Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Research Article

Effect of Hydrophilic Swellable Polymers on Dissolution Rate of Atorvastatin Using Simple Physical Mixing Technique

MD. RAIHAN SARKAR*, A.S.M.MONJUR-AL-HOSSAIN, MD. SAIFUL ISLAM, A B M FAROQUE

Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Dhaka, Dhaka 1000, BANGLADESH

ARTICLE DETAILS

Article history:
Received on 18 April 2012
Modified on 24 May 2012
Accepted on 29 May 2012

Keywords:
Atorvastatin,
Physical mixing technique,
Hydrophilic swellable
Polymer,
Fickian diffusion

ABSTRACT

Physical mixtures (PMs) of atorvastatin and four different hydrophilic swellable polymers (*pregelatinized starch, hydroxypropyl methyl cellulose, poloxamer 407 and sodium carboxy methyl cellulose*) were prepared at 1:0.5, 1:1 and 1:2 ratios. *In vitro* dissolution study was performed in distilled water for 60 minutes at 50 rpm and 37±0.5°C. Faster dissolution was achieved using poloxamer at 1:2 ratios; it was 87% after first 10 minutes of dissolution. However, considering complete dissolution for 60 minutes, atorvastatin release was increased in the following order: pregelatinized starch > poloxamer 407 > hydroxypropyl methyl cellulose > sodium carboxy methyl cellulose. In case of all the batches, statistically significant correlation between % release and polymer concentration was observed ($P < 0.5$, ANOVA single factor). Mean dissolution time (MDT), time for 25% release (t25), 50% release (t50) and 75% release (t75) were also calculated. Significant correlation was found between polymer concentration and corresponding mean dissolution time values ($P< 0.5$, ANOVA single factor). Highest MDT was 13.85 minute for pregelatinized starch and lowest MDT was 0.5 minute for poloxamer. Release data were fitted in different model and release was found to be fitted best in Korsmeyer-peppas model where fickian diffusion mechanism was predominant.

INTRODUCTION

In case of poorly aqueous soluble drugs, solubility in the solvents plays the major role in dissolution of the drug. The rate of oral absorption of these drugs therefore is controlled by their dissolution rate in the gastrointestinal tract. Thus solubility and dissolution rate are the key determinants of oral bioavailability. [1-3] Atorvastatin (ATV), a 3-hydroxy-3-methhylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, is a plasma lipid regulating agent. It is insoluble in aqueous solution of pH ≤ 4.0 and below; it is very slightly soluble in water and slightly soluble at pH 7.4 phosphate buffers and acetonitrile, slightly soluble in ethanol and freely soluble in methanol. [4] Because of having poor water solubility, its absorption is dissolution rate limited, which often results in irregular and delayed absorption. [5]

Author for Correspondence:
Email: raihan.rezvi@gmail.com

For improvement of solubility and dissolution rate of poorly soluble drugs, numerous commercially viable techniques are available such as liquisolid,[6-8] nanomorph,[9] *in situ* micronization,[10,11] and co precipitation using antisolvent.[12] Other techniques such as use of surfactants in the formulation, micronization of drug have also been reported but both have limitations.[13,14] But ahead of all, solid dispersion is the most promising method to formulators because of its ease of preparation, ease of optimization, and reproducibility.[15-18] Poorly soluble drugs are dispersed in an inert hydrophilic polymer or matrix by physical mixing, melting, solution formation, or solvent melting to yield solid dispersion.[15,17] Usually, solid dispersions (SDs) are prepared with water soluble low melting point synthetic polymers such as polyvinylpyrrolidone (PVP), mannitol, or polyethylene glycols (PEGs).[18,19] These polymers show superior results in drug dissolution enhancement, but the amount of these polymers required is relatively large, around 1:2 to 1:8 (drug/polymer) ratio.[20] In certain similar experiments it has been observed that, PVP and PEG get dissolved first in

dissolution media (owing to their high water solubility) leaving the drug back in undissolved state. In such case, though the drug is in controlled crystallization state or amorphous state, the polymers are unable to provide wetting ability to the drug particles. In such cases, there may be the possibility of rapid reversion of amorphous drug to the more stable crystalline state in presence of small amount of plasticizers such as water. [21]

