Formulation and Evaluation of Immediate-Release Tablet Containing Atorvastatin Phospholipid Solid Dispersion

Bashar K. K. GHYADH [1] * (iD), **Eman B. H. AL-KHEDAIRY** [1] (iD)

[1]   Department of Pharmaceutics, College of Pharmacy, University of Baghdad, Baghdad, Iraq.
*   Corresponding Author. E-mail: Bashaar.Kareem2100m@copharm.uobaghdad.edu.iq (B.G.); Tel. +964 770 748 1905.

ABSTRACT: Oral tablets containing solubilized drug in the presence of appropriate excipients may give us an immediate release of the drug. Phospholipid solid dispersion (PSD) is a branch of solid dispersion in which phospholipid acts as a hydrophilic polymer in the presence of a suitable adsorbent to enhance the solubility of poorly soluble drugs. The anti-hyperlipidemic drug Atorvastatin (ATR) is an example of such drug, as it belongs to the class II group according to the biopharmaceutical classification system (BCS) with low bioavailability due to its low solubility. Phosphatidylcholine in combination with magnesium aluminum silicate as an adsorbent in a ratio of ATR: PC: MAS 1:3:4 was used to prepare ATR PSD by the solvent evaporation method, the product showed acceptable physical properties and utilized for the preparation of immediate-release tablets (IRTs) of ATR. Ten formulas of ATR- IRTs were prepared by direct compression method using different types and concentrations of diluents (Avicel®PH102, Avicel®PH101, and starch) and superdisintegrants (crospovidone, croscarmellose sodium, and sodium starch glycolate) and evaluated for their drug content, weight variation, hardness, friability, *in vitro* disintegration time and dissolution profile. The tablets formula (T10) that were prepared with ATR-PSD and Avicel®PH102 as a diluent and Croscarmellose Sodium (CCS) 5% w/w as super disintegrant show the shortest disintegration time (DT) (38 ±1 sec.) and best drug release (91% within 15 min) in 0.05M phosphate buffer (pH 6.8).

KEYWORDS: Atorvastatin; Avicel® PH102; immediate-release tablets; Phospholipid solid dispersion.

1. INTRODUCTION

For many years, oral drug delivery has been recognized as the most commonly used method of administering drugs for systemic effects (1) Due to its simplicity, high patient acceptance, and cost-effective manufacturing process (2). Immediate-release tablets (IRT) are ones designed to be ingested as a whole and disintegrate quickly in the gastrointestinal tract, allowing for rapid release of the drug (3).

Atorvastatin (ATR) is a 3 - hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, it is a lipid-regulating drug. It is also used for primary and secondary prophylaxis of cardiovascular events (4). atorvastatin (Figure 1) is very slightly soluble in water; belongs to Class II of the BCS. It has an absolute oral bioavailability of 12 %. The poor oral bioavailability is attributed to presystemic clearance in the gastrointestinal mucosa and high hepatic first-pass metabolism in addition to its low solubility (5,6).

The most commonly employed method for improving the bioavailability of poorly water-soluble drugs is solid dispersion (SD), where the drug is dispersed in a highly soluble carrier substance (8).

Phospholipids, owing to their amphiphilic properties, can be utilized in oral dosage forms for various purposes such as emulsifying, wetting, solubilizing, and forming liposomes (9). However, when formulating them as solid dosage forms, phospholipids may present challenges due to their high adhesiveness and poor flow characteristics, unlike polymer-based solid dispersion systems. Therefore, the incorporation of adsorbents becomes necessary to transform phospholipid-based dispersion systems into a solid state (10).

In addition, This carrier was selected as it has lipid lowering effect, so synergistic effect may be obtained by the prepared tablets (11). In the present work, immediate-release tablets of ATR phospholipid-based solid dispersion (PSD) were prepared by direct compression method using different diluents and super disintegrants.
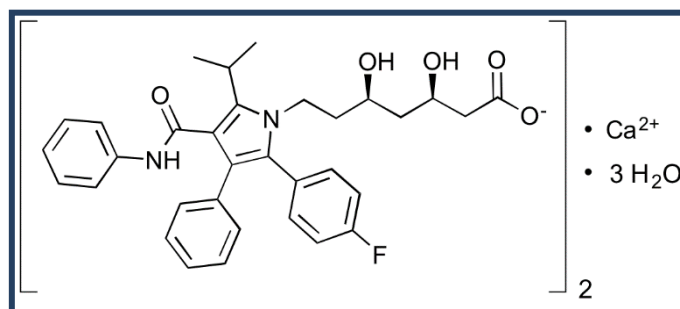
Figure 1. Chemical structure of atorvastatin calcium (7).

