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FORMULATION AND EVALUATION OF RIVAROXABAN IMMEDIATE RELEASE TABLETS

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ABSTRACT

The aim of the present study is to develop immediate release tablets of Rivaroxaban, to enhance solubility and dissolution for increasing its oral bioavailability. Rivaroxaban is widely prescribed as anti-coagulant drug which belongs to BCS class II.In present study, DOE trails was applied in the study by using solubilizing agent (SLS), Binding agent (HPMC), super disintegrant (CCS). Pre-compression studies were performed in formulation suggested by software and results were found to be within limits. The formulation were compressed by wet granulation method & evaluation tests were weight variation, hardness, friability, drug content, in-vitro drug release studies were performed. The cumulative drug release from all the formulations were compared with that of the Innovator. The enhanced Rivaroxaban release was by using 0.4 % SLS solution in dissolution media. Formulation trail F8 containing, Croscarmellose sodium(5.6mg), Hydroxy propyl methyl cellulose(4.0mg), Sodium Lauryl Sulphate(0.4mg) was selected as an optimized formulation as it showed same dissolution profile as innovator. It also matched the multimedia dissolution profile with the innovator.

Keywords: Solubility enhancer, Rivaroxaban, immediate release and Bioavailability.

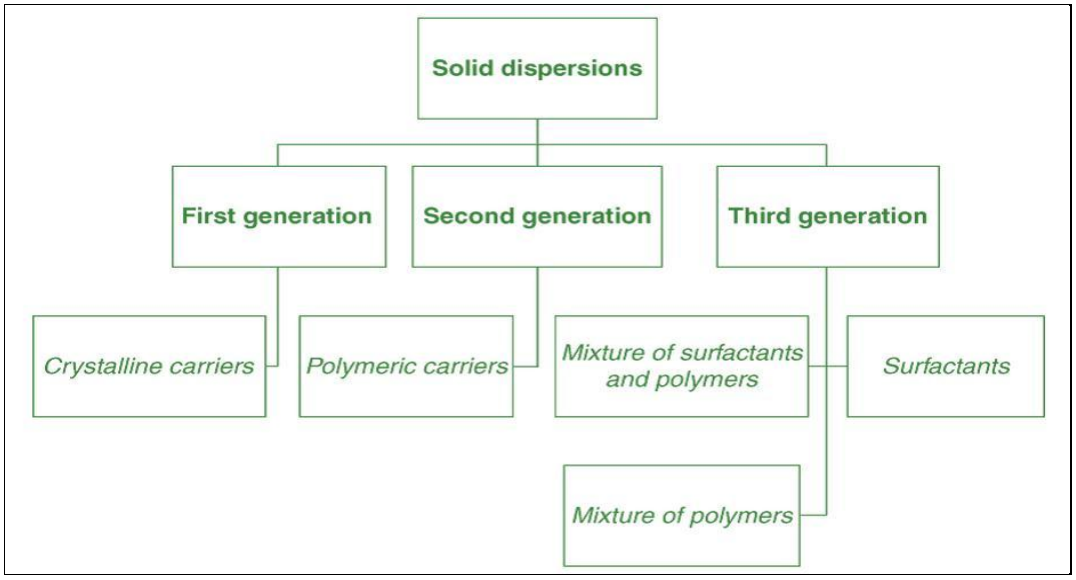
INTRODUCTION

Solid Dispersions

The term solid dispersion refers to a group of solid products consisting of at least two different components generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Chiou and Riegelman defined solid dispersions as "the dispersion of one or more active ingredients in an inert excipient or matrix, where the active ingredients could exist in finely crystalline, solubilized, or amorphous states"[17].Sekiguchi and Obi in 1961 first developed the concept of solid dispersion to enhance absorption of poorly water-soluble drugs. It involved the formation of eutectic mixtures of drugs with water-soluble carriers by melting of their physical mixtures, and once the carriers dissolved, the drug precipitated in a finely divided state in water. Later, Goldberg et al. demonstrated that a certain fraction of the drug might also be molecularly
Dispersed in the matrix, forming solid solutions, while other investigators reported that the drug might be embedded in the matrix as amorphous materials[19].

1.4.1 Classification of Solid dispersions[19]

Solid dispersions have been classified as follows depending on the type of carrier used for their preparation (Figure. 2)



I. First generation Solid Dispersions

These solid dispersions were prepared using crystalline carriers. Crystalline carriers include urea and sugars, which were the first carriers to be employed in solid dispersions. They have the disadvantage of forming crystalline solid dispersions, which were more thermodynamically stable and did not release the drug as quickly as amorphous ones.