Literature survey reveals that certain hydrophilic swellable polymers such as sodium carboxymethyl cellulose (Na CMC), hydroxypropyl methyl cellulose (HPMC), poloxamer 407 (POL407) and Pregelatinized starch (PS) have still been unexplored for their potential to form solid dispersion in order to improve dissolution properties of poorly soluble drugs. For this reason, in the present work, water-swellable polymers or normal excipients of solid dosage forms were used. These polymers were supposed to hold the drug in intimate contact with water (owing to their water retention potential) and increase its wettability.

MATERIALS AND METHODS

Materials

Atorvastatin calcium was received as generous gift from Beximco Pharmaceuticals Ltd., Bangladesh. Pregelatinized starch, sodium carboxymethyl cellulose, hydroxy propyl methyl cellulose (S.D.Fine Chemicals Ltd, Mumbai, India) and poloxamer 407 (Pluronic® F127, BASF, Germany) were used as received.

Preparation of atorvastatin-polymer physical mixture

Physical mixtures (PMs) of ATV with the polymers were prepared by simply mixing them in a mortar-pestle while maintaining the drug-polymer ratio at 1:0.5, 1:1 and 1:2. Mixing was performed moderately for 10 minutes for all formulations. Individual formulations were then filled in airtight vials and the vials were preserved in a desiccator until further use.

Preparation of calibration of atorvastatin

20 mg of ATV powder was taken in 1000 mL volumetric flask containing 100 mL of methanol previously and a clear solution was made after moderate shaking. Then the volume of this solution was made up to 1000 mL using phosphate buffer solution of pH 7.4. Concentration of ATV in this solution was 20µg/mL. Then by serial dilution, 9 another solution was prepared whose concentration was 18 µg/mL, 16 µg/mL, 14 µg/mL, 12 µg/mL, 10 µg/mL, 8 µg/mL, 6 µg/mL, 4 µg/mL and 2 µg/mL. Absorbance of these solutions was measured using a UV-VIS spectrophotometer (UVmini-1240, Shimadzu corporation, Japan) at 246 nm. Then by plotting absorbance against concentration, calibration curve was constructed. Following the same procedure, calibration curve was also constructed using distilled water.

In vitro dissolution study

Using a USP XXX apparatus type II (Electrolab, India), *in vitro* release study was performed for 60 minutes in 900 mL distilled water. Paddle rotation speed was 50, temperature was 37±0.5°C and withdrawn sample volume was 10 mL where sampling intervals were 10, 20, 30, 40, 50, 60 minutes. In a UV-VIS spectrophotometer (UVmini-1240, Shimadzu corporation, Japan), withdrawn samples were analyzed (either directly or after dilution) at 246 nm.

RESULTS AND DISCUSSION

As mentioned earlier, ATV is freely soluble in methanol. Though calibration curve was prepared using both distilled water and phosphate buffer solution of pH 7.4 where a fixed amount of ATV was dissolved in methanol, both the curves showed almost similar extent of linearity (Fig. 1). So, distilled water was used finally for dissolution purpose.

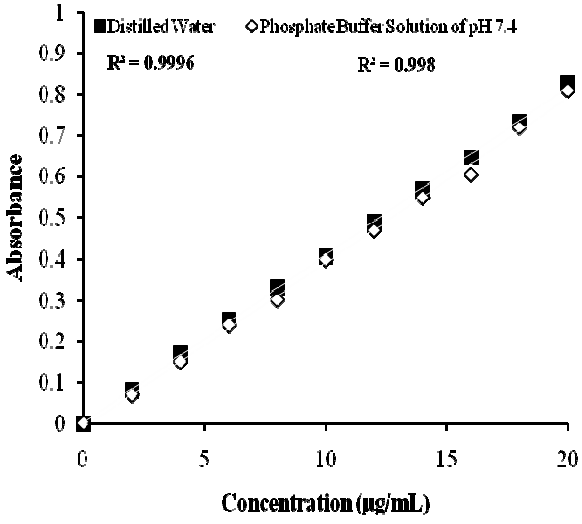

Figure 1: Calibration curve of atorvastatin

Fig. 2 shows the release curves of ATV. As maximum as 75% ATV was found to be released in case of physical mixtures (PMs) with pregelatinized starch (PS) (1:2 ratio) after first