2. RESULTS

2.1. Evaluation of phospholipid solid dispersion

A high percentage yield was obtained from the prepared formula (88.65%). This result indicates that this method was suitable and efficient. On the other hand, the findings of percentage drug content were (98.55% ±0.33) w/w for prepared formulas, aligning with the USP guidelines of (98-102%) (12).

In addition, the solubility of ATR was significantly improved (P-value <0.05) in PSD formulation (3151.33±49.36 µg/ml) as compared to the solubility of the pure drug (150.8±6.19 µg/ml). This result can be explained by the amphiphilic surfactant behavior of PC that increased the solubility of the drug (13,14), in addition to adsorption of this dispersed system onto hydrophilic adsorbent material with high surface area which increased surface area of the drug that is exposed to the solvent and hence increase in the solubility of the drug (15).

2.2. In-vitro dissolution studies of ATR-PSD

Comparing the *in-vitro* dissolution profiles of the pure ATR and the prepared ATR-PSD indicated that the prepared ATR-PSD exhibited improved dissolution rates with *f2* values of 27.62 as the prepared ATR-PSD released 91.65% in 15 minutes, in comparison to pure ATR which released 61% in 15 minutes) as shown in Figure 2. This enhancement of the dissolution profile can be explained by the enhanced solubility of the drug in addition to the disintegration effect of MAS in aqueous media (10, 16, 17).
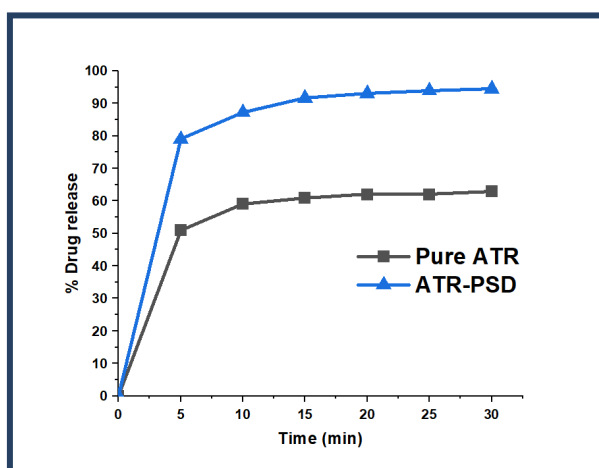

Figure 2. Comparison between the *in-vitro* dissolution profile of the pure ATR and the prepared ATR-PSD in 0.05M phosphate buffer (pH 6.8) at 37°C±0.5.

2.3. Pre-compression evaluation of powder blends

The angle of repose, Carr's index, and Hausner's ratio of ATR-PSD, the pure ATR, and the IRTs blends are listed in Table 1. The results indicate an improvement in flow properties (p<0.05) of prepared ATR-PSD compared to those of pure ATR powder.

In addition, the pre-compression study of the IRT blends indicated excellent flowability (small angle of repose) for all formulas, but not all of them exhibited good compressibility (high Hausner's and Carr's Index).

Table 1. Powder blends flow properties.

Formula Code	Hausner's ratio mean± SD (n=3)	Carr's Index mean± SD (n=3)	Compressibility	Angle of repose mean± SD (n=3)	Type of flow
Pure ATR	1.5 ± 0.03	33.3 ± 2.78	Very poor	40.1 ± 0.59	Fair
ATR-PSD	1.13 ± 0.13	11.59 ± 1.3	Good	31.5 ± 0.69	Good
T1	1.27±0.027	21.42±0.2	Passable	26.2±0.81	Excellent
T2	1.23±0.084	18.9±0.12	Fair	23.46±1.2	Excellent
T3	1.19± 0.03	16.3±0.01	Fair	19.24±0.55	Excellent
T4	1.22±011	18.47±0.26	Fair	23.1±0.6	Excellent
T5	1.17±0.016	14.53±0.53	Good	24.22±0.56	Excellent
T6	1.31±0.012	23.71±0.32	Passable	29.6±0.31	Excellent
T7	1.09±0.004	8.28±0.71	Excellent	25.04±1.3	Excellent
T8	1.16±0.06	13.85±0.11	Good	18.78±0.48	Excellent
T9	1.14±0.037	12.28±0.8	Good	19.01±0.8	Excellent
T10	1.13±0.076	11.57±0.22	Good	20.71±0.27	Excellent

2.4. Post-compression evaluation of ATR IRT powder blends

As shown in Table 2, T1, T2, T3, and T6 blends displayed a capping issue (18). This may be explained by the poor compression characteristics (19).