II. Second generation Solid Dispersions

These solid dispersions contain amorphous carriers instead of crystalline. Here, the drugs are molecularly dispersed in an irregular form within an amorphous carrier, which are usually polymers. Polymeric carriers have been the most successful for solid dispersions, because they are able to originate amorphous solid dispersions. They are divided into fully synthetic polymers and natural product-based polymers. Fully synthetic polymers include povidone (PVP), polyethylene glycols (PEG) and polymethacrylates. Natural product based polymers are mainly composed of cellulose derivatives, such as hydroxypropylmethylcellulos (HPMC), ethyl cellulose or hydroxypropylcellulose or starch derivates, like cyclodextrins. In second-generation solid dispersions, the drug is in its supersaturated state because of forced solubilization in thecarrier. These systems are able to reduce the drug particle size to nearly a molecular level, to solubilize or co-dissolve the drug by the water-soluble carrier, to provide better wetability and dispersibility of the drug by the carrier material, and to produce amorphous form of thedrug and carriers. In these solid dispersions, the carrier dissolution (or mixtures of carriers) dictates the drug release profile.

III. Third generation Solid Dispersions

It has been shown that the dissolution profile can be improved if the carrier has surface activity or self-emulsifying properties; therefore third generation solid dispersions appeared. These contain a surfactant carrier, or a mixture of amorphous polymers and surfactants as carriers. These third generation solid dispersions are intended to achieve the highest degree of bioavailability for poorly soluble drugs and to stabilize the solid dispersion, avoiding drug recrystallization. The use of surfactants such as Inulin, Gelucire 44/14 and Poloxamer 407 as carriers was shown to be effective in originating high polymorphic purity and enhancing in-vivo bioavailability. The inclusion of surfactants in the formulation containing a polymeric carrier may help to prevent precipitation and/or protect a fine crystalline precipitate from agglomeration into much larger hydrophobic particles.

However, solid dispersions can also be classified based on the solid-state structure of dispersion.

A. Drug and Polymer Exhibiting Immiscibility in Fluid State

If a drug and polymer are immiscible in their fluid state, it is likely that they would not exhibit miscibility on solidification of the fluid mixture. Such systems may be regarded as similar to their corresponding physical mixtures, although any enhancement in dissolution performance compared to physical mixture may be owing to modification in morphology of drug and/or polymer due to physical transformation (i.e., solid to liquid state and back), intimate drug–polymer mixing, and/or enhanced surface area. Formation of crystalline or amorphous solid

dispersions can be influenced by the rate of solidification of mixture and the rate of crystallization of drug, polymer, or both.

B. Drug and Polymer Exhibiting Miscibility in Fluid State

If the drug and polymer are miscible in their fluid state, then the mixture may or may not undergo phase separation during solidification, thereby influencing the structure of solid dispersion[19].

B.1 Eutectic Mixtures

Eutectic mixtures are formed when the drug and polymer are miscible in their molten state, but on cooling, they crystallize as two distinct components with negligible miscibility. When a drug and a carrier are co-melted at their eutectic composition, the melting point of the mixture is lower than the melting point of either drug or carrier alone. While some researchers claim eutectics to be an intimate but inert physical mixture of the two components, others claim that the reduction in the melting point of eutectic mixtures is a direct evidence of molecular interaction between the drug and the carrier. At the eutectic composition, both drug and carrier exist in finely divided state, which results in higher surface area and enhanced dissolution rate of drug. Although not every carrier can form a eutectic with every drug, carriers such as polyethylene glycols (PEG), urea, and Pluronics have demonstrated eutectic formation to enhance dissolution rates of many poorly water soluble drugs.

B.2 Crystalline Solid Dispersion

A crystalline solid dispersion (or suspension) is formed when the rate at which drug crystallizes from drug–polymer miscible mixture is greater than the rate at which drug polymer fluid mixture solidifies. Such a crystalline solid dispersion may differ from that solid dispersion described under Drug and Polymer Exhibiting Immiscibility in Fluid State, where even the drug–polymer fluid mixture is not miscible.

B.3 Amorphous Solid Dispersion

If the drug–polymer fluid mixture is cooled at a rate that does not allow for drug crystallization, then drug is kinetically trapped in its amorphous or a “solidified-liquid” state. Although such systems offer dissolution advantages owing to their higher thermodynamic activity, they also risk the potential for conversion to a more stable and less soluble crystalline form.

