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Formulation of pyridoxine hydrochloride sustained release capsules: Effect of propylene glycol co-solvent on the *in vitro* release

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The objectives of the present study were to formulate sustained release pyridoxine hydrochloride capsules and to study the effect of propylene glycol co-solvents on the *in vitro* properties of the capsules. All batches of formulations were made with fixed concentrations of binder-disintegrants, diluents and equal load of active pharmaceutical ingredient. The granules were prepared by wet granulation using propylene glycol water co-solvent as the wetting agent, sodium carboxymethylcellulose (SCMC) and maize starch were used as binder-disintegrant and kaolin was used as the diluents. The micromeritic properties of the granules were analysed by direct and indirect methods. The granules were encapsulated in hard gelatin capsule No. 1. The capsule weight uniformity, disintegration time and drug content were determined. *In vitro* dissolution test was performed in 0.1 N HCl, simulated gastric fluid (SGF, pH 1.2) and simulated intestinal fluid (SIF, pH 7.2). The results showed that the particles size of granules ranged from 245 to 259 µm and had good flowability. The capsules complied with British Pharmacopoeia (BP) requirement for capsule weight uniformity. The drug content was within 90 to 110% of the average values. The results of *in vitro* drug release in SGF (pH, 1.2) showed that the release of pyridoxine hydrochloride was very slow and was significantly ($P < 0.05$) lower than the release in 0.1 N HCl and in SIF (pH, 7.2), respectively. Therefore, pyridoxine hydrochloride sustained release capsules could be formulated with kaolin as the diluent and propylene glycol co-solvent as the moistening agent in order to reduce the frequency of administration of this drug and improve patient compliance.

Key words: Pyridoxine hydrochloride, sustained release, capsules, particle size analysis.

INTRODUCTION

Over the years, much work has been carried out to improve patient compliance of conventional oral and parenteral single dosage forms meant for repeated administration (Ravi-Kumar, 2000; Wissing et al., 2004; Mathew and Devi, 2007; Rhee et al., 2007; Jia et al., 2008; Kim et al., 2010). This has led to the development of effective sustained release dosage forms. Among all the factors that make for an ideal therapy, the most difficult to achieve is maintaining serum concentrations of drugs at therapeutic levels for a long period of time. This is usually done by repeated administration and poses serious problem of patient compliance. Sustained release dosage forms are preparations with controlled rate of absorption of drug into the body, which is achieved mainly by controlling the dissolution rate of the formulations (Umeyor et al., 2012). Sustained release dosage forms provide an initial release of drug sufficient to provide a therapeutic dose soon after administration, and then a gradual release over an extended period. The rationale for the controlled delivery of drugs is to promote therapeutic

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benefits, while at the same time minimizing toxic effects (Sinko, 2006). Capsules and tablets are the most common oral dosage forms. These formulations differ from each other in that material in capsules is less impacted than in compressed tablets. Once a capsule dissolves, the contents generally disperse quickly (Welling, 2002). In the formulation of capsules, particle, flowability is of paramount importance (Welling, 2002). The flow of powder during manufacturing dictates the quality of the product in terms of weight and content uniformity of the capsules (Aulton, 2007). The measurement of the flow properties of powders is essential before capsule filling, because variation in particle flow will automatically cause variation in capsule weight and active ingredient variation. The flow property of bulk material results from the cohesive forces acting on individual particles such as van der Waals, electrostatic, surface tension, interlocking, and friction (Aulton, 2007).

Pyridoxine is a water-soluble vitamin involved mainly in amino acid metabolism, and is also involved in carbohydrate and fat metabolism. It is required for the formation of haemoglobin and is usually given as the hydrochloride, although other salts such as the citrate, oxoglurate, phosphate, and phosphoserinate, have also been used. Pyridoxine is used in the treatment and prevention of pyridoxine deficiency states (Sean, 2011). It is usually given orally, the preferred route, but may also be given by the subcutaneous, intramuscular, or intravenous routes (Sean, 2009). It is used to treat certain metabolic disorders such as homocystinuria or primary hyperoxaluria, seizures due to hereditary syndromes of pyridoxine deficiency and premenstrual syndrome. The aim of this work was to formulate pyridoxine sustained release capsules and to study the effect of propylene glycol co-solvent on the *in vitro* release.