On the other hand, T4 exhibit chipping defects (18). Chipping can occur due to a brittle formulation (19). Therefore, these formulas were canceled from further investigation. A reduction of ATR-PSD loading in the blends from 40% to 32% by increasing the amount of Avicel which has good compressibility and compactibility, resulted in tablets from T5-T10 (except T6) blends were uniform and smooth.(19,20).

Furthermore, tablets with uniform appearance showed acceptable hardness, drug content, friability, weight mean, and DT according to USP criteria (12).

Table 2. General appearance, weight variation, drug content, hardness, friability, disintegration test.

Formula code	General appearance	Drug content mg / Tablet	Hardness (Kg) Mean ±std (n=3)	Friability % Mean (n=10)	Weight (mg) Mean ±std (n=20)	Disintegration time (sec) Mean ±std (n=3)
T1	Capping					
T2	Capping					
T3	Capping					
T4	Chipping					
T5		96.81±0.09	6.1±0.06	0.61%	253.4±0.9	64±1.8
T6	Capping					
T7		97.33±0.2	6.9±0.5	0.33%	256.1±0.81	51±2.1
T8		97.7±0.11	6.8±0.41	0.31%	249.2±1.1	55±0.9
T9		98.5±0.04	6.5±0.16	0.37%	251±1.02	48±1.3
T10		98.01±0.06	6.77±0.23	0.3%	255.2±.87	38±1

2.5. Factors influencing the physical properties of ATR IRTs

2.5.1. The effect of diluent type

As shown in Table 2, T7 (Avicel®PH102) shows the improved flowability when compared to T5 (Avicel®PH101) and T6 (starch) which can be attributed to the large particle size of Avicel®PH102 (approximately 100 mm) which enhance the flowability and compressibility (11,21).

Furthermore, T7 also shows a better dissolution profile as compared to T5 ($f2$= 33.159). This may be due to the shorter DT attributed to the high porosity of Avicel® PH102 particles, which enhances the penetration of dissolution media, causing the tablet to break apart and resulting in a higher dissolution profile (22), as shown in Figure 3.

2.5.2. The effect of superdisintegrant type

Although all superdisintegrants used in T7, T8, and T9 produced tablets with acceptable disintegration times (Table 2), a significant difference (P-value <0.05) in DT was obtained by these formulas. The order of DT according to superdisintegrants was CCS<CP<SSG.
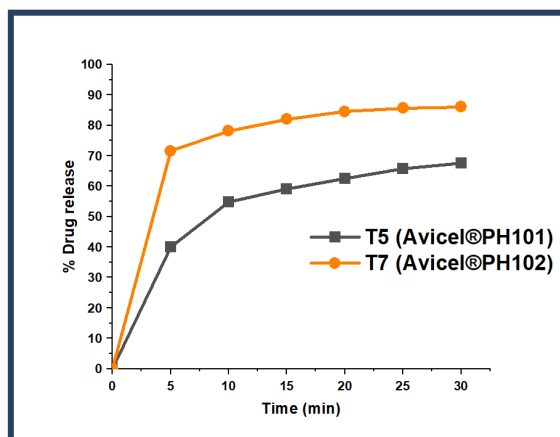
Figure 3. Effect of diluents on the release of ATR from ATR IRT in 0.05M phosphate buffer (pH 6.8) at 37±0.5 °C.

On the other hand, the choice of superdisintegrant had an impact on the dissolution profile. When using CP (T7) and CCS (T9), similar dissolution profiles were observed ($f2 = 81.74$) whereas using SSG (T8) showed slower release than T7 ($f2= 40.84$) and T9 ($f2= 39.14$) as shown in Figure (4). CCS and CP were superior to SSG because of combined swelling, wicking deformation mechanism results in a faster water penetration rate, which is a rate-limiting step in tablet dosage form for achieving a fast dissolution rate (23, 24).
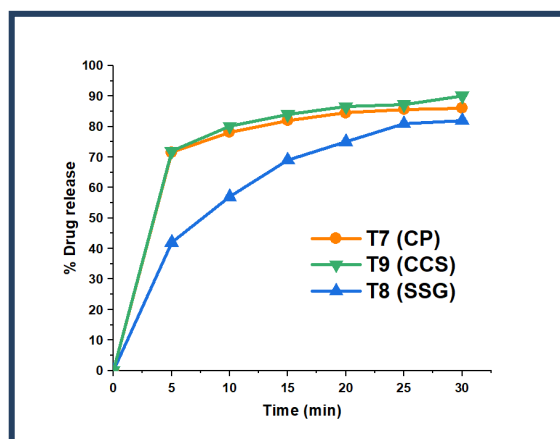

Figure 4. Effect of different types of superdisintegrants on the release of ATR from ATR IRT in 0.05M phosphate buffer (pH 6.8) at 37±0.5 °C.

