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Research Article

Quality By Design (QBD) Approach for The Modification of Poorly Soluble Drugs

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Abstract:

Quality by Design (QbD) has revolutionized pharmaceutical development by ensuring that quality is designed into processes and products from the outset, rather than relying solely on end-product testing. This systematic approach is particularly valuable in addressing the challenges posed by poorly soluble drugs, which often suffer from low bioavailability. The present work used Liquisolid technology to change the physicochemical characteristics of poorly soluble medicines Olmesartan Medoxomil (OLM) and Ranolazine (RAN) and develop and analyse rapid-release and extended-release liquisolid tablets. Various types of evaluation parameters were studied like thickness, hardness, friability, drug content as well as *in-vitro* drug release. Liquisolid tablets of OLM and RAN were prepared using Neusilin US as a carrier, Aerosil 200 as a coating material, Primojel as a disintegrant, and PEG 400 as a non-volatile solvent with varying R values and drug concentrations. OLM tablets showed rapid dissolution due to high Neusilin US content, low Aerosil 200, high R value, and low drug concentration. RAN liquisolid tablets were formulated with similar components and ratios. The optimized formulations exhibited enhanced dissolution profiles for both drugs.

Keywords: Quality by Design (QbD), Poorly soluble drugs, Bioavailability, Liquisolid technology, Olmesartan Medoxomil (OLM), Ranolazine (RAN), Rapid-release tablets, Extended-release tablets, Neusilin US, Aerosil 200, Primojel.

Introduction

The development of poorly soluble drugs poses significant challenges in achieving optimal bioavailability and therapeutic efficacy. [1,2] Traditional methods, which rely heavily on trial-and-error, often fail to deliver consistent quality and scalability. To overcome these limitations, the pharmaceutical industry has adopted the QbD approach, as advocated by regulatory agencies like the FDA and ICH. QbD emphasizes a deep understanding of the product and process through systematic risk assessment and scientific rationale. [3,4] This ensures that quality is built into the drug formulation and manufacturing processes, paving the way for more reliable and efficient drug delivery systems. [5]

The objective of the current study was to modify physicochemical properties of poorly soluble drugs; Olmesartan Medoxomil (OLM) and Ranolazine (RAN) using Liquisolid technique and to formulate and evaluate OLM liquisolid tablets (rapid release) and RAN liquisolid tablets (extended release). [6,7]

Formulation of Liquisolid tablets of OLM and RAN:

For OLM:

Liquisolid tablets of OLM were prepared each containing 20 mg drug, using the single punch tablet press. OLM was dispersed in PEG 400. Neusilin US and Aerosil 200 were added to the above mixture under continuous mixing in a mortar. Finally, Primojel as superdisintegrant and Lactose as filler were mixed and mixture was blended for a period 10 minutes. The blend was compressed into tablets using the single punch tablet press.

For RAN:

Liquisolid tablets of RAN were prepared each containing 375 mg drug, using the single punch tablet press. RAN was dispersed in PEG 400. PVP K30 was added in the mixture. Neusilin US2 and Aerosil 200 were added to the above mixture under continuous mixing in a mortar. Finally, Eudragit L100 55 was mixed and mixture was blended for a period 10 minutes. The blend was compressed into tablets using the single punch tablet press.

Evaluation of Liquisolid tablets of OLM and RAN:

Post compression parameters:

i. Thickness:

The thickness was measured using vernier caliper. Five tablets from each batch were used and average values were calculated.

ii. Hardness:

The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm2. Six tablets from each formulation were tested for hardness.

iii. Friability:

The test was performed using Roche friabilator. Twenty tablets were weighed and placed in the drum of the friabilator. The tablets were allowed to revolve, fall from height of six inches for 4 min. Then tablets were de-dusted and re-weighed.

