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FORMULATION AND EVALUATION OF LIQUISOLID COMPACTS OF RIVAROXABAN

Dr. Geeta K Patel[1], Jayant Patel[2]

Corresponding Author: Dr. Geeta Patel*

[1]Assistant Professor, Shree S K Patel College of Pharmaceutical Education and Research, Ganpat University, Gujarat, India.

E-mail: geeta.patel@ganpatuniversity.ac.in, gmppharmacist@gmail.com,

[2] PG student, Shree S K Patel College of Pharmaceutical Education and Research, Ganpat University, Gujarat, India.

ABSTRACT

The present work was aimed to enhance the dissolution rate of Rivaroxaban by delivering the drug as a liquisolid compact. The liquid solid technique is an innovate technique used in improved dissolution rate. Liquisolid compacts were prepared using Tween 80 as solvent, Avicel PH112 and 200 as carrier, and Aerosil as the coating material. The interaction between excipients was examined using physical mixing and differential scanning calorimetric method. The dissolution studies for the liquisolid formulation and the marketed product were carried out. The results showed no change in the crystallinity of the drug and no interaction between excipients. The dissolution efficiency of Rivaroxaban liquisolid formulation at 15 min was greater than that of innovator product. The increase in the dissolution rate was also found to be significant compared to the marketed product. The liquisolid technique appears to be a promising approach for improving the dissolution of poorly soluble drugs like Rivaroxaban.

KEY WORDS: Rivaroxaban, liquisolid technique, liquid load factor, non-volatile solvent, carrier material, coating material.

1. INTRODUCTION

Bioavailability is the key determinant of a drug for its therapeutic effectiveness, which in turn depends upon the solubility of that drug in gastrointestinal fluid. Solubility is one of the important parameters to achieve the desired concentration of drug in systemic circulation for pharmacological response (1). As a most discussed but still not completely resolved issue, solubility or dissolution enhancement techniques remain the most vibrant field for the researchers in formulation science. Solubility and dissolution are the core concepts of any physical or chemical science including biopharmaceutical and pharmacokinetic considerations in therapy of any medicine (2). As a result, about 40-50% of new candidates entering drug development pipeline fail because of non optimal biopharmaceutical properties (3). Over the years, various techniques have been employed to enhance the dissolution profile and, in turn, the absorption efficiency and bioavailability of water insoluble drugs and/or liquid lipophilic medication. Several researchers have shown that the liquisolid technique is the most promising method for promoting dissolution rate of poorly water soluble drugs. It is challenge to industry to increase solubility of unit dosage forms to overcome this liquid solid compact technology is best suitable one (4, 5).

A number of methodologies can be adapted to improve solubilization of poor water soluble drug and further to improve its bioavailability. The techniques generally employed for solubilization of drug includes micronization, chemical modification, pH adjustment, solid dispersion, complexation, co-solvency, micellar solubilization, hydrotropy, crystal engineering, self-emulsifying drug delivery systems, Hot melt extrusion, use of meso porous silica carriers, supercritical fluid techniques, nanotechnology based methods etc (6-11).

The concept of liquisolid tablets was developed from powdered solution technology that can be used to formulate liquid medication (12). The term “liqui-solid systems” (LS) is a powdered form of liquid drug formulated by converting liquid lipophilic drug or drug suspension or solution of water-insoluble solid drug in suitable non-volatile solvent systems, into dry looking, non-adherent, free-flowing and readily compressible powdered mixtures by blending with selected carrier and coating materials (13-14). Inert, preferably water-miscible organic solvent systems with high boiling point and not highly viscous organic solvent system such as propylene glycol, liquid polyethylene glycols, polysorbates, fixed oils, or glycerine are best suitable as liquid vehicles (15).

Rivaroxaban is used to treat or prevent blood clots (venous thrombo embolism, or VTE). Blood clots can occur in the legs (deep vein thrombosis, DVT) or the lungs (pulmonary embolism, PE) (16). Rivaroxaban has an elimination half-life of 26 hours, and is conventionally dosed once daily with immediate-release tablets. Rivaroxaban is bcs-II drug having poor aqueous solubility, particularly soluble at pH values above 4.5. To improve solubility and in turns bioavailability of Rivaroxaban liqui solid technique was selected as an efficient method for formulating water insoluble drugs.