2.5.3. The effect of superdisintegrant concentration

Although T9 and T10 show similar dissolution profiles ($f2= 61.313$), T10 shows a higher release of the drug in a shorter time (91% in 15 min) as compared to T9 (90.1% in 30 min) as shown in Figure 5. This is because the disintegrating effect of superdisintegrants is often concentration-dependent (25). As a result, T10 was selected as best formula for its good flow property and shortest DT and the highest amount of ATR release with shortest time.

2.6. Comparison between the selected formula release profile and marketed product Lipitor® (Pfizer)

As shown in Figure (6), T10 and Lipitor® dissolution profiles show more than 85% of ATR release within 15 minutes (93%,100% respectively) and they considered to be similar (26).

3. CONCLUSION

Phospholipid solid dispersion in presence of MAS was an efficient method for enhancing the solubility and dissolution of ATR. Furthermore, immediate release tablets containing ATR-PSD was successful by controlling the types and amount of additives. Using Avicel® PH102 as a diluent and CCS 5% as superdisintegrant show good flow property and shortest DT and the best ATR release profile.
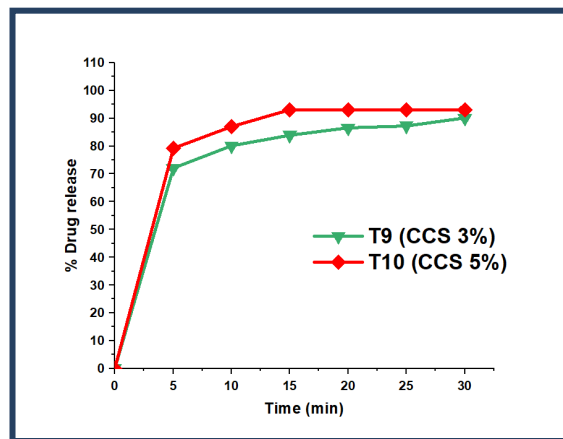
Figure 5. Effect of concertation of superdisintegrant on the release of ATR from ATR IRT in 0.05M phosphate buffer (pH 6.8) at 37±0.5 °C.
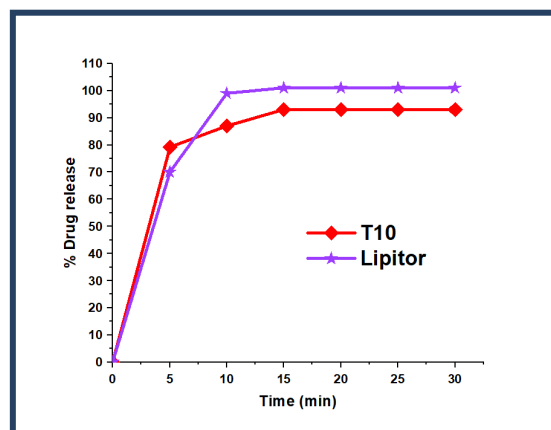

Figure 6: Comparison between release of ATR from T10 and marketed product Lipitor® in 0.05M phosphate buffer (pH 6.8) at 37±0.5 °C.

4. MATERIALS AND METHODS

4.1. Materials

Atorvastatin calcium (ATR), crospovidone (CP), croscarmellose sodium (CCS), and sodium starch glycolate (SSG) were supplied by Pioneer pharmaceutical company, Iraq as a gift sample. Phosphatidylcholine (PC) was purchased from Changai, Meryer biochemical technology, China. Magnesium aluminum silicate (MAS) was purchased from Hangzhou, Hyperchem. China. Microcrystalline cellulose (Avicel®) PH101, Microcrystalline cellulose (Avicel®) PH102, and starch were supplied by Modern company for drug industry, Iraq. Polyvinylpyrrolidone (PVP K30), talc, and magnesium stearate were supplied from Himedica, India.

4.2. Method

4.2.1. Preparation and evaluation of phospholipid solid dispersion

Phospholipid solid dispersion of ATR was prepared by solvent evaporation technique. A weight ratio of 1:3:4 (ATR: PC: MAS) was utilized for such preparation, in which ATR and PC were dissolved in methanol then MAS was added gradually to the solution with gentle stirring using a magnetic stirrer for 1 h. The resulting mixture was left for 24 hours in a 40°C oven for the removal of solvent. Finally, the mass was pulverized and sieved using no. 60 mesh sieve and stored in a desiccator for further use (27).