10 minutes of dissolution. It was 80% for sodium carboxymethyl cellulose (Na CMC), 85% for hydroxypropyl methyl cellulose (HPMC) and 87% for poloxamer (POL407). It was only 52% for pure ATV. That is release increasing order for the polymers was POL407 > HPMC > Na CMC > PS. After 60 minutes, cumulative percent release of ATV was found in a different order. It was 96% for PS, 88% for Na CMC, 93% HPMC and 95% for POL407. It was only 74% for pure ATV. That is release increasing order for complete release was PS > POL407 > HPMC > Na CMC after 60 minutes for the later portion of dissolution.

PS is a swellable polymer which is generally used in solid dosage forms as a diluent, disintegrating agent.[22, 23] In this experiment, we used PS to evaluate its solubility increasing property for physical mixtures (PMs) and a significant increase in ATV was found while PS concentration was increased gradually (ANOVA single factor, $P < 0.5$, table 2). In case of other polymers, gradual increase in % release was also found accordingly from the PMs while the polymer concentration was increased (Na CMC, $P < 0.5$; HPMC, $P < 0.5$; POL407, $P < 0.01$, table 2).[24-27] A corresponding increase in release rate (K_h) with increase in polymer concentration was also observed (Fig. 3, Table 1)

In case of SDs comprising hydrophilic polymers, drug dissolution is increased because of the following possible reasons:

- In solid dispersions, the drug is usually partially dissolved in melted or dissolved polymer. After drying of these SDs, the drug will not nucleate to form firm crystals resulting in formation of microcrystals. Drug microcrystals are embedded in the water-soluble matrix, where hydrophilic polymers present the ability of rapid wetting and thereby dissolution of drug. [28] Generally polyethylene glycols and polyvinyl pyrrolidone solid dispersions follow this principle.
- For solid dispersions of sodium starch glycolate, higher dissolution rates is observed when compared with other excipients and this may be owing to their easy and rapid dispersibility in the aqueous dissolution fluids.[29]
- SDs of hydrophilic swellable polymers such as HPMC, Na CMC, PS, POL407 etc. becomes gelatinized in the dissolution medium. This gelatinized solid dispersion is constantly crushed by the attrition during stirring, and these finely gelatinized SDs diffuse to bulk solution through the diffusion layer. [30] Being water retentive, gelatinized dispersions also increase wetting of the drug, which attributes to increase in dissolution? However, the gelatinized dispersion formed should not be a barrier for the drug diffusion owing to its viscosity.

The mechanism underlying the drug release from the PMs is yet to be elucidated completely like those for SDs. But few reasons behind this enhanced release of ATV from the formulated batches of two component systems may be drawn as suggested by Corrigan, Higuchi and Higuchi et al. [31,32,33] It can be stated as when the mixture of ATV-polymer were exposed to the dissolution media, both drug and polymer went for the dissolution solvent at a rate proportional to their respective solubility (C_s) and diffusion co-efficient (D) as was stated in Noyes-Whitney equation for single component. Having more solubility than ATV, polymers quickly formed a swellable mass through which ATV particles started to diffuse in the bulk of dissolution solvent. Fig. 4 shows about the probability of going in the dissolution for one component from two component systems. The model predicts that polymer (for example A) will form such a layer where (case 1, Fig. 5) N is the proportion of each component and the subscripts A and B refers to the polymer and drug respectively. Under these circumstances the dissolution rates will be given by the following equation where G is the dissolution rate/unit area and h is the diffusion layer thickness.