The % friability was then calculated using formula,

$$\% \text{ Friability} = \frac{Weight\ of\ tablets\ before\ test - weight\ of\ tablets\ after\ test}{Weight\ of\ tablets\ after\ test} \times 100$$

iv. Disintegration time:

The disintegration time of the tablets was measured in distilled water (37 ± 2°C) using disintegration test apparatus with disk. Five tablets from each formulation were tested for the disintegration time.

v. Drug content:

The OLM content in different liquisolid tablet formulations was determined by accurately weighing 20 tablets of each formula individually. Each tablet was then crushed and a quantity of powder equivalent to 10 mg of OLM was dissolved in 100 mL methanol. 1 mL of this solution was diluted to 10 mL with methanol and measured spectrophotometrically at

λmax of 257nm.

vi. In vitro drug release:

For OLM:

The in vitro drug release study of the OLM tablets was performed using USP Type II dissolution apparatus. Liquisolid tablets and pure drug (20 mg) separately, were put into each of 900 mL phosphate buffer pH 6.8, at 37±0.5°C with a 50-rpm rotating speed. Samples (10 ml) were withdrawn at regular time intervals (2, 4, 6, 8, 10, 15, 20 and 25min) and filtered using a 0.45 m filter. An equal volume of the dissolution medium was added to maintain the volume constant. The drug content of the samples was assayed using UV visible

spectrophotometric method at 257 nm.

For RAN:

The in vitro drug release study of the RAN tablets was performed using USP Type II dissolution apparatus Liquisolid tablets were put into each of 900 mL 0.1 HCl, at 37±0.5°C with a 100-rpm rotating speed. Samples (10 ml) were withdrawn at regular time intervals (1, 4, 8 and 12 hr) and filtered using a 0.45 m filter. An equal volume of

the dissolution medium was added to maintain the volume constant. The drug content of the samples was assayed using UV visible spectrophotometric method at 272 nm. All measurements were done in triplicate.

Results and Discussion

Post compression parameters:

Liquisolid tablets of OLM were successfully prepared and were used for further evaluation studies.

Thickness of liquisolid tablet was found to be in the range of 4.68 to 4.85 mm. It was observed that as the concentration of PEG 400 and Neusilin US changes thickness varies. As the PEG 400 concentration increases the thickness of liquisolid tablet decreases which results into squeezing out of PEG 400 during compression. Neusilin US has large surface area and porous nature, adsorbs high loads of oils or water and can be mechanically compacted into high quality tablets. Due to the presence of higher concentration of Neusilin US thickness does not decreases. This is due to coating of Neusilin US particles to drug and PEG 400 complex and avoids the squeezing out of PEG 400 as it adsorbs on the drug and PEG 400 complex. Thus there is combined positive effect of PEG 400 and Neusilin US on the liquisolid tablet thickness. Hardness of liquisolid tablet was found to be in the range of 5.06 to 5.15 kg/cm2 respectively. Neusilin US2 is superior in compressibility. Neusilin US makes hard tablets at low compression force and in addition, improves the hardness of other filler and binder excipients. Neusilin US with combination of Primojel and lactose here improves the hardness and increases the bulk of tablet. But concentration of lactose is same in all trials so there is no individual effect of lactose here on hardness. Increase in hardness and compression pressure did not affect the disintegration time and as well as friability. This indicates that as the concentration of Neusilin US and Primojel increases hardness of liquisolid tablet increases. Friability of tablets was found to be below 1% which is acceptable. Disintegration time of liquisolid tablets were in the range of 1-2 minutes. Drug content of all liquisolid tablets were found to be in between acceptable range.

Table 1: Evaluation of post compression parameters of OLM tablet formulations

Batches	Thickness (mm)	Hardness (kg/cm2)	Friability(%)	DisintegrationTime (min)	Drug content (%)
OL1	4.73	5.11	0.19	1.11	97.45
OL2	4.75	5.11	0.16	1.13	99.16
OL3	4.81	5.12	0.18	1.01	98.98
OL4	4.78	5.13	0.17	1.25	96.12
OL5	4.72	5.11	0.21	1.13	102.01
OL6	4.83	5.14	0.14	1.15	101.01
OL7	4.68	5.06	0.27	1.25	100.02
OL8	4.73	5.09	0.16	1.17	99.12
OL9	4.74	5.12	0.18	1.1	97.14
OL10	4.71	5.07	0.25	1.19	98.52

