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Dissolution enhancement of Fenofibrate tablet through Solid dispersion technique by Kneading method using various ratio of Poloxamer-188

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Abstract

Fenofibrate is a poorly water soluble drug of fibrate class, mainly used in patients at risk of cardiovascular disease in the treatment of hypercholesterolemia and hypertriglyceridemia. Hence this article investigates enhancement of dissolution profile of fenofibrate through the preparation of solid dispersions by kneading method using poloxamer-188 as hydrophilic carrier. Fenofibrate tablets were prepared from solid dispersion containing three different ratios of poloxamer-188; 1:1, 1:3 and 1:5. In vitro drug release studies were performed using US Pharmacopeia type II apparatus (paddle method) in 900 ml distilled water containing 0.75 % wt/v sodium lauryl sulfate at 100 rpm for 50 minutes. UV-Visible Spectrophotometric method was selected for assay as well as dissolution studies at λ_{max} 290 nm. The drug dissolution studies followed zero order, first order and Korsmeyer-Peppas release kinetics. Statistically significant improvements were found among the drug release profile from all the solid dispersion tablets. The formulations containing drug poloxamer at a ratio of 1:3 exhibited superior dissolution (99.47%) than all other as well as pure drug (24.58%). Thus solid dispersion technique using poloxamer-188 can be successfully used for improvement of dissolution as well as bioavailability of fenofibrate.

Key-Words: Fenofibrate, Solid dispersion, Kneading, Poloxamer-188, Dissolution

Introduction

The oral route is the most preferred route of drug delivery for treatment of a number of diseases. Nearly 35 to 40% of newly launched drug possess low aqueous solubility which leads to their poor dissolution and thereby low bioavailability, resulting in high intra and inter subject variability and lack of dose proportionality. For these drugs absorption rate from gastrointestinal tract is mainly governed by dissolution and improvement in solubility may lead to enhanced bioavailability¹. There are a number of techniques to overcome such problems arising out of low solubility and bioavailability, which may result into improved therapeutic efficacy of these drugs. Among various approaches, the preparation of solid dispersions has often proved to be successful, is essentially a multicomponent system, having drug dispersed in and around hydrophilic carrier²⁻⁶.

This technique has been used for a wide variety of poorly aqueous soluble drug such as nifedipine⁷, meloxicam⁸, lansoprazole⁹, valdecoxib¹⁰, aceclofenac¹¹, carbamazepine¹², glimepiride¹³, etoricoxib¹⁴. Various hydrophilic carriers, such as polyethylene glycols¹⁵, polyvinyl pyrrolidone¹⁶, sugars¹⁷, urea¹⁸ have been investigated for improvement of dissolution characteristics and bioavailability of poorly aqueous soluble drugs.

Fenofibrate (isopropyl ester of 2-[4-(4-chlorobenzoyl)phenoxy]-2-methyl propanoic acid) is a widely used hypolipidemic drug. Its pharmacological activity consists in reducing triglyceride and cholesterol concentration in plasma. This drug is used mostly in lipid regulation as it decreases low density lipoprotein (LDL) and very low density lipoprotein (VLDL) levels and increases high density lipoprotein (HDL) level. Solubility and permeability are the fundamental parameters controlling the rate and extent of drug absorption. According to Biopharmaceutics Classification System (BCS), fenofibrate is a Class II drug having low solubility and high permeability. Bioavailability of this drug solely depends on dissolution rate in the gastrointestinal tract¹⁹. Therefore, the present investigation was focused on

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exploring poloxamer-188 as a carrier to increase the dissolution rate of fenofibrate by formation of solid dispersions using kneading method and to see the possible mechanism of improved dissolution rate.

Material and Methods

Materials

Fenofibrate was obtained as a gift sample from Square Pharmaceuticals Ltd., Dhaka, Bangladesh. Poloxamer-188 was received from Merk chemicals, Mumbai, India. All other reagents and solvent used were of analytical grade.

Methods

Preparation of fenofibrate solid dispersion

A mixture of poloxamer-188 and fenofibrate (1:1, 1:3 and 1:5 by weight) was wetted with water and kneaded thoroughly for 30 minutes in a glass mortar. The paste formed was dried under vacuum for 24 hours. Dried powder was passed through sieve no. 60 and stored in a desiccator until further evaluation²⁰.

Formulation of fenofibrate tablet

Tablet containing 40 mg equivalent of fenofibrate solid dispersion were prepared by direct compression. Microcrystalline cellulose, lactose, disintegrant, magnesium stearate, talc and the solid dispersion were weighed properly and mixed uniformly. The final granules were blended with talc (2% wt/wt) and magnesium stearate (1% wt/wt) and compressed on a single-station tablet compression machine (Pressima version 1EUD, Germany) using 10-mm punches.