B.4 Solid Solution

Solid solution is a solid dispersion that is miscible in its fluid as well as solid state. Most pharmaceutical solid solutions are amorphous in nature. A crystalline solid solution may result when a crystalline drug is trapped within a crystalline polymeric carrier. Amorphous solid solutions (also termed as amorphous molecular dispersion) have shown to enhance the dissolution rate of poorly soluble drugs. As the drug is molecularly dispersed in the carrier matrix, its effective surface area is significantly higher and hence the dissolution rate is increased. Solid solutions have also improved physical stability of amorphous drugs by inhibiting drug crystallization by minimizing molecular mobility.

C. Multicomponent Solid Dispersion

Ternary agents have been added to solid dispersion of two components either to enhance drug dissolution rate or to overcome manufacturing or stability issues. Surfactants have been added to solid dispersions to improve the dissolution rate of poorly water-soluble drugs. They have also been used to improve miscibility between drug and polymer or simply to inhibit drug crystallization during storage. Ternary agents in the form of plasticizers have been used in manufacturing of solid dispersions using hot-melt extrusion (HME) technique. These agents act by lowering the processing temperature needed to extrude drug–polymer mixture, thereby minimizing potential degradation.

1.4.2 Advantages of solid dispersions

- Solid dispersions appear to be a better approach to improve drug solubility than these techniques, because they are easier to produce and more applicable.
- Solid dispersions are more acceptable to patients than solubilization products, since they give rise to solid oral dosage forms instead of liquid as solubilization products usually do

Disadvantages of Solid Dispersions[20]

- The effect of moisture on the storage stability of amorphous pharmaceuticals is also a significant concern, because it may increase drug mobility and promote drug crystallization.
- Most of the polymers used in solid dispersions can absorb moisture, which may result in phase separation, crystal growth or conversion from the amorphous to the crystalline state or from a meta stable crystalline form to a more stable structure during storage. This may result in decreased solubility and dissolution rate

LIST OF MATERIALS

Rivaroxaban, PlasdoneS360, Crospovidone, PEG 6000, PVP K30, MCC, Talc, Magnesium stearate, Pipperment flavor.

FORMULATION TABLE

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Rivaroxaban	10	10	10	10	10	10	10	10	10
Plasdone S 630	5	10	15	-	-	-	-	-	-
crospovidone	-	-	-	5	10	15	-	-	-
PEG 6000	-	-	-	-	-	-	5	10	15
PVP30	10	10	10	10	10	10	10	10	10
MCC	85	80	75	85	80	75	85	80	75
Talc	5	5	5	5	5	5	5	5	5
Mg.Stearate	5	5	5	5	5	5	5	5	5
Total weight	**120**	**120**	**120**	**120**	**120**	**120**	**120**	**120**	**120**

LIST OF EQUIPMENT'S

S. NO.	EQUIPMENT	MODEL/ SOURCE
1	UV-Spectrophotometer	Labindia UV 3000+
2	Digital Balance	Scale-TEC
3	Digital PH Meter	Systronic Electronics, Mumbai
4	Dissolution Apparatus	Electrolab TDT-08L
5	Hot Air Oven	Tempo Instruments & Equipments, Mumbai

RESULTS AND DICUSSION

1. **Construction of Standard calibration curve of Rivaroxaban in 6.8 phosphate buffer**

The absorbance of the solution was measured at 270nm, using UV spectrometer with 6.8 phosphate buffer as blank. The values are shown in table. A graph of absorbance Vs Concentration was plotted which indicated in compliance to Beer's law in the concentration range 2 to 10 µg/ml.

Standard Calibration graph values of Rivaroxaban in 6.8 phosphate buffer at λ_{Max} =270 nm

Concentration (µg / ml)	Absorbance
0	0
2	0.121
4	0.234
6	0.362
8	0.471
10	0.598

Standard plot of Rivaroxaban by taking absorbance on Y – axis and concentration (µg/ml) on X – axis, the plot is shown fig