The resultant product was evaluated for its production yield, drug content, saturated solubility study in water. Its dissolution in 0.05M phosphate buffer (pH 6.8) was also determined to be compared with that of the prepared tablets.

4.2.2. Immediate-release tablet preparation by direct compression

The tablets containing ATR-PSD formula equivalent to 10 mg ATR were prepared by direct compression method with different diluents and superdisintegrants (Table 3). The ATR-PSD formula, diluent, Superdisintegrant, and binder were mixed using a mortar and pestle for approximately 30 minutes. Then the lubricant and the glidant were added and mixed for 2 minutes. The resulting powder blend was compressed using a tablet machine.

Table 3: Composition of different ATR IRT blends.

Ingredient (mg)	Formula code									
	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10
ATR-PSD equivalent to 10 mg ATR	80	80	80	80	80	80	80	80	80	80
Cross Povidone (CP)	6 (3%)	6 (3%)	6 (3%)	6 (3%)	7.5 (3%)	7.5 (3%)	7.5 (3%)	-	-	-
Sodium Starch Glycolate (SSG)	-	-	-	-	-	-	-	7.5 (3%)	-	-
Croscarmellose Sodium (CCS)	-	-	-	-	-	-	-	-	7.5 (3%)	12.5 (5%)
PVP	4 (2%)	4 (2%)	4 (2%)	6 (3%)	7.5 (3%)	7.5 (3%)	7.5 (3%)	7.5 (3%)	7.5 (3%)	7.5 (3%)
Talc	2 (1%)	2 (1%)	4 (2%)	4 (2%)	5 (2%)	5 (2%)	5 (2%)	5 (2%)	5 (2%)	5 (2%)
Magnesium stearate	2 (1%)	-	-	-	-	-	-	-	-	-
Avicel® PH101	106	108	106	104	150	-	-	-	-	-
Starch	-	-	-	-	-	150	-	-	-	-
Avicel® PH102	-	-	-	-	-	-	150	150	150	145
Total weight of the tablet	200	200	200	200	250	250	250	250	250	250

4.2.3. pre-compressed evaluation of ATR -IRT powder blends

The pre-compression parameters of the powder blend were determined and compared with those of pure ATR and ATR-PSD, to investigate the factors affecting these parameters.

Angle of repose: The angle of repose is used for the evaluation of powder flow. It was determined by the funnel method. The sample was poured into the funnel, which was positioned with its lower tip 2.0 cm above the solid surface. The pouring continued until the top of the powder pile came into contact with the lower tip of the funnel. Then the cone's radius was measured, and the angle of repose was calculated using the following equation (28).

$$tan(\theta) = h/r \dots\dots\text{eq 1}$$

Where θ is the angle of repose obtained by calculating the tan^{-1}, h is the height of the resulting powder cone, and r is the resulting cone radius.

Bulk density: The powder density, which represents the ratio of the powder mass to its bulk volume, is influenced by particle packing. A specific weight of powder was poured into a graduated cylinder, and the initial volume is recorded. The density can then be calculated using the following equation (29).

$$Bulk\ density = \frac{Powder\ mass}{Bulk\ volume} \dots\dots \text{eq 2}$$

Tapped density: The powder density is defined as the ratio of the powder mass to its tapped volume. To measure it, a specific weight of powder was poured into a graduated cylinder. The cylinder was then manually tapped until no further changes in powder volume are observed. The final volume was recorded, and the density was then calculated using the following equation (29).

$$Tapped\ Density = \frac{Powder\ mass}{Tapped\ volume} \dots\dots \text{eq 3}$$

Compressibility index (Carr's index): The powder flow characteristics can be predicted by using Carr's index. It can be described as the powder's capacity to decrease in volume when subjected to pressure. Carr's index can be calculated by using the equation provided below (30).

$$Carr's\ index = \frac{Tapped\ density - Bulk\ dnsity}{Tapped\ dnsity} \times 100 \dots \dots\ eq\ 4$$

Hausner's ratio: It is an indirect method for the prediction of powder flow properties and it can be calculated by the following equation (7).

$$Hausner's\ ratio = \frac{Tapped\ density}{Bulk\ density} \dots..\ eq\ 5$$

4.2.4. Post compression evaluation

General Appearance: The tablets must not have any cracks and must be uniform and smooth throughout the entire surface (31).