2. MATERIALS

2Materials: Rivaroxaban was generously gifted by Zydus Cadila Pharmaceutical, India. Avicel PH 101, 102 and 112 were gifted from FMC Biopolymer, India. Colloidal Silicon Dioxide (Aerosil 200) was gifted from Evonik, India. Crospovidone (Polyplasdone) was gifted by Ashland Inc, India and Magnesium stearate was of laboratory grade.

3. METHODS

3.1. Solubility Studies

Solubility of Rivaroxaban was determined in various nonvolatile solvents such as polyethylene glycol, propylene glycol, tween, castor oil etc. Two ml of each component was taken in screw cap vials with excess amount of drug. After sealing, vials were kept on isothermal mechanical shaker at 37±2ºC for 72hours. After equilibrium, each test tube was centrifuged at 6000 rpm for 20 minutes. Supernatant was filtered through membrane filter using 0.45 μm filter disk. Filtered solution was appropriately diluted with methanol, and UV absorbance was measured at 249 nm wavelength. Concentration of dissolved drug was determined using standard equation (17).

3.2. Drug-excipients compatibility

To successfully formulate active into different dosage form, various excipients are considered based on previous experience and scientific literature search. These studies were done by physical mixing of drug and other excipients in the required proportion. API, excipients alone and binary mixture kept in USP-I glass vials (Open and closed condition) at 40ºC / 75% RH. The vials were closed with rubber stopper and were checked for any characteristics change. Drug excipients compatibility study was carried out by DSC (Differential scanning calorimetry) and FT-IR.

DSC of pure drug, their mixture with excipients as well as mixture of both drugs was taken and spectrum was recorded. Sample was scanned in the region of 30°C to 300°C. Heat from 30°C to 300°C at 20°C/min. Scanned graph of pure drug was compared with standard range.

FT-IR studies were carried out for pure drug alone and along with excipients. The drug-carrier mixture of Rivaroxaban were prepared and subjected for scanning from 4000cm^{-1} to 400cm^{-1} FTIR spectrophotometer. The FTIR spectraof sample drug matched with the standard FTIR spectrum of pure drug.

3.3 Measuring Angle of Slide

This experiment was designed to measure the flowable liquid retention potential (φ-value) for Avicel PH 102 and Aerosil (coating material, φ_{Co}) and the optimum liquid load factor (L_f). The φ-value of a powder is the maximum amount of given nonvolatile liquid that can be retained inside powder bulk (w/w) while maintaining acceptable flowability, whereas L_f is the mass ratio (w/w) of the liquid medication to the carrier powder in the Liquisolid formulation. Powder admixtures containing 5 g of either carrier or coating with increasing quantity

of nonvolatile liquid vehicle (Acrysol EL 135) were mixed using a mortar and pestle. Each admixture was then placed on a shiny metal plate; the plate was then tilted until the admixture slides. The angle formed between the plate and the horizontal surface, at which admixture slides were measured as angle of slide (θ).

The flowable liquid retention potential was calculated using the following equation:

φ-Value = Weight of nonvolatile liquid/ Weight of carrier or coat …….. (1)

Each admixture has specific φ-values which were determined and plotted against respective measured angle of slide for all nonvolatile liquid vehicles. The φ-value that corresponds to an angle of slide of 33º was reported to represent the flowable liquid retention potentials of powder admixtures (18).

3.4 Preparation of Powder for Liquisolid and Conventional Tablets

The liquid solid compacts were prepared according to the method described by Spireas and Bolton (19). Incorporation of liquid on solid phase for subsequent adsorption of drug on carrier and addition of excipients for better pharmaceutical performance. Calculated quantities of non-volatile tween 80 (polysorbate 80) were accurately weighed in glass beaker and then sonicated until homogenous solution was obtained. This sonicated medication was incorporated into a calculated quantity of carrier and coating material. All Liquisolid preparations were compacted into tablets using a ten station rotary compression machine (Rimek, Karnavati Engineering, India) using flat faced punch with a compression force that provide acceptable tablet hardness. Composition of liquids solid compacts batches is shown in table-1.