Characterization of tablet

Prepared tablets are evaluated for hardness (Monsanto hardness tester), thickness, friability (Roche friabilator, Erweka, Germany), weight variation, disintegration time (DT), % LOD and drug content showed in Table 2.

In vitro dissolution study of fenofibrate from solid dispersion

In vitro dissolution study was performed in a paddle type dissolution apparatus (USP apparatus type II, Veego, India) for pure drug, market preparation and solid dispersion containing 40mg equivalent of fenofibrate¹⁹. 900 ml distilled water containing 0.75% wt/v sodium lauryl sulfate (SLS) was used as dissolution medium. The dissolution was carried out at 100 rpm to a temperature of 37°C±0.5°C for 50 minutes and 5 ml sample was withdrawn at predetermined time intervals at 5, 10, 20, 30, 40 & 50 minutes and was compensated by another fresh media. Samples were withdrawn with the help of disposable syringe, filtered and were kept in a test tube. The absorbances of sample were measured at λ_{\max} 290 nm in a UV-Visible spectrophotometer (UV mini-1240, Shimadzu Corp., Kyoto, Japan).

Drug release kinetics

To study the release, data obtained from drug release studies were plotted in various kinetics; zero order (equation 1) as cumulative amount of drug released vs time, first order (equation 2) as

Log cumulative percentage of drug remaining vs time and Korsmeyer-Peppas model as log cumulative percentage of drug released vs log time and exponent n was calculated through the slope of straight line (equation 3)

$$Ct = C_0 + K_0t \quad (1)$$

Where, K_0 is the zero order rate constant expressed in units of concentration/time and t is the time in hours. A graph of concentration vs time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes²¹

$$\text{Log } C = \text{Log } C_0 - \frac{kt}{2.303} \quad (2)$$

Where, C_0 is the initial concentration of drug, k is the first order constant and t is the time²²

$$\text{Log} \left(\frac{M_t}{M_f} \right) = \text{Log } k + n \text{Log } t \quad (3)$$

Where, M_t is the amount of drug release at time t, M_f is the amount of drug release after infinite time, t is the release time, K is the kinetic constant characteristic of the drug polymer/system and n is an exponent that characterizes the mechanism of release of tracers²³ A value of $n = 0.45$ indicates Fickian diffusion (case-I) release; $0.45 < n < 0.89$ for non-Fickian diffusion (anomalous) release; $n = 0.89$ case-II transport and $n > 0.89$ indicates super case II release.

Mean Dissolution Time (MDT)

Mean Dissolution Time (MDT) value can be calculated from dissolution data using Mockel and Lippold equation and used to characterize the drug release rate from the dosage form and the retarding efficiency of the polymer²⁴.

$$\text{MDT} = \left(\frac{n}{n+1} \right) k^{-1/n}$$

Where, n is release exponent and k is release rate constant. A higher value of MDT indicates a higher drug retaining ability of the polymer and vice-versa.

Successive fractional dissolution time

To characterize the drug release rate in different experimental condition, $T_{25\%}$ (time required for 25% drug release), $T_{50\%}$, $T_{80\%}$ and MDT were calculated from dissolution data according to the equations: $T_{25\%} = (0.25/k)^{1/n}$, $T_{50\%} = (0.5/k)^{1/n}$, $T_{80\%} = (0.8/k)^{1/n}$ and $\text{MDT} = (n/n+1) k^{-1/n}$

Where n is a release exponent and k is the release rate constant for Korsmeyer- Peppas equation.

