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Research Article

Formulation and Evaluation of Cyclodextrin Loaded Rivaroxaban Fast Dissolving Tablets

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Abstract

The present investigation was undertaken in formulating fast dissolving tablets of the anticoagulant drug Rivaroxaban. Rivaroxaban is an orally bio available oxozolidine derivative and direct inhibitor of coagulation factor Xa with anti coagulant activity upon oral administration rivaroxaban selectivly bind to both free factor Xa bound in the prothrombinase complex. The main objective is to enhance the quick on set of action, convenience and compliance by the elderly and pediatric patients without the problem of swallowing and using water. Rivaroxaban belongs to BCS Class-II with low solubility and high permeability. The solubility of Rivaroxaban is enhanced by complexing with cyclodextrin. The inclusion complexes of Rivaroxaban were prepared by various techniques using HP β cyclodextrin in various ratios (1:1 and 1:2). Solubility study of Rivaroxaban was performed in which highest was observed for 1:2 ratio. The selected inclusion complexes were then utilized for the preparation of tablets by direct compression. Five formulae were prepared and evaluated for *in vitro* dissolution characteristics, *in vitro* disintegration time, wetting time, and their physico-mechanical properties. The promising tablets (F5) showed greatest drug dissolution (more than 85% within 30 min), satisfactory *in vitro* disintegration time (24 sec) and physico-mechanical properties that are suitable for fast dissolving tablets. By complexation

Introduction

The compressed tablet is the most popular dosage form in use today. About two-thirds of all prescriptions are dispensed as solid dosage forms, and half of these are compressed tablets. Among compressed tablets fast-dissolving tablets have gained considerable attention as a preferred alternative to conventional tablets and capsule due to better patient compliance [1]. FDTs are becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biochemical parameters pertinent to their performance [2]. Recent advances in Novel Drug Delivery (NDDS) aim to enhance the safety and efficacy of drug molecule by formulation and to achieve better patient compliance. New FDT technologies address many pharmaceutical and patient needs, ranging from enhanced life-cycle management to convenient dosing for pediatric, geriatric, and psychiatric patients with dysphagia. The mouth dissolving tablets (MDT) or ODTs by overcoming the drawbacks associated with conventional tablets. These tablets disintegrate/dissolve/disperse in saliva within few seconds. USFDA has defined FDTs tablets as "A solid dosage form containing medical substances, which disintegrate rapidly, usually within a matter of seconds, when placed upon the tongue" [3]. Rivaroxaban - the first orally dosed, direct Factor Xa inhibitor - is a small-molecule oxazolidinone derivative. It binds directly and reversibly to Factor Xa via the S1 and S4 pockets. Rivaroxaban is a type of medicine known as anticoagulant or blood thinner. It makes your blood flow through your veins more easily, this means your blood will be less likely to make a dangerous blood clot [4]. The present study includes the preparation of rivaroxaban fast dissolving tablets by complexing with betacyclodextrins to enhance solubility as well as improving patient compliance are prepared by direct compression method [5,6].

Materials and Methods

Materials

Rivaroxaban was obtained as gift sample from tirupathi medicare limited,paonta sahib, himachal Pradesh. Lactose, Hydroxy propyl beta cyclo dextrin (HPβCD), Sodium Starch Glycolate (SSG), Cross carmellose sodium(CCS),Micro crystalline cellulose (MCC), Magnesium stearate, and Aerosol are purchased from molychem pvt limited, Visakhapatnam.

Preparation of rivaroxaban cyclodextrin complex

The required quantities of the drug and hydroxyl propyl β-Cyclodextrin were weighed accurately in a molar ratio of 1:1 and 1:2. A homogenous paste of cyclodextrin was prepared in a mortar by adding water: ethanol mixture (1:1) in small quantities, then the drug was added with continuous kneading it was triturated for 2 hours, an appropriate quantity of water: ethanol (1:1) mixture was added further to maintain the consistency of the paste [7]. Then the paste was dried on hot air oven at 35-40°C for 24 hours. Then the dried complexes were then powdered and passed through sieve no 44 and then stored [8].