Weight variation: The weight of each of the twenty tablets was individually measured, and subsequently, the average weight was calculated. To meet the requirements, the weights of no more than two tablets should fall outside the percentage limit specified by USP. Additionally, no tablet should deviate in weight by more than double that percentage (32).

Drug content determination: Three tablets were weighed and crushed in a mortar. Powder equivalent to 10 mg of ATR was dissolved in 50 ml methanol, followed by sonication for 15 minutes, filtered, and then after suitable dilution the solution was assayed for drug content using UV spectrophotometric method at 246 nm (33).

Hardness test: The hardness test is employed to assess the tablet's crushing strength, ensuring its ability to endure various handling, transportation, and storage conditions. Three tablets were selected randomly from each formulation. The measurements were recorded by an electronic hardness tester, (YD-1, Beijing, China.) It was calibrated to zero, and the load was gradually raised until the tablet reached a point of fracture or breakage (34).

Friability: The friability test is conducted to assess the impact of friction and shocks on tablets, which can result in chipping, capping, or breakage. A total of twenty tablets were precisely weighed (W initial) and placed into the Friabilator (TAR 120, Erweka, Germany) where they were rotated for 4 minutes at 25 rpm. Subsequently, the tablets were removed, cleaned to remove any dust, and then accurately reweighed (W final). The accepted weight loss should not exceed 1% (35).

$$Friability\% = \frac{W\ intial - W\ final}{W\ intial} \times 100 \dots..\ eq\ 6$$

In-vitro disintegration test: The disintegration time (DT) was determined for the prepared IRTs. using a disintegration apparatus (Copley Scientific, UK), consisting of a basket rack assembly containing six open-ended tubes. In each tube, a single tablet was placed, and the basket, with a stainless-steel screen (mesh no. 10) on its bottom surface, was immersed in 900 ml of 0.1N HCl at 37 ±0.5 °C. The time taken for complete disintegration of the tablet in each tube was measured using a stopwatch (12).

In-vitro dissolution of ATR IRTs: The In-vitro dissolution of pure ATR, PSD, and ATR IRTs was assessed using a USP apparatus II (RC-6, China) in 900 ml of 0.05M phosphate buffer (pH 6.8) as a dissolution media, and the temperature was maintained at 37±0.5°C using a thermostatic water bath. The apparatus was set to rotate at a speed of 75 rpm (12). Samples were collected at regular intervals and replaced with a fresh dissolution medium. The samples were filtered and measured using spectrophotometry at 240 nm. This evaluation was conducted on the PSD formulations that exhibited the highest solubility in triplicate. The dissolution profile was statistically analyzed using a similarity factor (*f*2) as calculated by the following equation.

$$f2 = 50 \cdot \log \left\{ 100 \cdot \left[1 + \frac{1}{n}\sum_{t=1}^{n}(Rt - Tt)^2 \right]^{-0.5} \right\} \dots \dots..\ eq\ 7$$

At time t, (Rt) represents the dissolution value of the reference, (Tt) represents the dissolution value of the test, and (n) denotes the number of dissolution time points. Dissolution profiles are deemed similar when f2 values exceed 50 (ranging from 50 to 100), while dissolution profiles are deemed dissimilar if the f2 value falls below 50 (36).

Comparison between the selected formula release profile and marketed product Lipitor® (Pfizer): The comparison between selected formula and Lipitor® tablets (Pfizer) regarding release profile was done in 0.05M phosphate buffer (pH 6.8) at 37.5 °C±0.5 to know the similarity between the best prepared formula and the marketed one.

4.3. Statistical analysis

The mean and standard deviation (SD) of the triplicate samples were calculated and presented as the outcomes of the experiments. The statistical analysis was performed using one-way analysis of variance (ANOVA) and the test level of significance was set at ($P < 0.05$). The statistical software used for the analysis was SPSS version 26.

Author contributions: Concept – E.A.; Design – B.G., E.A.; Supervision – E.A.; Resources – B.G.; Materials – B.G.; Data Collection and/or Processing – B.G.; Analysis and/or Interpretation – B.G.; Literature Search – B.G., E.A.; Writing – B.G.; Critical Reviews – E.A.

Conflict of interest statement: "The authors declared no conflict of interest" in the manuscript.

REFERENCES

[1] Allen LV. Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, eleventh ed., Lippincott Williams and Wilkins, Philadelphia, USA, 2017.