Results and Discussion

The dissolution behaviour of fenofibrate from solid dispersion was analyzed in 900 ml of distilled water containing 0.75% wt/v SLS. The drug release data obtained were extrapolated by zero order, first order and Korsmeyer-Peppas equations to know the mechanism of drug release from these formulations (Figure 1, 2, 3). Release constant was calculated from the slope of the appropriate plot and the regression coefficient (r^2) was determined (Table 3). It was found that in vitro drug release of fenofibrate was best explained by Korsmeyer-Peppas equation as the plots showed highest linearity ($r^2 = 0.951$ to 0.976) whereas zero order kinetics with $r^2 = 0.417$ to 0.704 and first order kinetics with $r^2 = 0.876$ to 0.997 showed poor linearity. Korsmeyer's plot indicated an n value of 0.401 to 0.640 which was indicative of an anomalous diffusion mechanism or diffusion coupled with erosion; hence the drug release was controlled by more than one process. The tablets prepared from the solid dispersion of fenofibrate of the proposed formulations (MS1 to MS3) were evaluated for hardness, weight variation, thickness, friability, disintegration time, % LOD of granules and drug content showed in the Table 2 and were within the range. The dissolution rate of fenofibrate from all the solid dispersion was significantly higher than fenofibrate alone as well as market preparation. Table 4 enlists the dissolution parameters of fenofibrate solid dispersion with poloxamer-188 as carrier at three different concentrations. It is evident that, the highest percentage of drug release within 50 min is obtained from MS2 where the ratio of API and polymer is 1:3. But in MS3, the API and polymer ratio is 1:5 and the release of drug is controlled with 75.62 %. Successful fractional dissolution time and MDT values calculated for all the solid dispersion were illustrated in Figure 4. This result was in exact consonance with the drug release process indicating that MS2 with highest dissolution rate had least MDT values (3.935 min) and pure drug with slowest dissolution rate had highest MDT (104.709 min).

Relatively higher dissolution enhancement in such cases could be credited to more intimate drug-carrier interaction in the molten state during formulation of solid dispersions. Increased dissolution of fenofibrate solid dispersions could be ascribed to the probable reduction in its particle size, wetting of the hydrophobic particles and augmentation of its solubility by the said carrier^{3, 25}. Furthermore, kneading results in uniform distribution of drug in the

polymer crust in a highly dispersed state. Thus, when such a system comes in contact with an aqueous dissolution medium, the hydrophilic carrier dissolves and results in precipitation of the embedded drug in to fine particles, which increase the dissolution surface available. Moreover other factor such as absence of aggregation and/or reagglomeration phenomenon and also inhibition of crystal growth of drug during dissolution could be attributed to better dissolution profile^{26, 27}. Thus it can be concluded from the present investigation that dissolution rate as well as bioavailability of fenofibrate can be enhanced to a great extent by solid dispersion technique using kneading method by the polymer poloxamer-188.

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Table 1: Formulation of fenofibrate tablet containing equivalent amount of solid dispersions of fenofibrate

Formulation code	Fenofibrate (mg)	Poloxamer (mg)	Avicel PH 102 (mg)	Lactose (mg)	Talc (mg)	Mg-stearate (mg)	Crospovidone (mg)
MS1 (1:1)	40	40	300	75	10	5	30
MS2 (1:3)	40	120	220	75	10	5	30
MS3 (1:5)	40	200	140	75	10	5	30
PD	40	---	340	75	10	5	30

*PD = Pure drug without poloxamer-188

Table 2: Evaluation of physical properties of tablets containing fenofibrate solid dispersion

Formulation code	Hardness (kg/cm ²)	Thickness (mm)	Friability (%)	Weight variation (mg)	DT (min)	LOD (%)	Content (%)
MS1 (1:1)	4.96±0.2	4.98±0.3	0.07	496.6±2	7.09	2.72	99.50±1.1
MS2 (1:3)	5.40±0.4	4.50±0.3	0.73	499.1±2	7.53	1.72	99.11±0.9
MS3 (1:5)	5.75±0.6	4.96±0.5	0.08	502.9±1	6.84	1.73	98.89±1.2
PD	5.03±0.3	4.96±0.5	0.16	502.3±1	15	2.13	99.22±1.1

Table 3: Release kinetics of fenofibrate solid dispersion tablets with various ratio of poloxamer-188

Formulation code	Zero order		First order		Korsmeyer-Peppas	
	R ²	K ₀	R ²	K ₁	R ²	N
MS1	0.704	1.177	0.920	0.016	0.951	0.422
MS2	0.417	1.213	0.876	0.034	0.976	0.640
MS3	0.513	1.030	0.997	0.009	0.961	0.401
PD	0.993	0.476	0.997	-0.002	0.989	0.917
MP	0.826	1.99	0.990	-0.04	0.990	0.613

*MP = Market preparation

Table 4: Percentage release of fenofibrate from solid dispersion tablets with various ratio of poloxamer-188

Time (min)	% of drug released				
	MS1	MS2	MS3	PD	MP
0	0	0	0	0	0
5	48.13	83.71	54.07	2.80	0.42
10	57.11	87.52	61.17	6.82	14.86
20	75.41	89.65	70.62	11.31	61.56
30	78.13	93.46	71.64	16.11	70.05
40	81.77	96.61	73.22	20.91	71.75
50	89.32	99.47	75.62	24.58	86.18