Formulation of rivaroxaban fast dissolving tablets: (Composition of rivaroxaban)

Fast dissolving tablets of batch size fifty were prepared by using direct compression method with using different amount of MCC, SSG (Table 1). According to the batch size all ingredients are weighed and then pass through 2.0 mm sieve and added to polythene bag and mix for a period of 20 minutes to obtain a homogenious blend. Magnesium stearate and aerosil were weighed and sieved by using 0.25 mm sieve. The above mixture is added to polythene bag and mix 2 minutes. The powder is then tested for pre compression parameters like Angle of repose, Bulk density, Tapped density, Carr's index and Hausner's ratio. The compression of tablets was done on a rotary compression machine using 7mm flat round punch constant for all tablets. Compression force must be kept constant in all the formulation [9].

Construction of calibration curve for rivaroxaban

From the stock solution 10 mL is withdrawn in to volumetric flask, made the volume up to 100 mL with Acetonitrile : Water (60:40). From this second stock solution(100 µg/mL), concentrations of 10, 20, 40, 60, 80 and 100 µg/mL solutions were prepared and corresponding absorbance was measured at 250 nm in a UV/

Ingredients	F1	F2	F3	F4	F5
Rivaroxaban complex (Equivalent to 10 mg)	1:0	1:1 (a)	1:1 (b)	1:2(a)	1:2 (b)
Lactose	75	75	75	75	75
Micro crystalline cellulose	150	150	150	150	150
Sodium starch glycolate	50	75	75		
Cross carmellose sodium				75	75
Magnesium stearate	5	5	5	5	5
Aerosol	5	5	5	5	5

Table 1: Formulation composition for FDT of Rivaroxaban with HP beta cyclodextrin.

a, b are physical trituration, solvent evaporation methods.

Visible spectrophotometer against Acetonitrile: Water (60:40) solution as the blank. Calibration curve (Figure 1) was constructed by plotting the absorbance against the concentration of rivaroxaban. A regression equation was derived from the plot, which was used for the estimation of rivaroxaban in buffer solution (Table 2).

The method obeyed Beer's law in the concentration range of 10-100 µg/mL and is suitable for the estimation of rivaroxaban from different sample solutions. The correlation coefficient value (r) was found to be 0.999 indicating a positive correlation between the concentration of rivaroxaban and the corresponding absorbance values. The regression line describing the relation between concentration and absorbance was as follows [10].

$y = 0.0060x - 0.009$

Where,

y is the absorbance at 250 nm and

x is the concentration of rivaroxaban in µg/mL.

Concentration (µg/mL)	Absorbance
0	0.000 ± 0.00
10	0.056 ± 3.75
20	0.113 ± 3.98
40	0.260 ± 0.96
60	0.411 ± 1.19
80	0.538 ± 0.57
100	0.668 ± 0.40

Table 2: Data for standard rivaroxaban plot.

(All the values are expressed as mean ± RSD, n = 3).

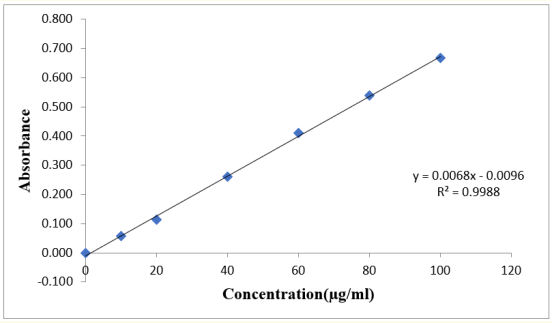

Figure 1: Standard calibration plot for rivaroxaban.

Drug - Excipient's compatibility study

FTIR spectroscopy

Study of the compatibility between the drug and the excipients is an important process in the development of a stable solid dosage form. Drug excipients compatibility testing at an early stage helps in the selection of excipients that increases the probability of developing a stable dosage form. Incompatibility between drug and excipients can alter stability and bioavailability of drugs, affecting its safety and/or efficacy.