Table 2: In vitro drug release of OLM tablet formulations OLF1 to OLF10

Time (min)	Pure Drug	OL1	OL2	OL3	OL4	OL5	OL6	OL7	OL8	OL9	OL10
0	0	0	0	0	0	0	0	0	0	0	0
2	11.81	53.11	53.38	56.45	52.22	53.2	54.72	52.92	51.66	52.75	52.18
4	12.45	62.23	60.64	68.76	59.46	61.46	67.64	59.44	69.32	62.24	58.37
6	14.08	67.81	66.42	82.48	65.12	66.38	74.28	65.59	83.1	67.57	64.58
8	15.71	74.26	75.62	89.53	74.26	76.63	79.47	74.48	89.92	73.62	73.29
10	17.52	81.52	82.73	98.75	80.53	83.37	87.81	83.32	92.57	84.48	81.67
15	18.95	87.29	88.25	101.9	87.24	88.72	94.35	88.56	95.61	87.15	87.45
20	22.23	97.17	96.41	94.69	95.38	97.21	98.32	94.69	97.21	96.33	93.89
25	24.36	98.78	98.28	96.52	97.55	97.56	98.74	98.45	98.86	98.65	97.38

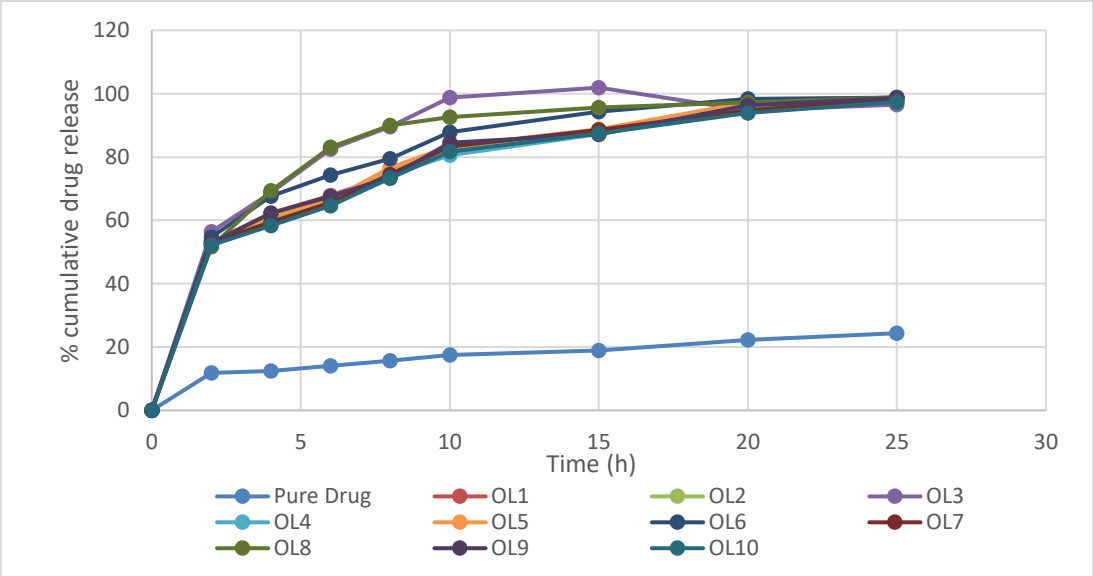

Fig 1: Dissolution profile of pure drug and Formulations OLF1 to OLF10

Liquisolid tabelts of RAN were successfully prepared and were used for further evaluation studies.

Thickness of liquisolid tablet was found to be in the range of 5.6 to 6.4 mm. The change in the concentration of Neusilin US2 and PEG 400 varies thickness of liquisolid tablet. Neusilin US2 has large surface area and porous nature, adsorbs high loads of oils or water and can be mechanically compacted into high quality tablets. Due to the presence of higher concentration of Neusilin US2 thickness does not decreases. This is due to coating of Neusilin US particles to drug and PEG 400 complex and avoids the squeezing out of PEG 400 as it adsorbs on the drug and PEG 400 complex. As the PEG 400 concentration increases the thickness of liquisolid tablet decreases which results into squeezing out of PEG 400 during compression. Thus there is combined effect of Neusilin US and PEG 400 on the liquisolid tablet thickness. Hardness of liquisolid tablet was found to be in the range of 7.6 to 8.6 kg/cm2. As concentration of PEG 400 increases the hardness of tablet decreases as it exhibit the more porosity to liquisolid formulation. Neusilin US is superior in compressibility.

Neusilin US2 makes hard tablets at low compression force and in addition, improves the hardness of other filler and binder excipients. Hence Neusilin US2 was used in less concentration. PVP K30 in less concentration gives the proper binding and hardness to the liquisolid tablet. Friability of tablets was found to be acceptable i.e. below 1%. Drug content of all liquisolid tablets were found to be in between acceptable range. Hardness and thickness varied depending on the change in the concentration of excipients.