Table-1: Formulations of Rivaroxaban liquisolid compacts.

Batch no.	Rivaroxaban (mg)	Tween 80 (mg)	R value	Name of carrier	Carrier material (Q) (mg)	Aerosil (q) coating material (mg)	Crospovidone (mg)	Magnesium stearate (mg)	Total Weigh (mg)
F1	20	10	30	MCC PH 200	175.3	5.94	12	1.74	194.98
F2	20	10	40		181.9	4.54	12	1.74	200.18
F3	20	10	50		193.1	3.862	12	1.74	210.702
F4	20	20	30		178.8	5.94	12	1.74	198.48
F5	20	10	30		175.9	5.83	18	1.74	201.47
F6	20	10	30	lactose	175.3	5.94	12	1.74	183.98
F7	20	10	30	Starch	175.3	5.94	12	1.74	194.98
F8	20	20	30	MCC PH 112	174.8	5.82	12	1.74	194.36
F9	20	20	40		181.2	4.53	12	1.74	199.47
F10	20	20	50		188.5	3.77	12	1.74	206.01

3.5 Pre compression Studies: Flowability of liquisolid admixture is important in formulation of tablet dosage form on industrial scale. Therefore, it was essential to study the flowability of these liquisolid powder admixtures prior to compression. Flowability can be evaluated using parameters such as Carr's index, angle of repose, and Hausner's ratio.

3.6 Evaluation of Compressed Tablets

The prepared liquisolid tablets were evaluated for hardness, friability and disintegration time. Hardness was determined by the Pfizer hardness tester and friability by a digital tablet friability tester. The disintegration time was measured using a USP disintegration tester (Electrolab). All the studies were done in triplicate. Dissolution studies were performed The USP paddle method at 37±0.5 º C.

3.7 Stability study

Stability analysis of optimized Rivaroxaban tablet was conducted in compliance with ICH guidance. Rivaroxaban tablets were wrapped in Alu Alu blister pack and held in a moisture chamber for 3 months at 40±20ºC and 75± 5% RH. The tablets were evaluated for hardness, assay, dissolution and disintegration.

4. RESULTS AND DISCUSSION

4.1 Drug excipients compatibility study

No characteristics change (NCC) was observed as per excipients selected and shown in table-2 and tbale-3 for compatibility study indicated drug excipient compatibility of blend.

Table-2: Sample Preparation for Drug Excipient Compatibility

Drug excipient compatibility studies at 40^0±2^0C/ 75% ±5% RH				
Sample detail	**Ratio D:E**	**Initial**	**15 DAY**	**1 MONTH**
API	1	NCC	NCC	NCC
API+ Tween 80	1:1	NCC	NCC	NCC
API+Micro crystalline cellulose PH 200	1:5	NCC	NCC	NCC
API+ Crosprovidone	1:1	NCC	NCC	NCC
API+Lactose	1:5	NCC	NCC	NCC
API+ Micro crystalline cellulose PH 112	1:5	NCC	NCC	NCC
API+ Magnesium stearate	1:0.5	NCC	NCC	NCC
API+ Starch	1:5	NCC	NCC	NCC

Table-3: Results of Drug-Excipients Compatibility Studies at 40ºC±2ºC /75±5%RH

Sample detail	Chromatographic Purity*				
	Ratio D:E	Initial	1 Week	2 Week	3 week
API	1	Compliance	Compliance	Compliance	Compliance
API+Tween 80	1:1	Compliance	Compliance	Compliance	Compliance
API+Micro crystalline cellulose PH 200	1:5	Compliance	Compliance	Compliance	Compliance
API+Crosprovidone	1:1	Compliance	Compliance	Compliance	Compliance
API+Lactose	1:5	Compliance	Compliance	Compliance	Compliance
API+Micro crystalline cellulose PH 112	1:5	Compliance	Compliance	Compliance	Compliance
API+ Magnesium stearate	1:0.5	Compliance	Compliance	Compliance	Compliance
API+ Starch	1:5	Compliance	Compliance	Compliance	Compliance

