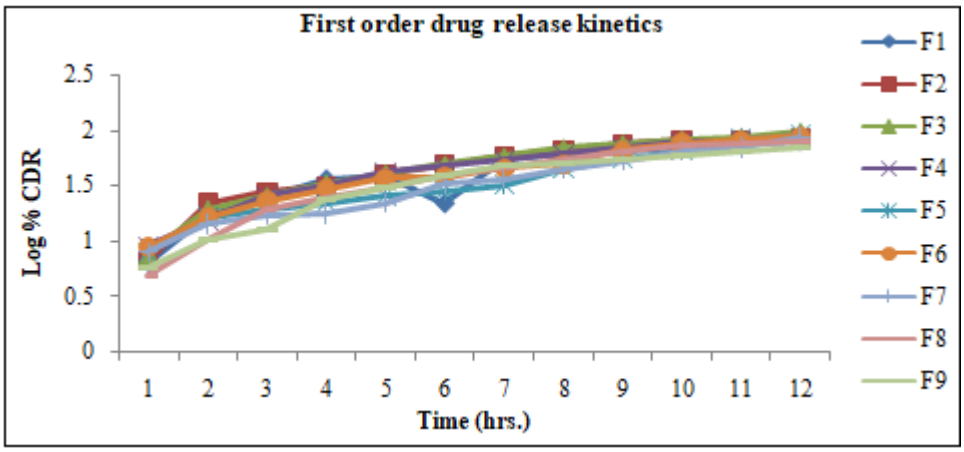

Figure 15: Model graph for comparative evaluation of First order release kinetics

Higuchi and Connor's model release kinetics:

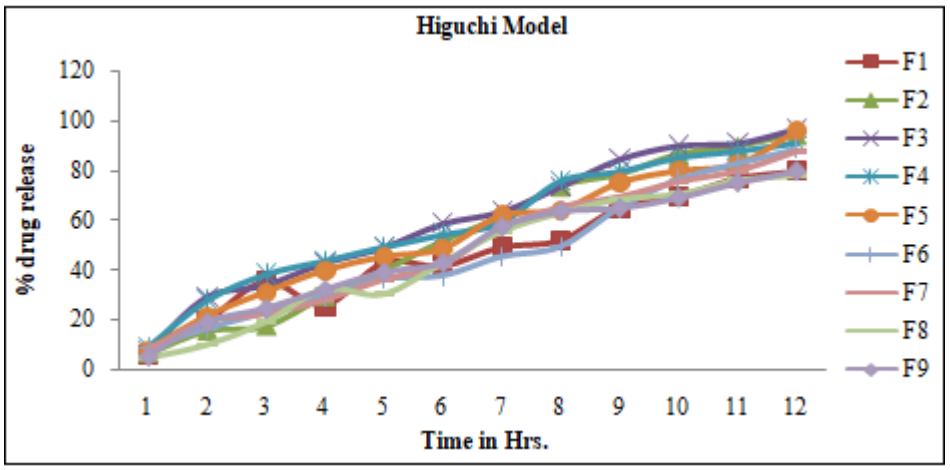

Figure 16: Model graph for comparative evaluation of Higuchi Connor's release kinetics

Korsemeyer's peppas comparative evaluation model kinetics:

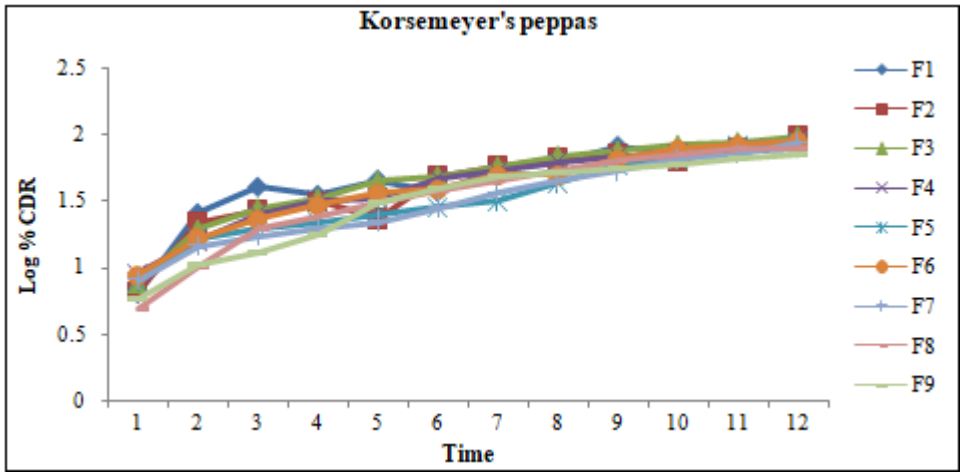

Figure 17: Model graph for comparative evaluation of Korsemeyer's peppas release kinetics