MATERIALS AND METHODS

The following materials were used: pyridoxine hydrochloride (BDH Chemicals Ltd., England), sorbic acid, sodium carboxymethylcellulose (SCMC), maize starch, ferric chloride, hydrochloric acid, sodium hydroxide, sodium chloride and monobasic potassium phosphate, sodium benzoate (BDH Chemicals Ltd., England), kaolin, propylene glycol (Merck, Darmstadt, Germany). All other reagents and solvents were of analytical grade and were used as supplied.

Preparation of granules

The granules were prepared by wet granulation using propylene glycol water co-solvent as the wetting agent; details of formulation are shown in Table 1. SCMC and maize starch were used as binder-disintegrant, sorbic acid and sodium benzoate were used as the preservative and kaolin was used as the diluents. The powders were mixed for 10 min in a tumbler mixer (Rotor mixer S42P43, Forster Equipment Co. Ltd., England) together with pyridoxine hydrochloride. The powder mixtures were moistened with the appropriate amount of the wetting agent and were triturated in a mortar to a homogenous mix. The homogeneous wet mass was then screened through a 1.7 mm sieve and the wet granules were dried in a hot air oven at 55°C for 1 h (Memmer, U25, Western Germany). Thereafter, the dried granules were screened through a 1.0 mm sieve.

Evaluation of granules

Particle size distribution

The particle size of the granules was determined using nest of sieves (numbers 16, 52, 100 and 200) arranged in descending order of aperture size with a pan collector underneath. Eighteen grams quantity of each batch of granulations was accurately weighed using an electronic weighing balance (Ohaus Adventurer, SNR – 1121 R53860, China), and transferred to the top most of a series of sieves. The sieve arrangement was transferred to an Endecott mechanical sieve shaker (Endecott 1 MK 11, 6315, London, England) and was shaken for 5 min. At the end of 5 min, the fraction of powder retained by each sieve was weighed. Three determinations were carried out and the mean particle diameter (d_{av}) was determined using the relation (Ansel et al., 2007; Okoye et al., 2012):

$$d_{av} = \frac{\Sigma(\text{Percentage powder retained} \times \text{Mean aperture size})}{100} \quad (1)$$

Bulk and tapped densities

A 25 g quantity of each granule sample was placed in a 100 ml measuring cylinder and the volume occupied by the sample was noted as the bulk volume. The bulk density (ℓ_B) was calculated using the equation:

$$\text{Bulk density } (\ell_B) = \frac{\text{Mass of powder } (M)}{\text{Bulk volume of powder } (V_B)} \quad (2)$$

The tapped volume was determined by tapping the cylinder on a wooden flat surface from a height of 1 inch at 2 s interval until there was no significant change in volume reduction (Aulton, 2007; Ngwuluka et al., 2010; Chime et al., 2012). The volume occupied by the sample was then recorded as the tapped volume. The tapped density (ℓ_T) was calculated using the formula:

$$\text{Tapped density } (\ell_T) = \frac{\text{Mass of powder } (M)}{\text{Tapped volume of powder } (V_T)} \quad (3)$$

Flow rate and angle of repose

A 25 g quantity of pyridoxine hydrochloride granules was weighed out and gradually placed into the funnel clamped onto a retort stand; the funnel orifice was closed with a shutter. The time taken for all the granules to flow through the orifice was noted. The flow rate was calculated using Equation 4:

$$\text{Flow rate } (w) = \frac{\text{Mass of powder } (g)}{\text{Time of flow } (s)} \quad (4)$$

The angle of repose was determined by measuring the height of heap of powder formed using a cathetometer; the radius was gotten by dividing the diameter by two. Angle of repose (ɵ) for each granule

Table 1. Composition of pyridoxine hydrochloride sustained release capsules.