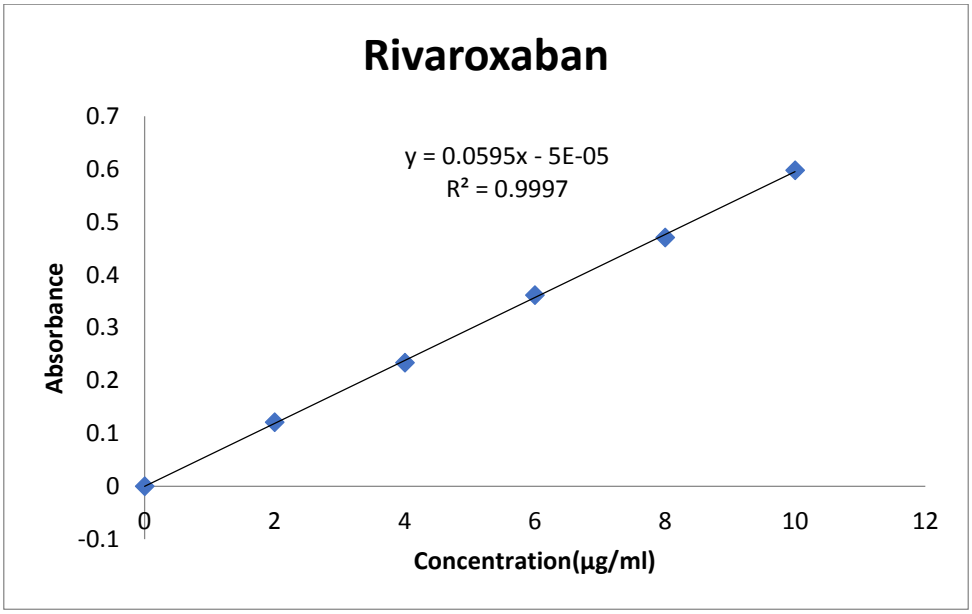


Fig. 12: Standard calibration curve of Rivaroxaban in 0.1N HCl

Inference

The standard calibration curve of Rivaroxaban in 6.8 phosphate buffer showed good correlation with regression value of 0.999

III. Evaluation of Tablets

Table 13: Pre compression studies of Rivoroxaban immediate release tablets

Formulation Code	Bulk density (Kg/cm^3)	Tapped density (Kg/cm^3)	Cars index	Hausners ratio	Angle of repose (˚)
F1	0.28	0.32	12.95	1.15	32.62
F2	0.29	0.31	8.29	1.09	29.47
F3	0.29	0.31	4.90	1.05	25.58
F4	0.32	0.34	5.66	1.06	26.77
F5	**0.31**	**0.34**	**7.99**	**1.09**	**28.47**
F6	0.32	0.35	7.79	1.08	27.17
F7	0.30	0.32	8.83	1.10	29.58
F8	0.29	0.32	9.70	1.11	30.11
F9	0.28	0.32	10.52	1.12	31.42

Inference

- The prepared tablets were evaluated for their flow properties; the results for the blends of compression tablets were shown in Table.
- The bulk density and the tapped density for all formulations were found to be almost similar.
- The Carr's index and Hausner's ratio were found to be in the range of ≤ 18 and 1.0 to 1.56 respectively, indicating good flow and compressibility of the blends.
- The angle of repose for all the formulations was found to be 25.58 to 33.72 which indicating passable flow (i.e. incorporation of glidant will enhance its flow).

Post compression studies of Rivaroxaban Immediate Release Tablets

Formulation Code	% weight variation	Thickness (mm)	Hardness (Kg/cm^2)	% friability	Disintegration time (Sec)	Dispersion time (Sec)	Water absorption ratio	% Drug Content
F1	3.02	3.17	3.8	0.38	56.49	49.58	73.58	99.86
F2	4.13	3.12	3.7	0.28	42.47	35.39	79.68	99.35
F3	2.19	3.08	3.6	0.51	39.59	34.96	76.4	100.83
F4	5.31	3.18	3.7	0.37	41.59	40.87	89.57	100.43
F5	**2.93**	**3.12**	**3.6**	**0.54**	**25.39**	**21.98**	**91.47**	**101.16**
F6	3.82	3.16	3.6	0.28	22.94	16.49	92.48	100.34
F7	4.39	3.12	3.6	0.36	28.49	21.43	87.48	99.38
F8	5.22	3.19	3.7	0.34	29.51	19.39	88.39	99.51
F9	2.99	3.07	3.7	0.36	30.59	24.51	85.39	99.61

Inference

- The variation in weight was within the range of ±10% complying with pharmacopoeia specifications of USP.
- The thickness for different formulations was found to be between 3.07 to 3.19 mm
- The hardness for different formulations was found to be between 3.6 to 3.8 kg/cm^2, indicating satisfactory mechanical strength
- The friability was < 1.0% W/W for all the formulations, which is an indication of good mechanical resistance of the tablet.
- The disintegration for different formulations was found to be between 22.94 to 56.49 sec
- The dispersion time for different formulations was found to be between 19.39 to 49.58 sec
- The water absorption ratio for different formulations was found to be between 73.58 to 92.48 %
- The drug content was found to be within limits 98 to 102 %.