Fourier transform infrared spectroscopy (FTIR) is a simple technique for the detection of changes within excipients - drug mixture. Disappearance of an absorption peak or reduction of the peak intensity combined with the appearance of new peaks gives a clear evidence of interactions between the drug and the excipients [11]. The sample (pure or drug plus excipients) was ground gently with anhydrous KBr and was compressed to form a pellet. This pellet was taken up for FTIR spectroscopy. The scanning range was 400 cm^{-1} to 4000 cm^{-1}.

Evaluation of rivaroxaban FDT

Rivaroxaban ODT tablets were evaluated for Uniformity thickness (Vernier calipers), Hardness (Monsanto hardness tester), Friability (Roche's friabilator), Wetting time, Water absorption time, *in vivo* Taste evaluation, *in vitro* disintegration time, Weight variation, Drug content uniformity, *in vitro* dissolution [12].

Uniformity of thickness

The thickness of three tablets was measured using Vernier calipers. The extent to which the thickness of each tablet deviates from ± 5% of the standard value was determined.

Hardness test

The tablet crushing load 'which is the force required to break a tablet by compression in the radial direction was measure during a Monsanto hardness tester (Elite scientific and equipment's). The test was performed on three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

Friability test

Friability of the tablets were determined using roche's friabilator (elite scientific and equipments) at 25 rpm for 4mins. Pre weighing of 10 tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and re weighed.

Wetting time

A piece of double folded tissue paper was placed in a Petri plate (internal diameter; 6.5 cm) containing 6ml of the tablets were measured in seconds. The method was slightly modified by maintaining water at 37°C. Wetting time corresponds to the time for the tablets to disintegrate when kept motionless on the tongue.

In vitro disintegration time

Disintegration test was measured using disintegration test apparatus. 1 tablet was placed in each of the 6 tubes of disintegration test apparatus. I.P methods was following using disc. The time required for completed disintegration of tablet in each tube was determined using stop watch.

Weight variation test

20 tablets were taken and their weight was determined individually and collectively on a digital weighing balance the average weight of 1tablet was determined from the collective weight. The U.S. Pharmacopoeia allows a little variation in weight of a tablet.

Drug content uniformity

Drug content of prepared tablet of each batch of formulation was determined. From each batch; five tablets were taken, weighed and finely grounded. An amount of powder equivalent to 100mg of powder was accurately weighed and dissolved in 40 ml of methanol. The resulting solution was suitably diluted and analyzed on ELITE UV-150 double beam spectrophotometer at 276 nm.

In-vitro dissolution testing

The USP type II rotating paddle method was used to study the drug release from the tablet. The dissolution parameters are mentioned in table 3.The dissolution medium consists of 900 mL acetate buffer of ph 4.5. The release study was performed at 37 ± 0.5°C with a RPM of 50. Aliquots were withdrawn at regular time intervals and replace with fresh medium to maintain sink condition [13]. The samples were filtered with buffer and were analyzed by using UV/Visible spectrophotometer at 250 nm [14].

Kinetics of *in vitro* drug release:

In vitro release data is applied to all the formulation (F1-F5) as per the given table 1 by using the equation and find the release mechanism [15].

Zero order kinetics

It describes the system in which the drug release rate is independent of its connection.

$Q_t = Q_0 + K_0 t$

Where: Q_t = Amount of drug dissolved in time t

Q_0= Initial amount of drug in the solution, which is often zero

K_0= zero order release constant.

If the zero order drug release kinetics obeyed, then a plot of Q_t versus t will give a straight line with a slope of K_0 and an intercept at zero [16].

First order kinetics

It describes the drug release from the system in which the release rate is concentration dependent.

$\log Q_t = \log Q_0 + K_t/2.303$

Where Q_t = amount of drug released in time t

Q_0= Initial amount of drug in the solution

K_t = first order release constant.

If the first order drug release kinetic is obeyed, then a plot of $\log(Q_0 - Q_t)$ versus t will no straight line with a slope of $K_t/2.303$ and an intercept at t = 0 of $\log Q_0$ [17].