Ingredient	Weight/capsule (mg)				
	F1	F2	F3	F4	F5
Pyridoxine hydrochloride (mg)	50.00	50.00	50.00	50.00	50.00
SCMC (mg)	50.00	50.00	50.00	50.00	50.00
Maize starch (mg)	25.00	25.00	25.00	25.00	25.00
Sorbic acid (mg)	1.25	1.25	1.25	1.25	1.25
Sodium benzoate (mg)	1.25	1.25	1.25	1.25	1.25
Propylene glycol (ml)	1.00	2.00	3.00	4.00	5.00
Magnesium stearate (1%)	2.50	2.50	2.50	2.50	2.50
Kaolin q.s (mg)	250.00	250.00	250.00	250.00	250.00

SCMC: Sodium carboxymethylcellulose.

granule sample was calculated using the formula:

$$\theta = \tan^{-1} \frac{\text{height of powder heap}}{\text{radius of powder}} \quad (5)$$

Compressibility index and Hausner's quotient

Carr's compressibility index (%) of the granules was obtained using the formula:

$$\text{Carr's index (\%)} = \frac{\ell_T - \ell_B}{\ell_T} \times 100 \quad (6)$$

While Hausner's ratio was obtained using Equation 5:

$$\text{Hausner's ratio} = \frac{\ell_T}{\ell_B} \quad (7)$$

where ℓ_T and ℓ_B are tapped and bulk densities, respectively.

Preparation of capsules

The granules were treated with magnesium stearate as shown in Table 1, and then filled manually using capsule shell No 1.

Evaluation of capsules

Weight uniformity

Twenty capsules were selected from each batch, and weighed individually, the contents of the capsule were emptied and weighed and also the empty capsule shell was also weighed. The mean standard deviation and percentage coefficient of variation of the mean weight was calculated.

Disintegration time test

Disintegration time test was conducted using an Erweka ZT 120 basket and rack assembly. Distilled water maintained at 37.0 ± 1.0°C was used as the disintegration medium. Ten capsules from each batch were used for the test and the procedure being as stipulated in the British Pharmacopoeia (BP, 2009) for disintegration time of capsules.

Content of active ingredient

Beer's calibration curve for pyridoxine hydrochloride was obtained at a concentration range of 2.0 to 10.0 mg% in 0.1 N HCl at a predetermined wavelength of 450 nm. Twenty capsules were randomly selected from each batch of the tablets. The capsules were emptied and the content weighed together. An amount equivalent to the average weight of the capsule was weighed out in an analytical balance. The weighed amount was dispersed in the medium and was filtered. Two drops of ferric chloride was added to an aliquot of the filtrate and was assayed using spectrophotometer (Pye Unicam SP6 450 UV/VIS spectrophotometer, England) at 450 nm. The concentration of the drug in each capsule was calculated using the absorbance readings.

In vitro release studies

Beer's plot was obtained for pyridoxine hydrochloride in 0.1 N HCl, simulated gastric fluid (SGF, pH 1.2) and simulated intestinal fluid (SIF, pH 7.2), respectively at a concentration range of 2 to 10 mg%. USP paddle method was adopted in the study. The dissolution medium consisted of 900 ml of freshly prepared medium maintained at 37 ± 1°C. A capsule from each batch was placed inside a tightly secured basket and the basket was placed in the bottom of the beaker. The paddle was rotated at 100 rpm. About 5 ml was withdrawn from the dissolution medium at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5 and 5.0 h, and was filtered with a non adsorbent filter paper (Whatman No. 1). Two drops of ferric chloride was added to an aliquot of the filtrate and assayed using spectrophotometer (Pye Unicam SP6 450 UV/VIS spectrophotometer, England) at predetermined wavelengths of 450 nm in 0.1 N HCl and SGF and 296 nm in SIF. An equal volume of the withdrawn sample was replaced with a fresh medium to maintain sink condition in each case. The amount of drug released at each time interval was determined with reference to the standard Beer's plot for each drug. The experiment was repeated two times for each sample and the mean was calculated.

In vitro release kinetics

The dissolution data for the capsules were analysed to determine the *in vitro* release kinetic mechanism using three kinetic models including the first order equation, Higuchi square root equation and Ritger-Peppas empirical model. Drug release is said to be of first-

order if it obeys the following equation:

$$\ln Q_t = \ln Q_0 - K_1 t \quad (8)$$

where Q_t is the amount of drug released or dissolved at time t, Q_0 is amount of drug released or dissolved at time t = 0, k_1 is first-order release rate constant (Singh et al., 2011).