Table 16: In-vitro Dissolution results for formulation trails

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	**0**	0	0	0	0
3	30.29	32.94	32.19	31.84	**42.98**	43.19	35.38	39.29	43.29
6	47.28	54.27	63.86	63.29	**76.37**	75.47	54.12	71.39	73.49
9	71.39	77.47	87.97	87.46	**99.71**	99.97	74.25	92.38	93.74
12	88.27	92.46	99.46	98.46			91.38	99.51	99.96
15	99.31	99.21		99.93			99.73		

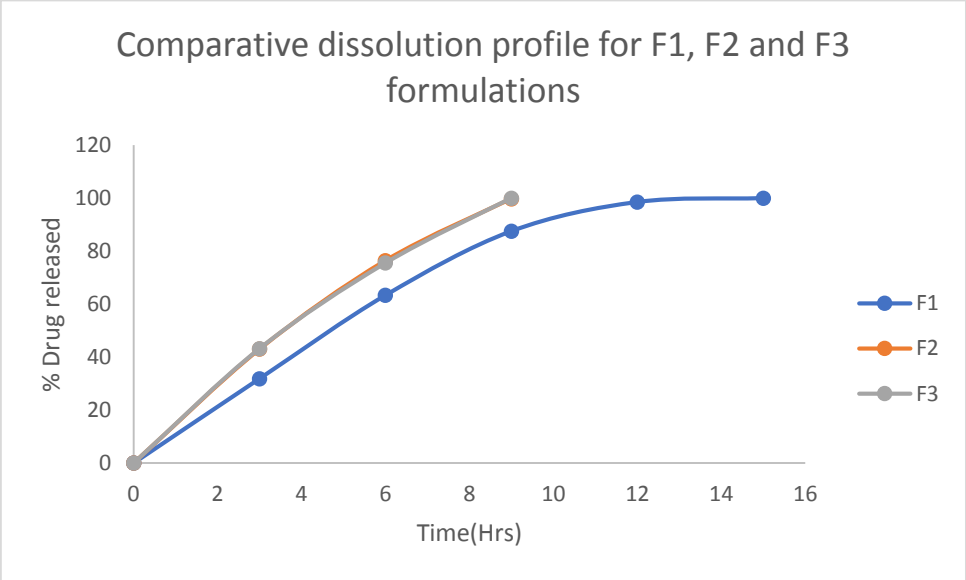


Fig. 13: Comparative dissolution profile for F1, F2 and F3 formulations

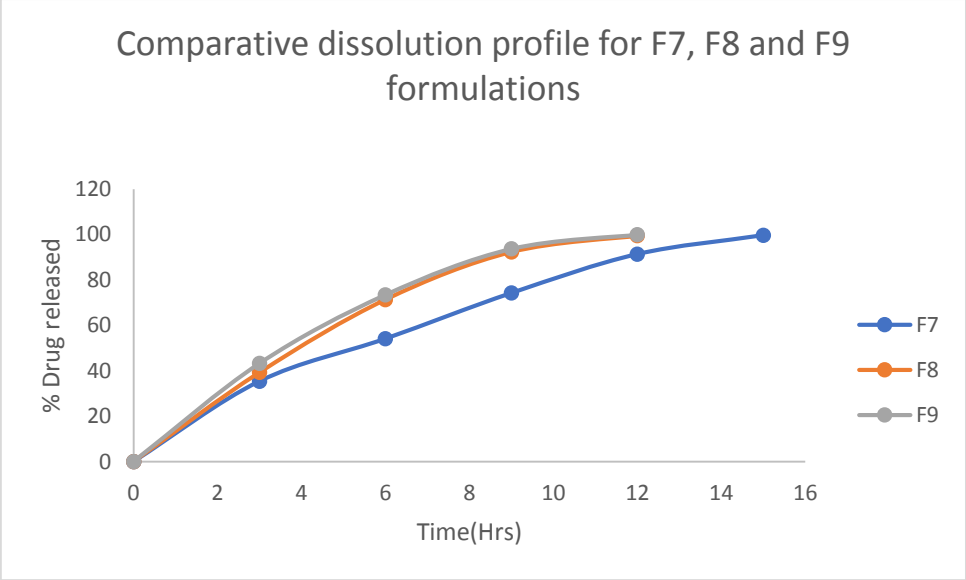
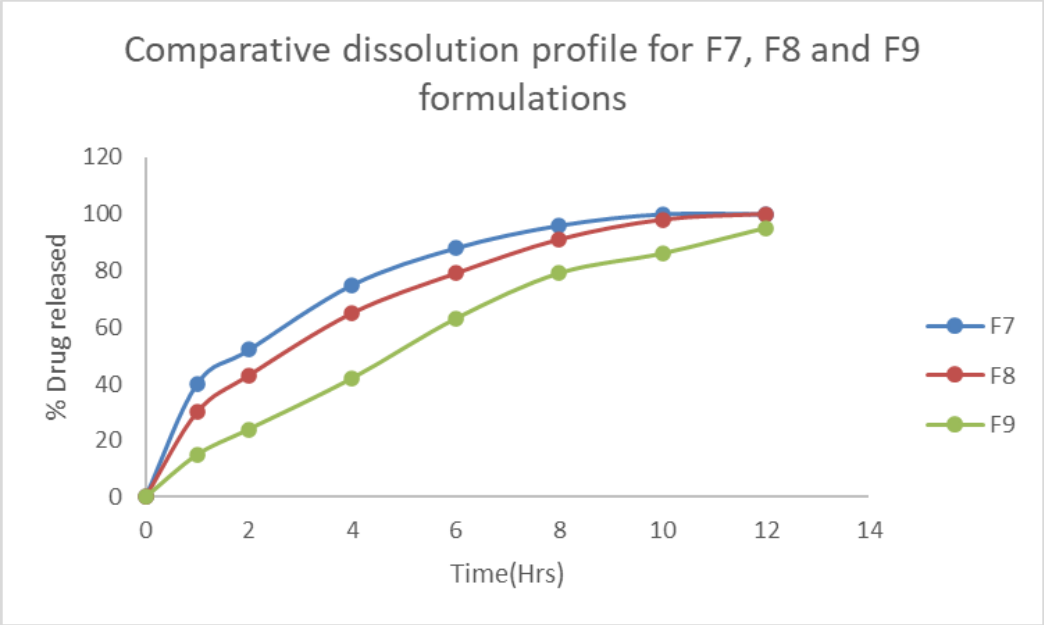
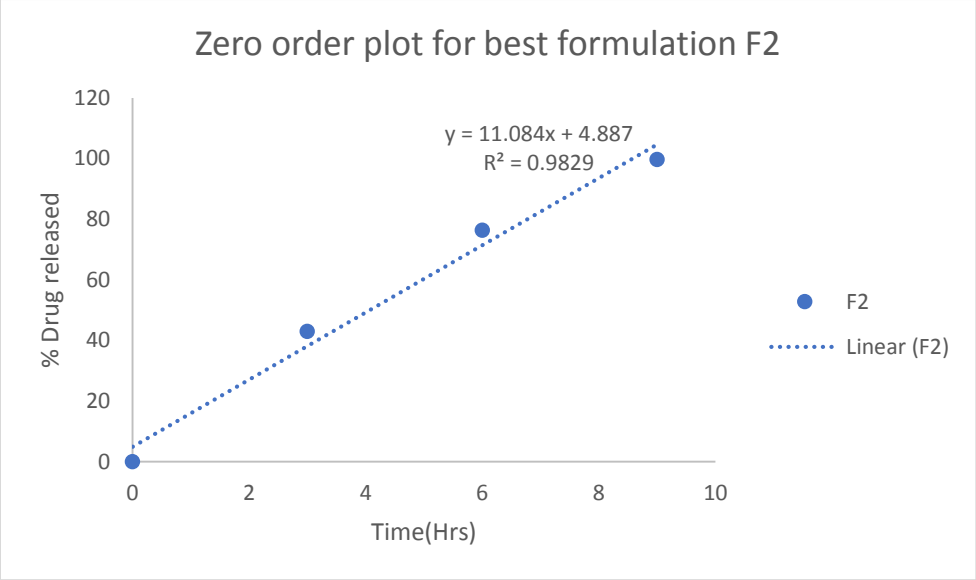