$$G_A = \frac{D_A C_{SA}}{h} \text{ and } \qquad G_B = \frac{N_B}{N_B} G_B$$

In such cases, dissolution of the drug is highly dominated by the dissolution behavior of the carrier which was observed practically by Corrigan (1986) [34] Nevertheless, enhancement in drug release from PMs of drug-carrier has been an effective technique and also reported previously. [35, 36]

In the present work, HPMC, Na CMC, PS and POL407 showed comparatively slower release rate at later portion of the dissolution than the earlier portion of dissolution e.g. release rate from these polymers was found to be slower as dissolution proceeded. It might be due to the formation of swelled mass around the drug particles and degree of swelling was increased with time.

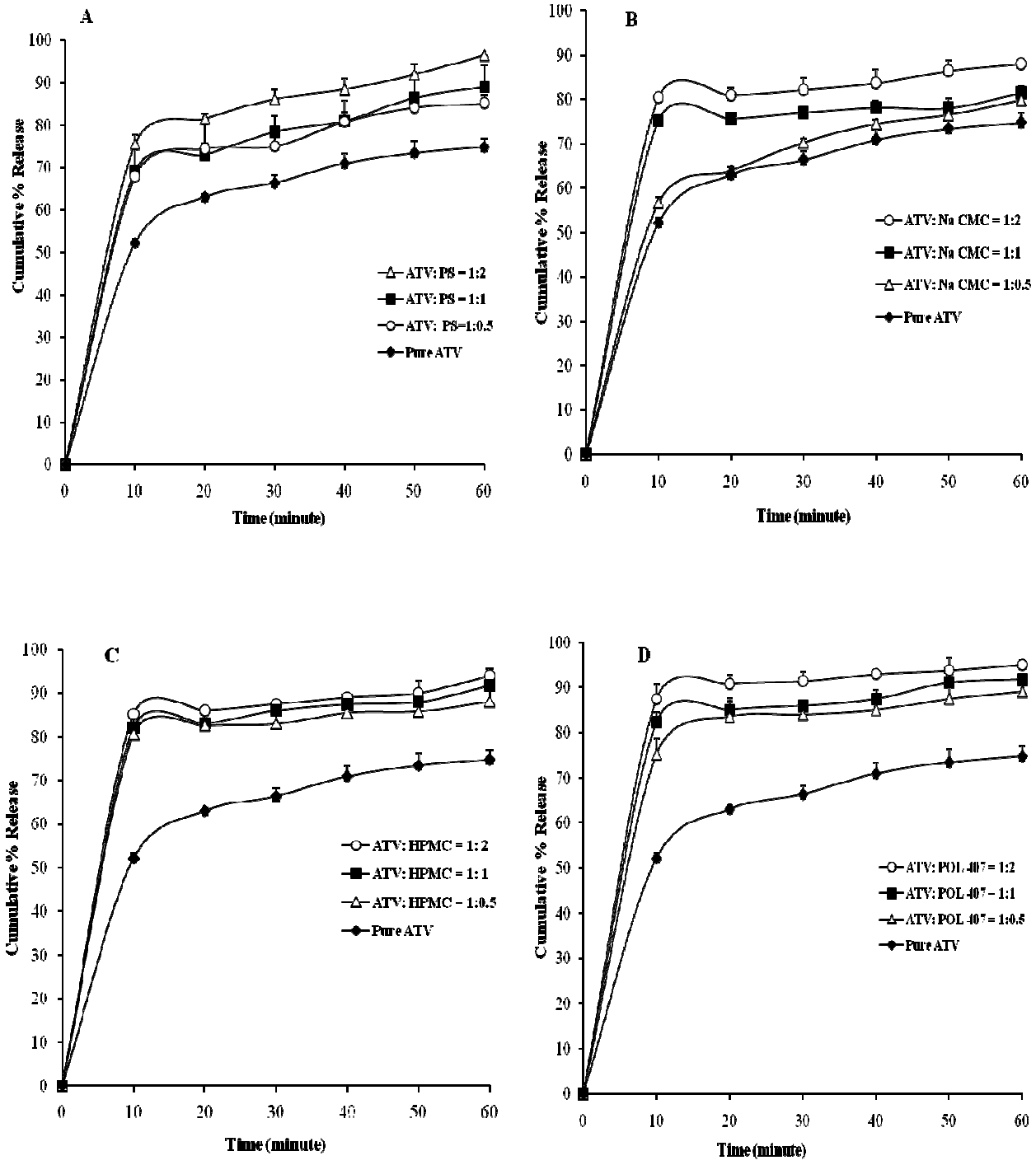

Figure 2: Zero order release curves of ATV from physical mixtures of ATV with pregelatinized starch (A), sodium carboxymethyl cellulose (B), hydroxypropyl methyl cellulose 4.5 cps (C) and poloxamer 407 (D) (n = 6).