A comparative DSC spectrum of pure Rivaroxaban and with final formulation is shown in the figure-1 (a) and (b). The DSC spectra of pure drug showed a sharp endothermic melting peak at 234.72 °C which is characteristics of pure drug as reported in literature. However, with formulation excipients the peak was obtained at 234.72^{0}C revealed no interaction between drug and formulation excipients.

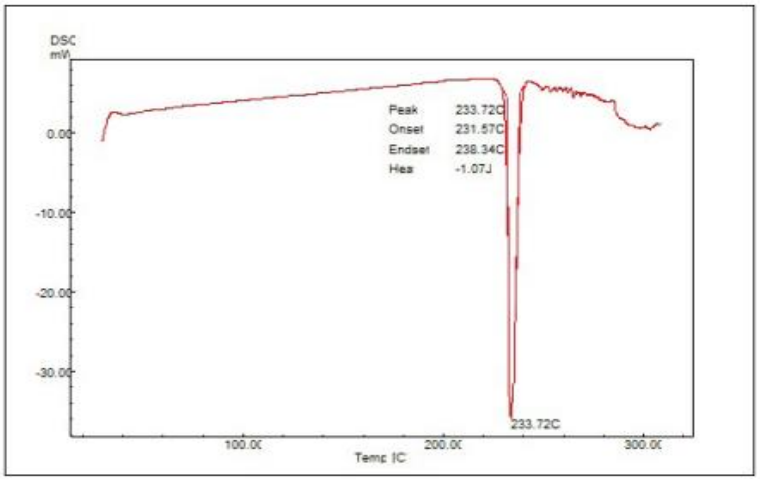

Figure-1(a): DSC spectra of Rivaroxaban

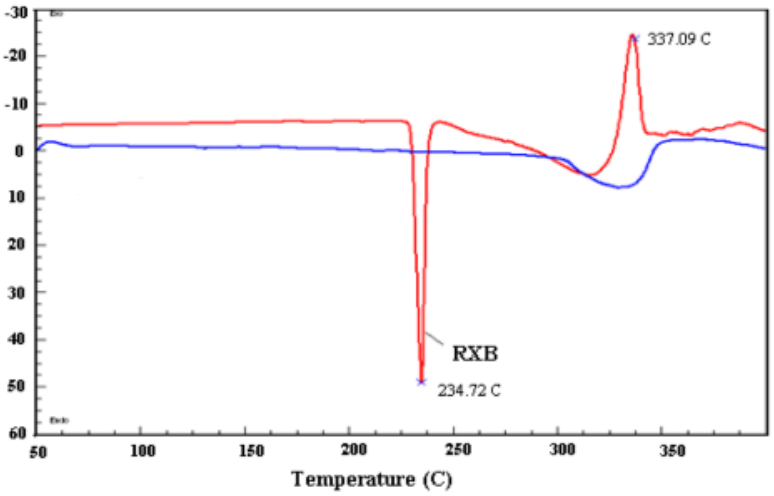

Figure-1 (b): DSC spectra of Rivaroxaban with formulation excipients

4.2. Solubility Study

Solubility data of drug Rivaroxaban in various liquid vehicles is shown in Table-4. Rivaroxaban appears to be more soluble in tween 80. The solubility is an important factor in liquisolid systems, as higher solubility of drug in liquid vehicle can lead to higher dissolution rates since the drug will be more molecularly dispersed and more surface of drug will be exposed to the dissolution media.