[2] Homayun B, Lin X, Choi HJ. Challenges and recent progress in oral drug delivery systems for biopharmaceuticals. Pharmaceutics. 2019;11(3). https://doi.org/10.3390/pharmaceutics11030129

[3] Palanisamy P, Chandira RM, Jaykar B, Pasupathi A, Venkateshwarlu B. Formulation, development and evaluation of immediate release tablets of atorvastatin calcium USP. World J Pharm Res. 2015; 4:861-85.

[4] Azemawah V, Movahed MR, Centuori P, Penaflor R, Riel PL, Situ S, et al. State of the art comprehensive review of individual statins, their Differences, pharmacology, and clinical implications. Cardiovascular Drugs and Therapy. 2019;33(5):625–39. https://doi.org/10.1007/s10557-019-06904-x

[5] A, Moffat, Osselton M WB. Clarcke's analysis of drug and poisions. fourth ed., Pharmaceutical Press, London, UK, 2011.

[6] Ali AH, Abd-Alhammid SN. Enhancement of solubility and improvement of dissolution rate of atorvastatin calcium prepared as nanosuspension. Iraqi Journal of Pharmaceutical Sciences. 2019;28(2):46–57. https://doi.org/10.31351/vol28iss2pp46-57

[7] British Pharmacopoeia Commission. British Pharmacopoeia 2020. London: TSO, UK, 2020.

[8] Khaleel NY, Abdulrasool AA, Ghareebowafaq MM, Hussain SA. Solubility and dissolution improvement of ketoprofen by solid dispersion in polymer and surfactant using solvent evaporation method. International Journal of Pharmacy and Pharmaceutical Sciences. 2011;3(4):431–5.

[9] Van Hoogevest P. Review – An update on the use of oral phospholipid excipients. Eur J Pharm Sci. 2017;108:1–12. https://doi.org/10.1016/j.ejps.2017.07.008

[10] Zhang Z, Chen Y, Deng J, Jia X, Zhou J, Lv H. Solid dispersion of berberine-phospholipid complex/TPGS 1000/SiO 2: Preparation, characterization and in vivo studies. Int J Pharm. 2014;465(1–2):306–16. https://doi.org/10.1016/j.ijpharm.2014.01.023

[11] Sheskey P, Cook W, Cable C. Handbook of pharmaceutical excipients, eight ed., Pharmaceutical Press, London, UK, 2017.

[12] The United State Pharmacopeia (USP) 41, NF36. Convention Inc. Rockville, MD. 2018.

[13] Jo K, Cho JM, Lee H, Kim EK, Kim HC, Kim H, et al. Enhancement of aqueous solubility and dissolution of celecoxib through phosphatidylcholine-based dispersion systems solidified with adsorbent carriers. Pharmaceutics. 2019;11(1):1–14. https://doi.org/10.3390/pharmaceutics11010001

[14] Telange DR, Sohail NK, Hemke AT, Kharkar PS, Pethe AM. Phospholipid complex-loaded self-assembled phytosomal soft nanoparticles: evidence of enhanced solubility, dissolution rate, ex vivo permeability, oral

bioavailability, and antioxidant potential of mangiferin. Drug Deliv Transl Res. 2021;11(3):1056–83. https://doi.org/10.1007/s13346-020-00822-4

[15] Ali SK, Al-Khedairy EBH. Solubility and dissolution enhancement of atorvastatin calcium using solid dispersion adsorbate technique. Iraqi J Pharm Sci. 2019;28(2):105–14. https://doi.org/10.31351/vol28iss2pp105-114

[16] Yoshie K, Yada S, Ando S, Ishihara K. Chemical structural effects of amphipathic and water-soluble phospholipid polymers on formulation of solid dispersions. J Pharm Sci. 2021;110(8):2966–73. https://doi.org/10.1016/j.xphs.2021.03.025

[17] Ahmed A, Ali SA, Hassan F, Ayub S, Haque N. Effect of disintegrants and hardness on the disintegration time of acetaminophen tablets. Pak J Pharm Sci. 1998;11(1):41–6.

[18] Khan SA. Essentials of Industrial Pharmacy, first ed., Springer Ltd, Switzerland, 2022.

[19] Qiu Y, Chen Y, Zhang GGZ, Yu L, Mantri RV. Developing solid oral dosiage forms: Pharmaceutical theory & practice. second ed., Elsevier Ltd, Amsterdam, 2017.