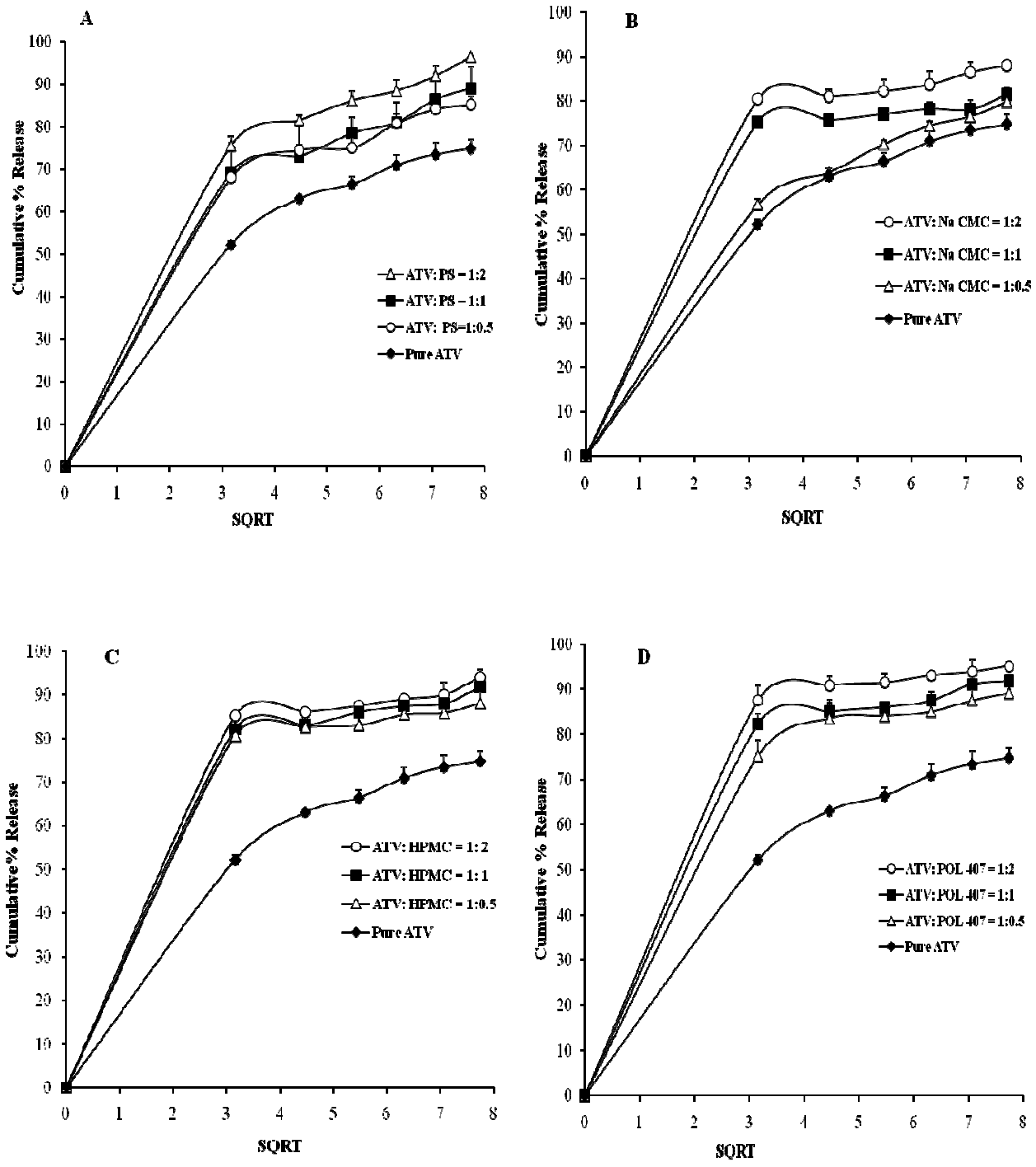

Figure 3. Higuchi release curves of ATV from physical mixtures of ATV with pregelatinized starch (A), sodium carboxymethyl cellulose (B), hydroxypropyl methyl cellulose (C) and poloxamer 407 (D) (n = 6).

Table 1: Kinetic parameters of atorvastatin release curves

PM	Ratio	Zero Order		First Order		Higuchi Model		Peppas Korsmeyer	
		r^2	K_0	r^2	K_1	r^2	K_h	r^2	n
ATV: PS	1:0.5	0.57	1.05	0.78	0.01	0.82	10.3	0.95	0.12
	1:1	0.6	1.1	0.85	0.01	0.85	10.7	0.96	0.14
	1:2	0.57	1.17	0.89	0.01	0.83	11.4	0.98	0.13
ATV: Na CMC	1:0.5	0.65	1.03	0.83	0.009	0.89	9.8	0.99	0.19
	1:1	0.43	0.9	0.52	0.008	0.71	9.3	0.76	0.03
	1:2	0.45	0.99	0.61	0.01	0.75	10.2	0.81	0.04
ATV: HPMC 4.5 cps	1:0.5	0.44	0.99	0.59	0.01	0.72	10.2	0.91	0.04
	1:1	0.46	1.04	0.67	0.01	0.74	10.6	0.88	0.05
	1:2	0.45	1.05	0.67	0.01	0.73	10.8	0.80	0.04
ATV: POL407	1:0.5	0.49	1.04	0.69	0.01	0.77	10.6	0.92	0.08
	1:1	0.42	1.05	0.69	0.01	0.74	10.7	0.91	0.06
	1:2	0.44	1.07	0.66	0.01	0.72	11.1	0.98	0.04
Pure ATV	-	0.64	0.98	0.8	0.008	0.88	9.3	0.98	0.19

PM = physical mixture, ATV = atorvastatin calcium, PS = Pregelatinized Starch, Na CMC = Sodium carboxymethyl cellulose, HPMC = Hydroxypropyl methyl cellulose, POL407 = Poloxamer 407