Table -4: Solubility data of drug Rivaroxaban in various liquid

Sr no.	Solvent	Solubility (mg/ml)
1	Water	0.01
2	Propylene Glycol	7.7 ± 0.30
3	Tween 80	15.5 ± 0.15
4	PEG 400	9.2 ± 0.1
5	Castor oil	5.5 ± 0.4
6	Capmul MCM	11.2 ± 0.3

4.3 Measuring Angle of Slide

For Determination of Flowable Liquid Retention Potential, angle of slide was determined which is an important step in the formulation of liquisolid tablets. The relationship of angle of slide with corresponding φ of Avicel, φ_{Co} of Aerosil for liquid vehicle is shown in Figure-2. The Lf was then used to decide the optimum amount of carrier and coating materials required to ensure dry-looking, free-flowing and compactable powdered systems. The lowest liquid factor was obtained for Avicel PH102, and accordingly, the amount of carrier was higher than other formulations.

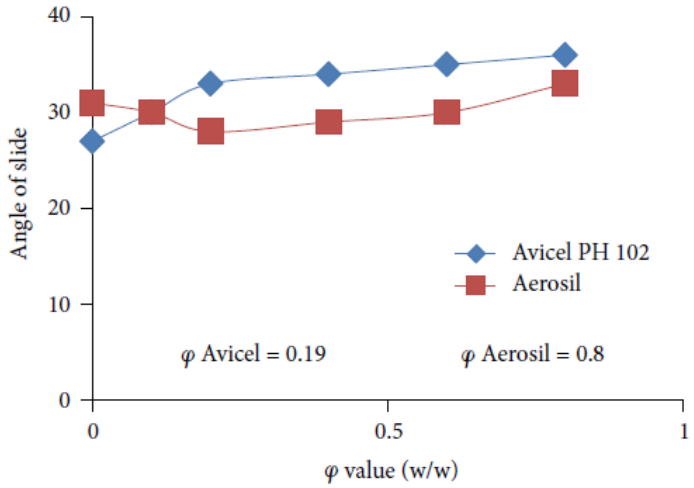

Figure -2: The angle of slide of Avicel and Aerosil

4.4 Pre compression Studies

Powder flowability is crucial in the industrial production of tablet dosage forms, as a uniform powder stream through hopper confirms uniformity of both tablet weight and drug content. The results of various flow parameters are shown in Table-5.

Table-5: Pre-compression study of preliminary trail formulation

Batch no.	Bulk density (g/cm^3)	Tapped density (g/cm3)	Angle of Repose	Carr's Index (%)	Hausner's ratio
F1	0.313	0.432	28.37	19.341	1.387
F2	0.323	0.411	26.87	17.254	1.272
F3	0.343	0.428	27.75	17.345	1.247
F4	0.363	0.410	29.61	16.547	1.129
F5	0.359	0.432	28.37	16.981	1.203
F6	0.330	0.407	25.23	17.214	1.233
F7	0.329	0.403	25.29	16.335	1.224
F8	0.335	0.447	26.87	17.266	1.234
F9	0.329	0.410	27.03	19.780	1.246
F10	0.344	0.440	29.25	21.622	1.276

4.5 Post compression parameters (Quality Control Studies)

All prepared tablets complied with the pharmacopoeial required specifications for physical properties of liquisolid compacts. Results of hardness, friability, and disintegration time are represented in table-6. Hardness test showed hardness of liquisolid tablets ranging from 42-49 N. Another measure of tablets strength is friability. Conventional compressed tablets that lose less than 1% of their weight are generally considered

acceptable. The percentage friability for all formulations was <1%, indicating that the friability is within the prescribed limits. This indicates acceptable resistance was shown by liquisolid tablets to withstand handling. Disintegration time was found to be in the range of 29-55 seconds for liquisolid preparations intended for immediate drug release characteristics.