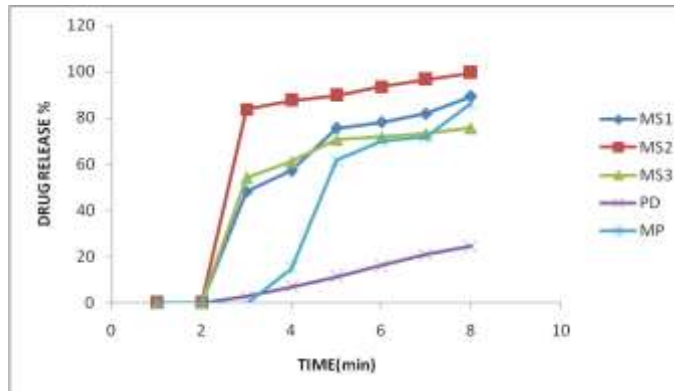


Fig. 1: Zero order release kinetics of fenofibrate solid dispersion tablets with various ratio of poloxamer-188

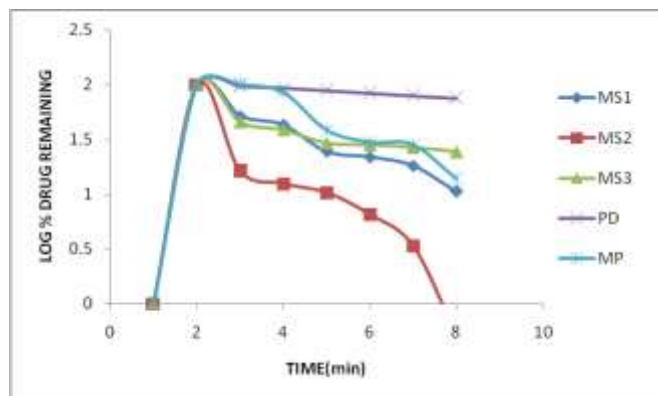


Fig. 2: First order release kinetics of fenofibrate solid dispersion tablets with various ratio of poloxamer-188

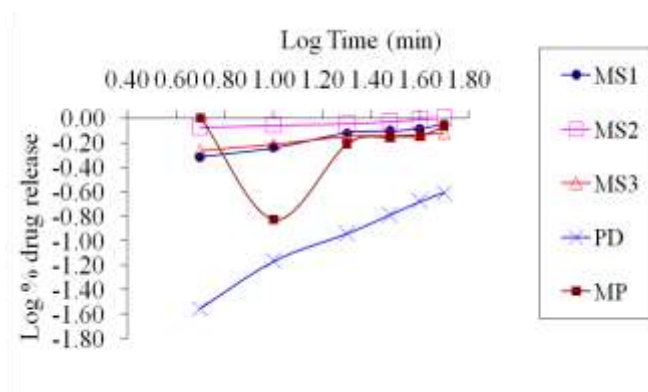


Fig. 3: Korsmeyer-Peppas release kinetics of fenofibrate solid dispersion tablets with various ratio of poloxamer-188

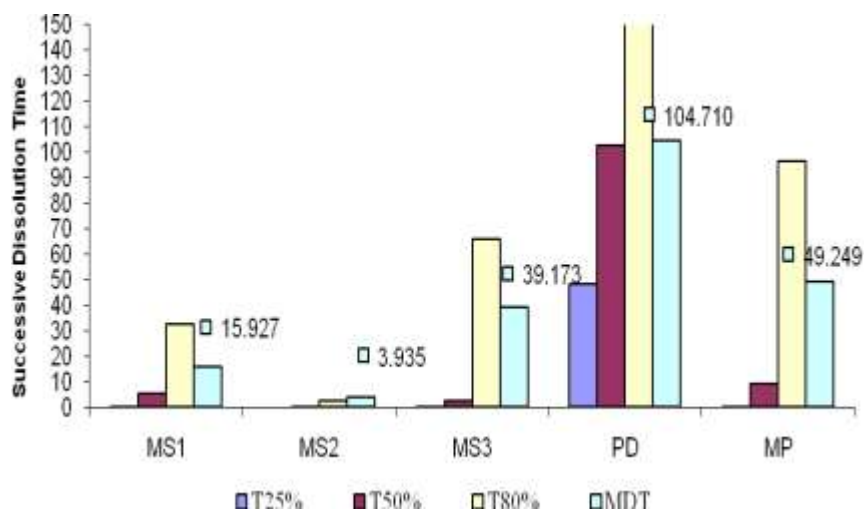


Fig. 4: Successive fractional dissolution time and MDT values of fenofibrate solid dispersion tablets with various ratio of poloxamer-188

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