Table 2: Analysis of Variance (ANOVA) of the optimized PMs of atorvastatin

PM	Ratio	*Source of Variation*	*SS*	*df*	*MS*	*F*	*P-value*	F_{crit}
ATV: PS	1:0.5	Between Groups	4739.8	1	4739.81	6.91	0.021	4.74
		Within Groups	8225.6	12	685.47			
	1:1	Between Groups	5091.4	1	5091.43	7.17	0.020	4.74
		Within Groups	8509.4	12	709.11			
	1:2	Between Groups	6850.2	1	6850.25	8.64	0.012	4.74
		Within Groups	9508.7	12	792.39			
ATV: Na CMC	1:0.5	Between Groups	3212.5	1	3212.54	5.19	0.041	4.74
		Within Groups	7417.0	12	618.08			
	1:1	Between Groups	4671.1	1	4671.17	7.01	0.021	4.74
		Within Groups	7989.4	12	665.78			
	1:2	Between Groups	6087.2	1	6087.24	8.25	0.013	4.74
		Within Groups	8845.2	12	737.10			
ATV: HPMC	1:0.5	Between Groups	6235.5	1	6235.56	8.38	0.013	4.74
		Within Groups	8919.5	12	743.29			
	1:1	Between Groups	6795.7	1	6795.70	8.80	0.011	4.74
		Within Groups	9261.6	12	771.80			
	1:2	Between Groups	7386.4	1	7386.45	9.25	0.010	4.74
		Within Groups	9578.9	12	798.24			
ATV: POL407	1:0.5	Between Groups	6182.2	1	6182.20	8.27	0.013	4.74
		Within Groups	8969.0	12	747.42			
	1:1	Between Groups	7025.3	1	7025.36	8.97	0.011	4.74
		Within Groups	9394.6	12	782.88			
	1:2	Between Groups	8332.4	1	8332.42	9.92	0.008	4.74
		Within Groups	10078.7	12	839.89			