Table-6: Physical evaluation of liquid solid tablet

Batch no.	Diameter (mm)	Thickness (mm)	Hardness (N)	Friability (%)	DT (sec.)	% Assay
F1	8.28±00	4.44	42	0.85	33	97.20
F2	8.28±00	4.63	45	0.62	36	98.60
F3	8.28±00	4.72	46	0.63	39	97.20
F4	8.28±00	4.59	43	0.75	42	99.10
F5	8.28±00	4.72	45	0.66	36	98.68
F6	8.28±00	4.29	45	0.82	29	98.68
F7	8.28±00	4.25	47	0.77	32	98.27
F8	8.28±00	4.31	45	0.43	54	97.35
F9	8.28±00	4.31	47	0.48	53	98.45
F10	8.28±00	4.30	49	0.45	55	99.48

4.6 *In Vitro* Dissolution Studies

The dissolution profiles of the liquisolid tablets for fast release formulations and conventional tablets of Rivaroxaban tablets are shown in Figure-3. From the dissolution profile, it can be seen that all liquisolid formulations significantly improved drug dissolution compared to conventional tablets. Formulations F8, F9 and F10 released 96.14%, 98.14% and 97.01% drug released respectively. Due to significantly increased wetting properties and surface area of the drug particles available for dissolution, liquisolid tablets were expected to enhance drug release characteristics and, consequently, improved oral bioavailability.

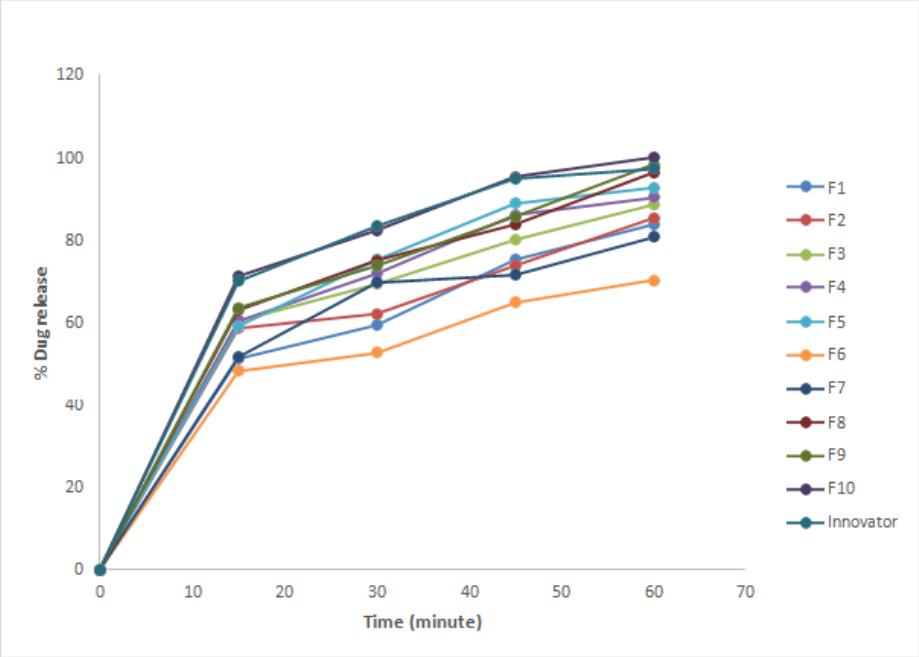

Figure-3: Percentage drug released for formulations batches F1 to F10

4.7 Stability study

The selected optimized formulation F10 was evaluated for stability studies which were stored at $40^0 \pm 2^0$C or 75% RH±5% RH for 15 days and 1 month and were analyzed for their assay, hardness, disintegration time, friability, dissolution study etc. There was no significant change in the physicochemical properties of liquisolid tablet during the stability period. There was a slight increase in disintegration time for the stored formulation, but it was well within the acceptable limit.

5. Conclusion

The study proved that liquisolid technique can be efficient approach for improving the dissolution profile of drugs having poor water solubility. The present study shows liquid solid tablet could be promising strategy in improving dissolution of poorly soluble drug in form of immediate release tablet. Rivaroxaban tablet improve dissolution rate compare to innovator tablet. The non-volatile solvent and the fix ratio of carrier and coating material shows the maximum in-vitro drug release profile. The **o**ptimize tablet F10 shows the fast drug release as per the target compare to other batches. Stability studies revealed that there was no significant change in any pivotal characteristics of the formulation during storage period.

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