Type of apparatus	USP II (Paddle type)
Dissolution media	pH 4.5 acetate buffer with 0.4 % sodium dodecyl sulphate
Bath temperature	37°C ± 0.5
Volume of dissolution	900 mL
Revolution per minute	50
Time points	0,5,10,15,30,45,60

Table 3: Dissolution study of rivaroxaban tablets.

Results and Discussion

Drug - Excipients compatibility study

FTIR techniques have been used here to find the physical and chemical interaction between drug and excipients used. Compatibility studies were conducted using FTIR spectrophotometer. The IR spectrum of pure rivaroxaban was studied. The FTIR scans show characteristic absorption peaks. The FTIR spectrum of pure drug and different excipients and tablet formulations were studied. The FTIR spectrum of formulations shows only slight changes were observed in characteristic peaks when compared with the FTIR spectrum of pure rivaroxaban, rivaroxaban with HP β cyclodextrin figure 2.

According to the DSC study, the thermodynamic peak of rivaroxaban formulation is observed at 154.5°C. The results indicated that the combination of drug with the optimized formulation does not affect the actual stability of rivaroxaban. It indicates the combination might be safe during formulation and storage conditions figure 3.

Based on this study, it was concluded that there is no chemical interaction between drug and excipients used and thus it can be safely used in formulation.

Evaluation parameters of FDT

Thickness of all the tablets was found to be in acceptable range between 5.80 mm to 6.03 mm and results were shown in table 4 and the diameters of all the formulations were found to be uniform. The values of friability test were in the range from 0.46% to 0.65%. The percent friability of all the formulation is less than 1% ensuring that the tablets were mechanically stable. The average wetting

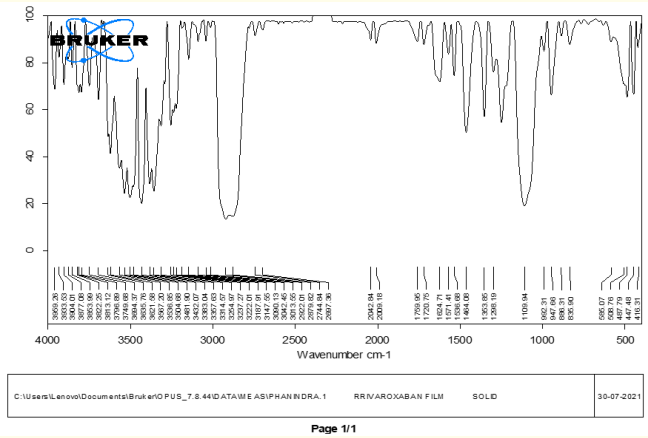

Figure 2: FT-IR spectrum of rivaroxaban fast dissolving tablet.

Figure 3: DSC spectrum of rivaroxaban fast dissolving tablet.

time of the various different formulations were found in the range of 24 to 55 seconds. Formulation F5 had lowest wetting time of 24 sec as compared to other formulations F1-F6. Thus these results indicate that these tablets would disintegrate almost instantaneously when they will come in contact with even slight quantity of saliva in the mouth. This is the most important test with respect to ODT formulations. Among all formulations F5 was found to have best disintegration time of 24sec under experimental conditions at room temperature. The drug content of all the formulations (F1-F6) in 4.5 ph acetate buffer was found to be between 98.9 to 99.9%.

Formulation Code	Thickness in mm	Hardness (Kg/cm^2)	Friability %	Wetting time (sec)	% drug release
F1	5.8 ± 0.02	2.17 ± 0.29	0.65 ± 0.54	55.67 ± 4.93	50.34 ± 2.00
F2	6.01 ± 0.27	3.17 ± 0.29	0.54 ± 0.24	44.67 ± 1.53	59.67 ± 1.15
F3	6.02 ± 0.08	4.83 ± 0.76	0.49 ± 0.19	42.67 ± 1.53	82.33 ± 0.72
F4	5.9 ± 0.15	3.50 ± 0.50	0.57 ± 0.41	43.00 ± 2.00	92.33 ± 1.05
F5	6.03 ± 0.09	4.83 ± 0.76	0.46 ± 0.27	24.33 ± 0.58	98.70 ± 1.05

Table 4: Physicochemical evaluation of fast dissolving tablets of rivaroxaban.