According to Higuchi relationship, the amount of drug released per unit surface area is proportional to the square root of time. This equation explains diffusion release rate as indicated below:

$$Q_t = K_H t^{1/2} \quad (9)$$

where k_H is Higuchi rate constant, Q_t has same meaning as defined earlier (Singh et al., 2011). The integral form of Higuchi equation is employed in seeking to establish whether mixed order release kinetics exists. Diffusion controlled process is dominant where the log-log plot of the integral form of Higuchi equation approaches 0.5 (Ofoefule and Chukwu, 2002).

Ritger and Peppas (1987a,b) developed an empirical equation to analyze both Fickian and non-Fickian release of drug from swelling as well as non-swelling polymeric delivery systems. The equation is represented as:

$$M_t/M_\infty = Kt^n \quad (10)$$

where M_t/M_∞ is the fraction of drug released at time t, n is diffusion exponent indicative of the mechanism of transport of drug through the polymer, K is the kinetic constant (having units of t^{-n}) incorporating structural and geometric characteristics of the delivery system. The release exponent $n \leq 0.5$ for Fickian diffusion release from slab (swellable matrix), $0.5 < n < 1.0$ for non-Fickian release (anomalous), this means that drug release followed both diffusion and erosion controlled mechanisms and n = 1 for zero order release, that is, drug release is independent of time (Ritger and Peppas, 1987a, b).

Statistical and data analysis

Data were analyzed using Statistical Package for Social Sciences (SPSS) Version 16.0 (SPSS Inc. Chicago, IL.USA). All values were expressed as mean ± standard deviation (SD). Data were analysed by one-way analysis of variance (ANOVA). Differences between means were assessed using student's t-test. $P < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Granule properties

Particle size of granules

The results of particle size of pyridoxine granules are shown in Table 2. From the results, the particle size ranged from 245 to 259 µm. As the dimensions of particles increase and the particles change in nature, the forces acting on them change. Fine powder particles less than 100 µm in diameter are acted upon primarily by surface forces, while particles above 1000 µm in diameter are governed by gravitational forces (Fukumori and Ichikawa, 2002). Therefore, the balance of interactive forces determines powder behavior. With relatively small particles, the flow through an orifice may be restricted, because the cohesive forces between the particles are of the same magnitude as gravitational forces. Large particles however with respect to the orifice through which it has to flow can cause arching that can block flow from hopper to die cavity (Fukumori and Ichikawa, 2002). The flowability of powders decreases as the shapes of particles become more irregular. Efforts to relate various shape factors to powder and their surfaces such as size, shape, surface morphology, packing conditions, and interparticle forces must therefore be considered. To make the situation more complex, the interparticle forces can be of a number of types: mechanical forces, surface tension, electrostatic forces, van der Waals forces, solid-bridge forces, or plastic welding forces; none of these can be readily quantified (Fukumori and Ichikawa, 2002). The results therefore showed that the granules were within limits for good flow of powders as shown in Table 2.

Flow properties

The results of the flow properties of pyridoxine hydrochloride granules are shown in Table 2. The results of loosed densities (bulk and tapped densities) showed that the granules had reduced densities and hence had good flowability. The flow of powder during manufacturing dictates the quality of the product in terms of weight and content uniformity of the capsules (Lachman et al., 1990). The measurement of the flow properties of powders is essential before capsule filling because variation in particle flow will automatically cause variation in capsule weight and active ingredient variation. The flow property of bulk material results from the cohesive forces acting on individual particles such as van der Waals, electrostatic, surface tension, interlocking, and friction (Lachman et al., 1990). Bulk and tapped densities are important, because they are used as an indirect method of assessing powder flowability. Hausner's ratio, determines the degree of interparticulate friction and values ≤ 1.25 indicates good flow, while Hausner's ratio > 1.25 indicates poor flow. The results indicated that Hausner's ratio ranged from 1.10 to 1.22; therefore, they were within the limits for good powder fluidity. Carr's compressibility index also reveals the degree of interparticulate friction and values between 5 and 17 indicates good flow (Aulton, 2007; Yüksel et al., 2007). The results showed that Carr's index ranged from 9.1 to 17.3% and hence exhibited good flowability. Values for angles of repose ≤ 30° generally indicate a free flowing material and ≥ 40° suggest a poorly flowing material. Angle of repose was also used as an indirect method of assessing flowability of granules and the results also showed that the granules had low interparticulate friction and hence had good flowability. The results of flow rate (that is, flow under gravity) also showed that the granules had good flowability.