*PM = physical mixture

This eventually slowed down the release of ATV owing to the formation of highly viscous barrier layer at the interface of drug and dissolution medium. Due to the presence of the gelatinized layer, release slowed down but did not stop rather continued to increase. It is clearly explained by the fact that formed gelatinized masses of ATV-polymer were continuously crushed by paddle rotation which is explained earlier. This type of case, driving force for dissolution is written as (C_{GO}-C_{GS}) as shown in Fig. 5 where C_{GO} represents concentration of ATV and polymer in gelatinized SD and C_{GS} represents concentration of ATV and polymer in bulk solution. [37] ATV was released from the crushed gelatinized masses through a diffusion process and this was in accordance with values of diffusion exponents (Table 1). As values of diffusion exponent for all the batches were below the standard, it indicated about the fickian diffusion controlled release of ATV. [38]

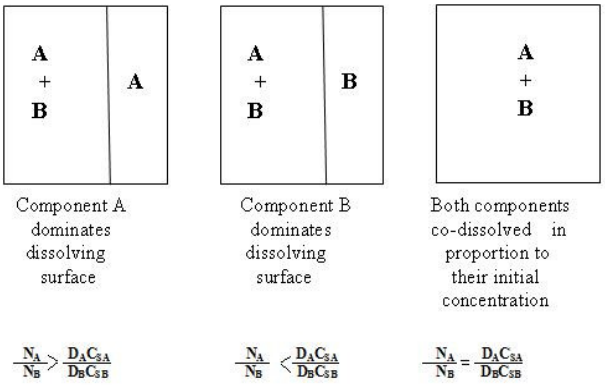

Figure 4: Dissolution model for a two component system (after Higuchi et al., 1965).

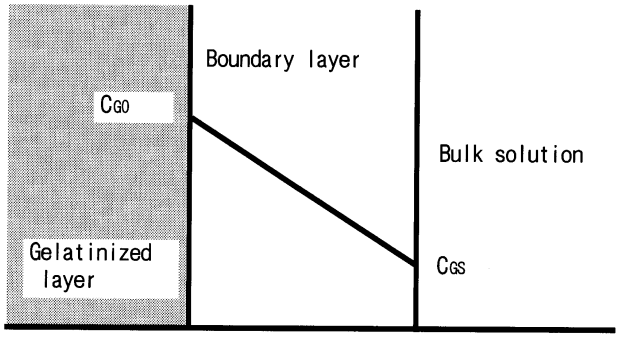

Figure 5: Dissolution pattern of gelatinized solid dispersion formulations

However, the goodness of fit for various models investigated for the PMs of ATV and polymer was found as following order: Peppas Korsmeyer > Higuchi Model > First Order > Zero Order e.g. the best fitted model was Peppas Korsmeyer's model.