(All the values are expressed as mean ± SD, n = 3).

In vitro dissolution study

From the dissolution profile of all the formulations i.e. (F1-F6), it was found that the cumulative percentage drug release increased with increase in concentration of Sodium Starch Glycolate, cross carmellose sodium in varying ratios. Out of six formulations, F5 showed best drug release profile when compared to the other five formulations.

It has observed that comparatively with sodium starch glycollate cross carmellose sodium formulations gave better release more than 80 % release in 30 minutes. Among that F5 showing better release, further increasing crosscarmellose sodium also there is no effect on the dissolution and results were shown in the table 5.

In vitro release kinetics

The drug release profile of all formulations of fast dissolving tablets of rivaroxaban prepared were fitted into zero order. The data were processed for regression analysis using MS- Excel statistical functions. The drug release profiles, correlation coefficient (r) values of cyclodextrin loaded fast dissolving tablets are shown in table 6 and in figure 4 and 5. Analysis of the release data as per zero order and first order kinetic models indicated that drug release from fast dissolving tablets followed zero order kinetics. All the formulations followed zero order kinetics.

Time (in min)	Cumulative percentage drug release of formulated tablets				
	F1	F2	F3	F4	F5
0	00.00 ± 0.00	00.00 ± 0.00	00.00 ± 0.00	00.00 ± 0.00	00.00 ± 0.00
5	12.33 ± 2.52	13.67 ± 1.53	16.67 ± 2.08	15.67 ± 1.15	18.33 ± 0.58
10	16.34 ± 1.16	18.33 ± 1.53	23.00 ± 1.73	20.00 ± 1.73	23.00 ± 2.00
15	27.67 ± 2.52	35.00 ± 2.00	37.33 ± 1.53	39.33 ± 1.53	40.00 ± 1.00
20	42.33 ± 0.58	44.67 ± 2.52	48.00 ± 1.00	53.67 ± 2.08	54.67 ± 1.53
30	50.32 ± 1.53	58.00 ± 2.00	71.00 ± 3.61	74.33 ± 4.04	86.33 ± 1.53
45	50.36 ± 1.26	59.67 ± 2.52	75.00 ± 2.65	85.00 ± 2.65	90.00 ± 2.65
60	50.34 ± 2.08	59.67 ± 2.52	82.33 ± 2.08	92.33 ± 2.08	98.70 ± 1.00

Table 5: *In vitro* dissolution studies (F1-F5) of FDT of Rivaroxaban

(All the values are expressed as mean ± SD, n = 3).

Figure 4: Zero order drug release profiles of different formulations (F1-F5) of cyclodextrin loaded rivaroxaban fast dissolving tablets.

S. No	Zero order	First order
	R^2	R^2
F1	0.573	0.002
F2	0.788	0.029
F3	0.866	0.171
F4	0.907	0.262
F5	0.951	0.313

Table 6: Kinetics of drug release.

Figure 5: First order drug release profiles of different formulations (F1-F5) of cyclodextrin loaded rivaroxaban fast dissolving tablets.

Conclusion

Rivaroxaban belongs to BCS class II drug having low solubility and high permeability and having bitter in taste. The aim the study was to enhance the solubility and acceptability of the patient who are facing swallowing difficulties that is geriatric and bed ridden patients faces difficulties in swallowing. Inclusion complexes are entities comprising two or more molecules in which one of the molecules is the "host" molecule and the second one is a "guest" molecule. Either whole molecules or part of molecules which are hydrophobic and can fit into the cavity of host in the presence of water are included into the host cavity. Cyclodextrins are able to form inclusion complexes in aqueous solutions, with drugs, by taking up the drug molecule or lipophilic moiety of the molecule, into the central cavity in which the polar cyclodextrin cavity is occupied by water molecules that are in an energetically unfavoured

state and are therefore readily replaced by an appropriate guest molecule that is less polar than water [18]. For enhancing solubility and improve taste we have chosen cyclodextrins as complexing agents that improves solubility as well as taste of the fast dissolving tablets. It can be concluded that the formulation F5 shows better release than remaining formulations.