Capsule properties

The results of the weight uniformity of the capsules are

Table 2. Micromeritic properties of pyridoxine hydrochloride granules.

Batch	Particle size (µm ± SD)	ℓ_B (g/ml ± SD)*	ℓ_T (g/ml ± SD)*	AR (^{o} ± SD)*	HR	CI (%)	FR (g/sec ± SD)
F1	259.0 ± 0.1	0.68 ± 0.27	0.75 ± 0.07	27.82 ± 0.03	1.10	9.10	8.62 ± 0.05
F2	256.0 ± 0.2	0.61 ± 0.23	0.74 ± 0.06	29.94 ± 0.01	1.21	16.70	6.65 ± 0.07
F3	245.0 ± 0.1	0.53 ± 0.17	0.63 ± 0.12	29.93 ± 0.09	1.19	15.80	5.12 ± 0.03
F4	252.0 ± 0.3	0.51 ± 0.11	0.61 ± 0.19	21.80 ± 0.11	1.20	16.00	8.32 ± 0.05
F5	249.0 ± 0.2	0.50 ± 0.17	0.61 ± 0.21	24.86 ± 0.05	1.22	17.30	8.61 ± 0.07

Values shown are mean ± SD (*n = 3); ℓ_B and ℓ_T = Bulk and tapped densities, AR = Angle of repose, HR = Hausner's ratio, CI = Carr's compressibility index, FR = Flow rate; batches F1, F2, F3, F4 and F5 contain propylene glycol 1, 2, 3, 4 and 5 ml respectively.

Table 3. Properties of pyridoxine capsules.

Batch	Capsule weight (mg ± CV)*	Disintegration time (min ± SD)[a]	Drug content (mg ± SD)[a]
F1	253.00 ± 0.94	3.54 ± 0.37	52.50 ± 0.13
F2	260.00 ± 1.01	3.31 ± 0.17	49.00 ± 0.27
F3	255.00 ± 0.92	3.30 ± 0.29	49.00 ± 0.15
F4	263.00 ± 2.64	3.40 ± 0.11	50.00 ± 0.31
F5	257.00 ± 0.81	3.56 ± 0.32	53.50 ± 0.11

*Mean for 20 capsules, [a]Mean for 10 capsules, CV: coefficient of variation, SD: standard deviation, batches F1, F2, F3, F4 and F5 contain propylene glycol 1, 2, 3, 4 and 5 ml, respectively, $P < 0.05$ was considered significant.

Table 4. Release kinetics of sustained release pyridoxine hydrochloride in SIF.

Batch	Higuchi			First order		Ritger-Peppas		
	(r^2)	(n)	K (h^{-1})	(r^2)	K (h^{-1})	(r^2)	(n)	K (h^{-n})
F1	0.936	0.097	69.2	0.867	1.559	0.953	0.099	0.81
F2	0.937	0.169	76.7	0.975	1.687	0.953	0.173	1.26
F3	0.943	0.230	65.3	0.878	1.655	0.998	0.183	1.34
F4	0.958	0.036	93.3	0.953	1.002	0.954	0.040	1.07
F5	0.961	0.048	64.9	0.750	1.578	0.866	0.022	1.08

Batches F1, F2, F3, F4 and F5 contain propylene glycol 1, 2, 3, 4 and 5 ml, respectively.

shown in Table 3. The results showed that all the capsules complied with requirement for capsule weight uniformity (BP, 2009) and the percentage deviations obtained from the capsule weight uniformity test were significantly below 5%. The results of the disintegration time of the capsules showed that they disintegrated within 3.31 to 3.56 min, and hence did not vary significantly within the batches ($P < 0.05$). This may be due to the kind of capsule shell used. The product being a modified release product, one would ordinarily expect prolonged disintegration time, but the granules were not encapsulated with gastro-resistant capsules. Therefore, the capsule shell was not the cause of the sustained release and was not designed as such. The results of the drug content of the capsules also showed that pyridoxine hydrochloride capsules had high percentage drug content and complied with BP standards for drug content. The results showed that the drug content were within 90 to 110% of the average values specified in the official book (BP, 2009) as shown in Table 3.