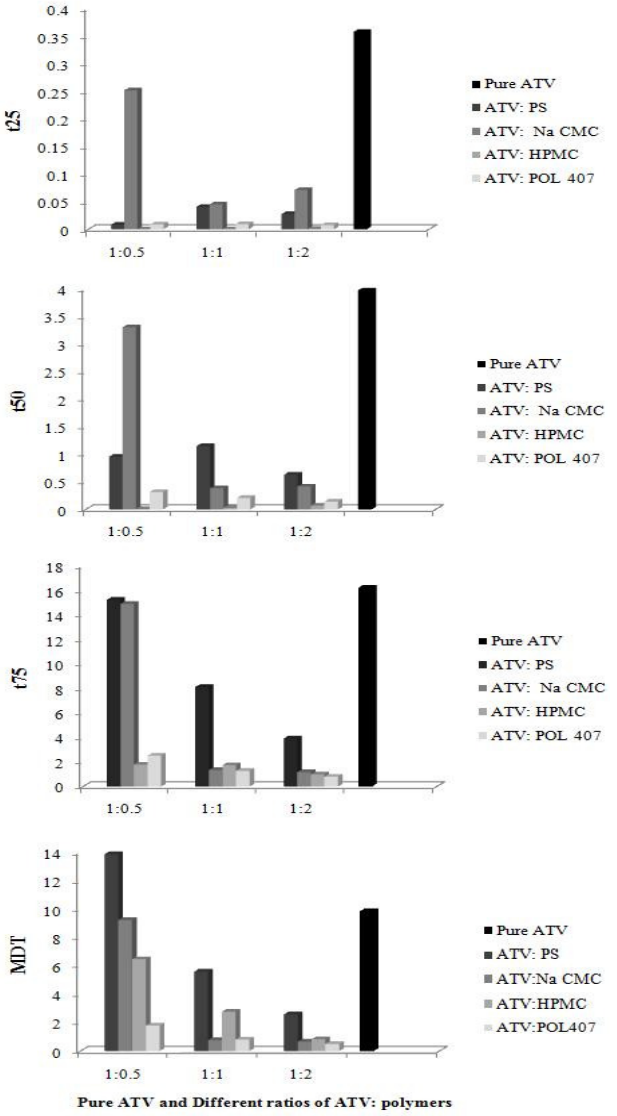

Figure 6. Time (in minute) for 25% release (t25), 50% release (t50), 75% release (t75), and mean dissolution time (MDT) of pure ATV and different SDs

(where ATV = atorvastatin, PS = Pregelatinized starch, Na CMC = sodium carboxymethyl cellulose and POL407 = poloxamer 407).

Time for 25% release (t25), 50% release (t50), 75% release (t75), and mean dissolution time (MDT) of ATV release were also calculated which are shown in Fig. 6. In case of PS, increment in concentration showed comparatively larger column of t25 indicating formation of gelatinous mass due to the presence of higher polymer concentration. This was also evident for HPMC also in case of t50, t75 and this indicates about the formation of gelatinous mass at the later portion of dissolution. In case of Na CMC at 1:0.5, t50 was 3.3 minute and t75 was 14.9 minute e.g. it took 11.6 minutes to release the later 25% of

ATV. In case of POL407, lowest values of t25, t50 and t75 indicate that ATV release rate was the fastest from these formulations. MDT value for pure ATV was 9.8 minute whereas it was 2.6 minute for PS, 0.68 minute for Na CMC, 0.86 minute for HPMC and 0.51 minute for POL407 (P <0.5).

CONCLUSION

It can be inferred that swellable polymers like sodium carboxymethyl cellulose, hydroxypropyl methyl cellulose, poloxamer 407 and pregelatinized starch could be used in PMs for poorly aqueous soluble drugs like atorvastatin. From the obtained results it suggests that 1:2 ratio of ATV: polymer showed remarkable enhancement in the dissolution. Unlike other solubility enhancing compound, these swellable polymers are regularly used in conventional solid dose preparations and this ensures about the availability, feasibility in use and cost effectiveness of the PMs formulations. Besides, physical mixing is very simple in technique and it needs very cheap tools to prepare. Overall, this research work presents about a very simple but effective technique for dissolution enhancement of ATV using very common polymers. But we need to proceed with this research for *in vivo* evaluation for ensuring about the capability of PMs to enhance oral bioavailability of atorvastatin.

ACKNOWLEDGEMENT

Authors would like to express their gratitude toward Beximco Pharmaceuticals Ltd., Bangladesh for providing with the chemicals.

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