Fig. 15: Comparative dissolution profile for F7, F8 and F9 formulations



Zero order plot for best formulationF2



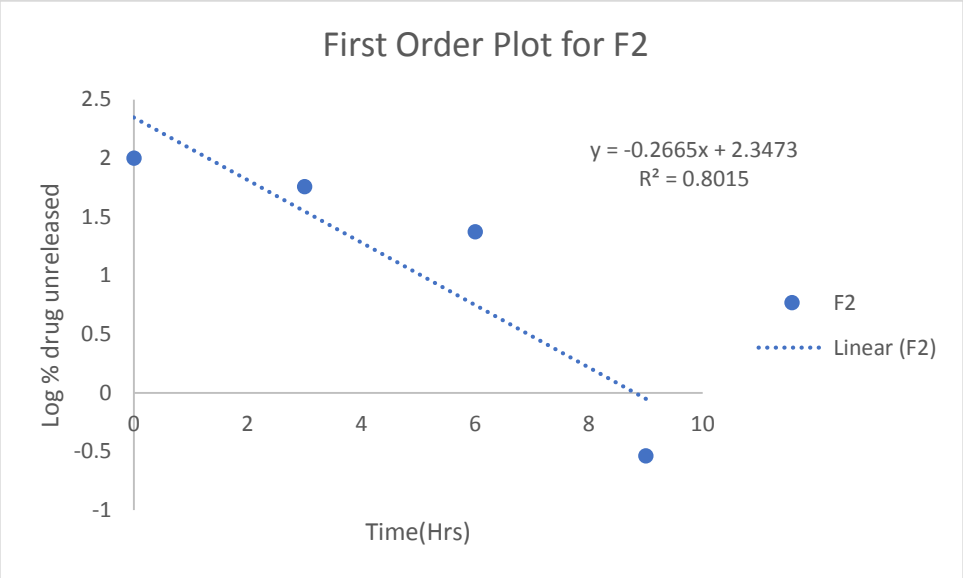


Fig. 13: First order plot for best formulation F2

SUMMARY AND CONCLUSION

1. From the FT-IR spectra the interference was verified and found that Rivaroxaban did not interfere with the excipients used.
2. Direct compression method was established to manufacture immediate release tablets of Rivaroxaban.
3. Immediate release tablets of Rivaroxaban were successfully prepared using Plasdone S630, Crospovidone and PEG 6000.
4. Evaluation parameters like Weight variation, Thickness, Hardness, Friability,and drug content indicate that values were within permissible limit for all formulations.
5. *In vitro* drug release study was carried out and based on the results; F5 was identified as the best formulation among all the other formulations.
6. The Plasdone S630 used formulation has shown better release profile than compared with other formulations.

   Thus, we are able to achieve our objective of preparing oral disintegrating tablets of Rivaroxaban with minimum excipients and simple method of manufacture and enhance the solubility of the drug.

BIBILOGRAPHY

1. Alfred martin, Physical pharmacy, fifth edition, Lippincott, Williams and wilking, Newyork. 2007; 230-245 and 337-345.
2. Michael E Aulton. Pharmaceutics the scienece of dosage form design, second edition, Churchill Living stone, New York. 2002;15-32.
3. James swarbrick and James Boylan. Encyclopedia of pharmaceutical technology second edition, marcel Dakker, Ic. 2002;1:717-727.
4. Brahmankar DM and Sunil B Jaiswal. Biopharmaceutics and pharmacokinetics A treatise, first edition,Vallabhprakashan, Delhi. 1995;19-25.
5. Gong Y, Grant DJW and Brittain HG. Principles of Solubility in Augustijns P, Brewster ME (Eds.). Solvent Systems and Their Selection in Pharmaceutics and Biopharmaceutics. Springer Science Business Media, LLC, New York. 2007;1- 27.
6. USP 28-NF 23. The United States Pharmacopoeial Convention, Rockville, MD. 2005;2875.
7. Zamora I, Ridderstrom M, Ungell A, Andersson T and Afzelius L. Progress in ADME Prediction Using GRID-Molecular Interaction Fields, in: G. Cruciani (Ed.), Molecular Interaction Fields - Applications in Drug Discovery and ADME Prediction, Wiley-VCH, Verlag, GmbH & Co. KGaA, Weinheim. 2006;228.
8. Mannhold R, Berellini G, Carosati E and Benedetti P. Use of MIF-based VolSurf Descriptors in Physicochemical and Pharmacokinetic Studies in G. Cruciani (Ed.). Molecular Interaction Fields - Applications in Drug Discovery and ADME Prediction, Wiley-VCH, Verlag, GmbH, KGaA Co and Weinheim. 2006;180.
9. Brittain HG. Ionic Equilibria and the pH Dependence of Solubility, in: P. Augustijns, M. E. Brewster (Eds.), Solvent Systems and Their Selection in Pharmaceutics and Biopharmaceutics, Springer Science + Business Media, LLC, New York. 2007;43.
10. Yu L. An Integrated Model for Determining Causes for Poor Oral Drug Absorption. Pharm Res. 1999;16:1883–1887.
11. Prentis RA, Lis Y and Walker SR. Pharmaceutical Innovation by Seven UK owned Pharmaceutical Companies. Br. J Clin Pharmacol. 1988;25:387–396.
12. Bai JPF, Guo J and Chaubal MV. Use of Nonactive Pharmaceutical Excipients in Oral Drug Formulations: Biopharmaceutical Classification System Considerations, in: A. Katdare, M. V. Chaubal (Eds.), Excipient Development for Pharmaceutical, Biotechnology, and Drug Delivery Systems, Informa Healthcare, USA. 2006;182-188.
13. Brewster ME, Mackie C, Noppe M, Lampo A and Loftsson T. The Use of Solubilizing Excipients and Approaches to Generate Toxicology Vehicles for Contemporary Drug.
14. Pipelines in Augustijns P and Brewster ME. (Eds.), Solvent Systems and Their Selection in Pharmaceutics and Biopharmaceutics. Springer Science Business Media, LLC, New York. 2007; 222.
15. Guidance for Industry, Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, U.S. Department of Health and Human Services, Food and Drug Administration Center for Drug Evaluation and Research (CDER). August 2000. <http://www.fda.gov/cder/guidance/index.htm >.
16. Shinde AJ. Solubilization of Poorly Soluble Drugs: A Review. Latest Reviews. 2007;5(6).
17. Leuner C and Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm. 2000;50:47-60.
18. Chiou WL and Riegelman S. Pharmaceutical application of solid dispersion systems. J Pharm Sci. 1971;60(9):1281-1302.
19. Vasanthavada M, Tong W and Serajuddin ATM. Development of Solid Dispersion for Poorly Water-Soluble Drugs, in: R. Liu (Ed.), Water-Insoluble Drug Formulation, second edition., CRC Press, Taylor and Francis Group, Boca Raton, FL. 2008;499-529.
20. Vasconcelos T, Sarmento B and Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov Today. 2007;12:1068-1075.
21. Serajuddin ATM. Solid dispersion of poorly water-soluble drugs: Early promises, subsequent problems, and recent breakthroughs. J Pharm Sci. 1999;88:1058–1066.
22. Sharma DK and Joshi SB. Solubility Enhancement Strategies for Poorly Water-Soluble Drugs in Solid Dispersions: A Review. Asian J Pharm. 2007;1:9-19.
23. Jung KE, Chun MK, Jang JS, Lee IH, Lee KR and Choi HK. Preparation of a solid dispersion of felodipine using a solvent wetting method, Eur. J. Pharm. Biopharm. 2006;64:200–205.
24. Dhirendra K, Lewis S, Udupa N and Atin K. Solid Dispersions. A Review. Pak J Pharm Sci. 2009; 22(2):234-246.