[20] Hassan DH, Ammar AA, Ramadan AA, Younis MK. Enhanced bioavailability and pharmacokinetics parameters of Enalapril solid self nanoemulsifying oral dispersible tablet: formulation, in vitro and in vivo evaluation. Pharmaceutical Development and Technology. 2023; 28:3-4, 371-382. https://doi.org/10.1080/10837450.2023.2198005

[21] Yohana Chaerunisaa, A., Sriwidodo, S., & Abdassah, M. (2020). Microcrystalline Cellulose as Pharmaceutical Excipient. IntechOpen. doi: 10.5772/intechopen.88092.

[22] Kusumadewi AP, Rahmawati N. The influence of Avicel PH-102 as filler-binder agent and explotab as disintegrant agent against andrographolide dissolution rate of sambiloto extract tablets. international Conference: Research and Application. 2012;22–3.

[23] Ikasari ED, Cahyani IM, Collusy DM. Optimization of croscarmellose and sodium starch glycolate on orally disintegrating metoclopramide Hcl tablets. Jurnal Farmasi Sains dan Praktis. 2022;8(3):261–7. http://dx.doi.org/10.31603/pharmacy.v8i3.4830

[24] Shobana K, Subramanian L, Rajesh DM, Sivaranjani K. A review on superdisintegrants. International Journal of Pharmaceutical Sciences Review and Research. 2020;65(2):149–54. http://dx.doi.org/10.47583/ijpsrr.2020.v65i02.023

[25] Steffens KE, Wagner KG. Immediate-release formulations produced via twin-screw melt granulation: Systematic evaluation of the addition of disintegrants. AAPS PharmSciTech. 2021;22(5):1–13. https://doi.org/10.1208/s12249-021-02056-0

[26] Cardot JM, Garcia Arieta A, Paixao P, Tasevska I, Davit B. Implementing the biopharmaceutics classification system in drug development: reconciling similarities, differences, and shared challenges in the EMA and US-FDA-recommended approaches. AAPS Journal. 2016;18(4):1039–46. https://doi.org/10.1208/s12248-016-9915-0

[27] Yeo S, An J, Park C, Kim D, Lee J. Design and characterization of phosphatidylcholine-based solid dispersions of aprepitant for enhanced solubility and dissolution. Pharmaceutics. 2020;12(5). https://doi.org/10.3390%2Fpharmaceutics12050407

[28] Kahtan JH, Mowafaq MG. Evaluation of innovative co-processed additive for direct compression tablets using atorvastatin and diazepam as model drugs. International Journal of Pharmacy and Pharmaceutical Sciences. 2016; 8(2): 201-207.

[29] Aulton ME. Powder flow. Taylor KMG, Aulton ME. Aulton's pharmaceutics: The design and manufacture of medicine, 6th ed., Elsevier Ltd, London, UK, 2022.

[30] Al-Mahmood AA, Alhammid SNA. Formulation and characterization of floating biphasic tablet consisting of cefdinir nanosuspension. International Journal of Health Sciences. 2022; 6(S4): 12154–12172. https://doi.org/10.53730/ijhs.v6nS4.11821

[31] Sunil kumar K, Chandrakala RG, Sravanthi AR, Swarna latha P, peeravali D, Vamsi A. Formulation and evaluation of colon targeted matrix tablet of ibuprofen. World J Adv Res Rev. 2023;18(2):519–35. https://doi.org/10.30574/wjarr.2023.18.2.0562

[32] Abdul Karim F.Jumaa, Alaa A.Abdulrasool, Hikmet A.Al –Dujali. Formulation and Clinical Evaluation of Orphenadrine citrate as a Plain Tablet. Iraqi J Pharm Sci. 2006;15 (1).

[33] Hadi BM, Al-Khedairy EBH. Preparation and characterization of atorvastatin calcium trihydrate -cyclodextrin inclusion complex. Int J Drug Deliv Technol. 2022;12(3):1171–9. https://doi.org/10.25258/ijddt.12.3.41

[34] Chaturvedi H, Garg A, Rathore US. Post-compression evaluation parameters for tablets-an overview. Eur J Pharm Med Res. 2017;4(11):526–30.

[35] Nasser SJ, Sameen LH, Ghareeb MM. Preparation and Evaluation of Oral Disintegrating Tablets of Ketoprofen by Dirct Compression. Iraqi Journal of Pharmaceutical Sciences. 2012; 21(2):63-68. https://doi.org/10.31351/vol21iss2pp63-68

[36] Muselík J, Komersová A, Kubová K, Matzick K, Skalická B. A critical overview of FDA and EMA statistical methods to compare in vitro drug dissolution profiles of pharmaceutical products. Pharmaceutics. 2021;13(10). https://doi.org/10.3390/pharmaceutics13101703