Table 3: In vitro drug release of RAN tablet formulations RAF1 to RAF10

Time (hour)	Pure Drug	RAF1	RAF2	RAF3	RAF4	RAF5	RAF6	RAF7	RAF8	RAF9	RAF10
0	0	0	0	0	0	0	0	0	0	0	0
1	18.43	24.46	23.95	25.24	23.36	25.24	25.85	24.85	22.35	26.64	28.58
4	26.25	44.12	43.57	45.31	45.05	45.31	46.61	44.61	42.11	47.4	49.59
8	29.26	64.23	63.42	64.72	64.19	64.72	67.38	65.38	61.08	67.07	70.08
12	31.25	92.11	91.42	93.34	91.32	93.23	94.44	92.87	90.45	93.45	96.69

Table 4: Evaluation of post compression parameters of RAF tablet formulations

Batches	Thickness (mm)	Hardness (kg/cm2)	Friability (%)	Drug content (%)
RAF1	5.67	8.39	0.2	98.35
RAF2	5.67	8.4	0.2	98.47
RAF3	5.6	8.25	0.24	97.91
RAF4	5.73	8.5	0.23	97.67
RAF5	5.68	8.42	0.18	98.26
RAF6	5.82	8.75	0.15	99.59
RAF7	5.68	8.42	0.18	97.88
RAF8	5.7	8.45	0.18	98.69
RAF9	5.65	8.35	0.22	99.75
RAF10	5.75	8.65	0.17	101.23

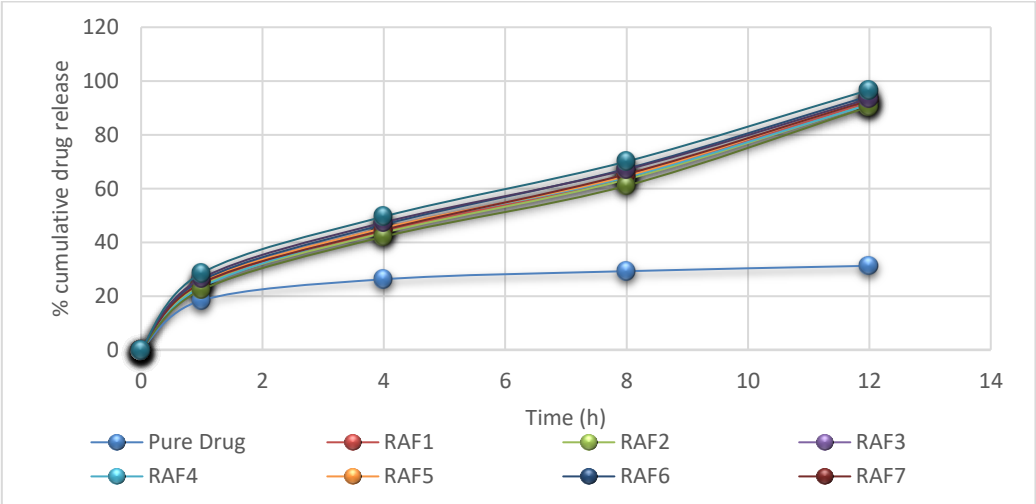

Fig 2: Dissolution profile of pure drug and Formulations RAF1 to RAF10.

Summary and Conclusion

Liquisolid technique was successfully used to design and develop the solid oral dosage form of poorly soluble drugs, OLM and RAN. Rapid release tablets of OLM and extended release of RAN were screened, optimized and evaluated using QbD approach. Liquisolid tablets of OLM were successfully prepared by using Neusilin US as a carrier material, Aerosil 200 as a coating material, Primojel as a disintegrant, PEG 400 as a non-volatile solvent with two different ratios of R values and drug concentration. The dissolution of liquisolid tablet of OLM was found to be rapid due to the presence of high quantity of Neusilin US2, low quantity Aerosil 200, high R value and low drug concentration. Liquisolid tablets of RAN were successfully prepared by using Neusilin US as a carrier material, Aerosil 200 as a coating material and PEG-400 as a non-volatile solvent with two different ratios of R values and drug:solvent ratios. The outstanding findings of the current studies, therefore, ratified OLM and RAN with high degree of formulation robustness and potential for improved therapeutic performance for the management of hypertension and gastrointestinal problem.

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