25. Thompson DO. Cyclodextrins—Enabling Excipients: A Case Study of the Development of a New Excipient—Sulfobutylether β-Cyclodextrin (Captisol), in: A. Katdare, M. V. Chaubal (Eds.), Excipient Development for Pharmaceutical, Biotechnology, and Drug Delivery Systems, Informa Healthcare, USA. 2006;51-67.
26. Karmarkar AB, Gonjari ID, Hosmani AH, Dhabale PN and Bhise SB. Dissolution Rate Enhancement of Fenofibrate Using Liquisolid Tablet Technique. Part II: Evaluation of In Vitro Dissolution Profile Comparison Methods. Latin American Journal of Pharmacy. 2009;28(4):538-43.
27. Dissolution enhancement of Glipizide using liquisolid tablet technique. Indian drugs. 2008;45(4): 318.
28. Keraliya RA, Soni TG, Thakkar VT, Gandhi TR and Patel RC. Formulation and Physical characterization of microcrystals for dissolution rate enhancement of Tolbutamide. Int J Res. Pharm Sci. 2010;1:69-77
29. Junghanns JA and Müller RH. Nanocrystal technology, drug delivery and clinical applications. Int J Nanomedicine. 2008;3:295–310.
30. Remington the science and practice of pharmacy, 20th edition, Lippincott, Williams and wilking. 1:897-898.
31. Piyush Patel, Ravi Patel and Yogesh Patel. Formulation, Development and Evaluation of Rivaroxaban Tablets by Using Solubility Enhancement Technique. Int J Pharm Sci and Scient Res. 3(3):51-55.
32. Gambhire MS, Gujar KN and Vaidhya AA. Formulation, Optimization and Evaluation of Immediate Release Tablet of Apixaban, International Journal of Chem Tech Research CODEN (USA). IJCRGG. 2017;10(10):424-435.
33. Sunitha Reddy M and Himavarsha M. Formulation Development and Evaluation Of Immediate Release Anti-Coagulant Drug Rivaroxaban Film Coated Tablets. International Journal of Pharmacy and Biological Sciences IJPBSTM. 2018;8(4):369-378.
34. Remya PN, Saraswathi TS, Sangeetha S, Damodharan N, Kavitha R and Remya P N. Formulation and Evaluation of Immediate Release Tablets of Acyclovir. J Pharm Sci and Res. 2016;8(11):1258-1261.