Bibliography

1. Sachin G., *et al.* "Formulation and evaluation of fast dissolving tablets of etoricoxib". *world journal pharmacy and pharmaceutical science* 4 (2015): 1357-1376.
2. Prameela Rani A., *et al.* "Formulation and Evaluation of Fast Disintegrating Tablets of Anti-inflammatory Drug Flurbiprofen". *Scholars Research Journal* 10 (2018): 68-77.
3. Swati S., *et al.* "Formulation and Evaluation of Glipizide Fast Dissolving Tablets". *Journal of Pharmaceutical Sciences and Research* 12 (2020): 609-611.
4. https://www.statpearls.com/ArticleLibrary/viewarticle/86483
5. Madhuri TH and Ravi DH. "Formulation and Evaluation of Fast Dissolving Tablet of Lamotrigine". *International Journal of Pharmaceutical Sciences and Drug Research* 7 (2018): 50-57.
6. Pavan KR., *et al.* "Fast Dissolving Tablets of Pioglitazone Hydrochloride by Use of Various Super disintegrants". *International Journal of Advanced Research in Biological Sciences* 3 (2013): 74-79.
7. Rao MT., *et al.* "Formulation and characterization of indomethacin cyclodextrin loaded mouth dissolving films". *International Journal of Current Advanced Research* 8 (2018): 15110-15117.
8. Hannan AP., *et al.* "Oral dispersible system: A new approach in drug delivery system". *Indian Journal of Pharmaceutical Sciences* 78 (2016): 2-7.
9. Reddy HL., *et al.* "Fast dissolving drug delivery systems: A Review of the Literature". *Indian Journal of Pharmaceutical Sciences* 64 (2002): 331-336.
10. Rao MT., *et al.* "Development and validation of RP-HPLC method for the determination of itraconazole in bulk and capsule dosage form". *International Journal of Pharmaceutical Sciences Review and Research* 31 (2015): 221-225.
11. Wyawahare NS., *et al.* "Fast dispersing tablets of diclofenac sodium with natural superdisintegrants". *International Journal of Current Research and Review* 4 (2010): 20-29.
12. Chilate VC., *et al.* "To Mask the Bitter Taste of Rizatriptan Benzoate and Develop Water Dispersible Tablets". *International Journal of Current Research and Review* 9 (2017): 39-48.
13. Korsmeyer RW., *et al.* "Mechanism of solute release from porous hydrophilic polymers". *International Journal of Pharmaceutical* 15 (1983): 35-39.
14. Dasari N and Maruvajala V. "Preparation and evaluation of fast dissolving tablets of pitavastatin by 32 full factorial design". *International Journal of Applied Pharmaceutics* 12 (2020): 108-114.
15. Costa P., *et al.* "Modelling and comparison of dissolution profiles". *European Journal of Pharmaceutical Sciences* 13 (2001): 123-133.
16. SG Gattani and RS Moon. "Formulation and evaluation of fast dissolving tablet containing vilazodone nanocrystals for solubility and dissolution enhancement using soluplus: *in vitro-in vivo* study". *Journal of Applied Pharmaceutical Science* 8 (2018): 045-054.
17. Vishal Dhiman., *et al.* "Formulation and *in-vitro* evaluation of fast dissolving tablets of telmisartan". *International Journal of Pharmacy and Life Sciences* 3 (2012): 2159-2164.
18. Bhavani BK., *et al.* "Preparation and evaluation of inclusion complexes of Felodipine". *Journal of Global Trends in Pharmaceutical sciences* 3 (2012): 576-584.