4. Conclusion

The present study was carried out to develop the vaginal disintegrating drug delivery of dolutegravir. After procurement of drug sample it was characterized for identification by FTIR. After identification check compatibility of drug with all excipient. It was found that it is compatible with all excipient there is no change in functional group. Physical property of dolutegravir vaginal disintegrating tablet i. e. hardness, friability, average weight, thickness also complies with standard reference.

The *In - vitro* drug release profile indicated that batch (F3) was most promising formulation as the extent of drug release from this formulation was high as compare to other formulations, which are suitable for sustained release drug delivery system. The batch F3 shows 96.35% release in 12 hrs, so we concluded that rate of drug release increases in vaginal mucosa in vaginal cavity. Release kinetic data of all the formulation show that F1 - F9 formulation follows Korsmeyer - Peppas model. Stability study was conducted on tablets of batch F3 at 40±2^{0}C for 3 months. Tablets were evaluated for drug release pattern, hardness, floating behavior and *In - vitro* mucoadhesion. From the discussion it was concluded that the tablets of batch F3 had considerable mucoadhesion along with considerable floating and swelling behaviors with good drug release pattern. Tablets of batch F3 was selected as optimum batch and evaluated for stability study.

References

[1] Alam AM, Ahmad FJ, Khan ZI, Khar R K, Ali M. Development and Evaluation of Acid - buffering Bioadhesive Vaginal Tablet for Mixed Vaginal Infections. AAPS PharmSciTech.2007; 8 (4): Article109.

[2] Indian Pharmacopoeia 2007, Government of India, ministry of health & welfare, published by The Indian Pharmacopoeia Commission, Ghaziabad volume I; 177 - 184

[3] United States Pharmacopeia XXIII & National Formulary XVII 1995. Published by United States Pharmacopeia Convention, Inc., Rand McNally, Taunton; 1950.

[4] Baloglu E, zyazıcı MO, Hızarcıog˘lu SY, Karavana HA. An in vitro investigation for vaginal bioadhesive formulations: bioadhesive properties and swelling states of polymer mixtures. Il Farmaco.2003; 58: 391 - 396.

[5] Alka G, Garg S, Khar RK. Measurment of bioabhesive buccal tablet: Design of an in vitro assembly. Indian Drugs 1992; 30 (4): 152 - 5.

[6] Krishna . S. V, Asho k. V, Chatterjee A: Areview on vaginal drug delivery system. International journal of biology and allied sciences, March, 2012, 1 (2): 152 - 167.
[7] Sahoo C. K, Nayak P. K, Sarangi D. K, Sahoo T. K: intravaginal drug delivery system: an overview . an American journal of advanced drug delivery.
[8] Hill G. B, Eschenbach D. A, Holmes KK: bacteriolo gy of vagina. Scandinavian journal of urolo gy and nephrology, supplementum [01 jan 1984 86: 23 - 39]
[9] Valence M. K. Ndesendo, Viness Pillay, Yahya E. Choonara, Edkhart Buchmann, David N. Bayever, Leith C. R. Meyer: A review of current intravaginal drug delivery approaches employed for the prophylaxis of HIV/AIDS and prevention of sexually transmitted infections. AAPS Pharmascitech, vol.9 No.2, June2008.
[10] Hiorth M, Nilsen S and Tho I: Bio adhesive mini tablet of vaginal drug delivery. Pharmaceutics 2014 sep; 6 (3): 494 - 511
[11] Choudhury A, Das S, Kar M: A review on novelty and potentiality of vaginal drug delivery. International journal of pharmatech research CODEN (USA): IJPRIF VOL.3, NO.2, Aprill- June2011: 1038 - 1039.