In vitro drug release

The results of the *in vitro* drug release are shown in Figure 1a to c. From the results of the *in vitro* release of pyridoxine hydrochloride capsules in 0.1 N HCl (Figure 1a), the results showed an initial high release of drug between 0.5 and 2 h before maintaining the sustained drug release over time between 2 and 3 h. Batch F1 containing

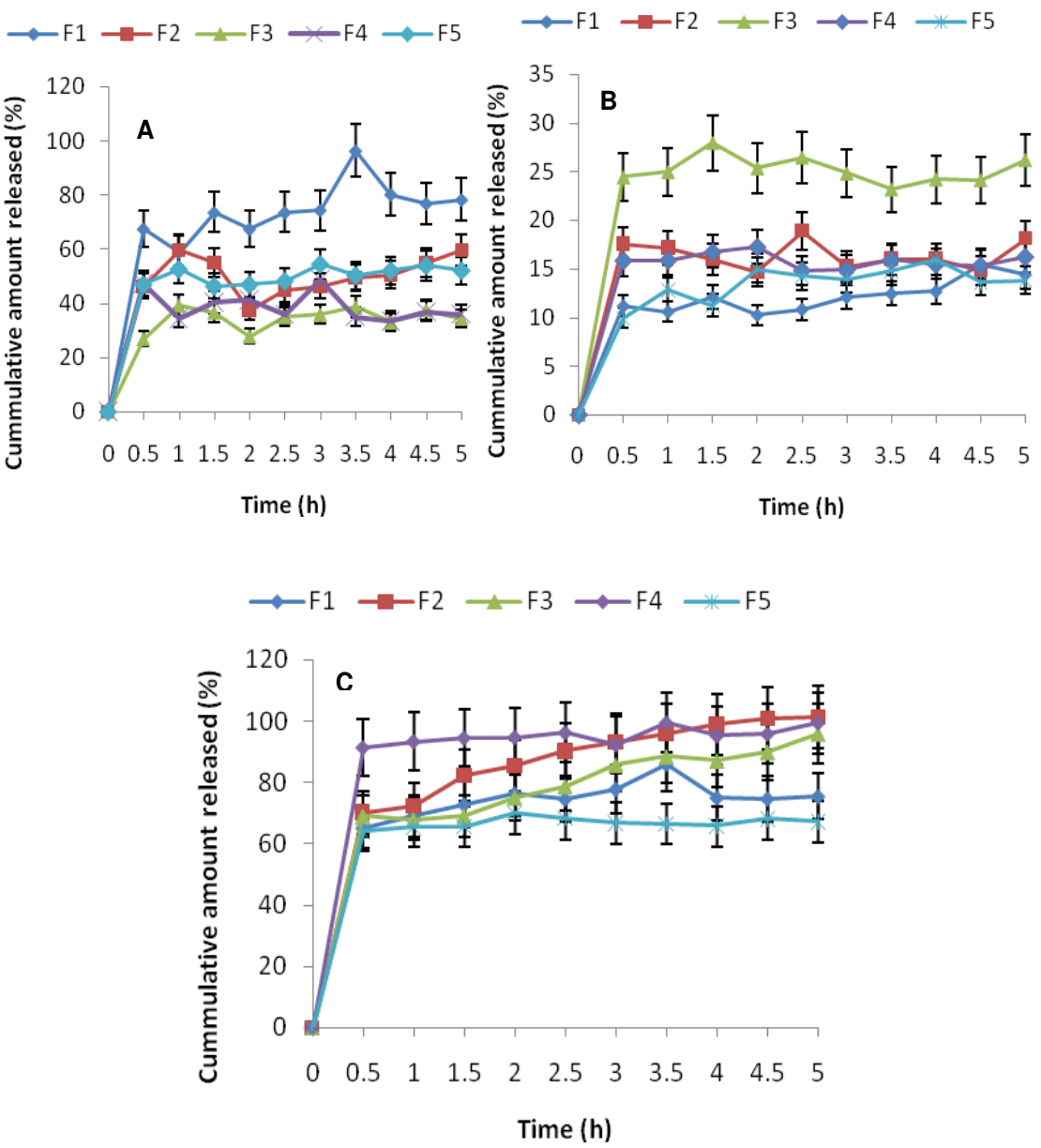

Figure 1. Release profile of pyridoxine hydrochloride in (A) 0.1 N HCl, (B) SGF (pH 1.2), and (C) SIF (pH 7.2). Batches F1, F2, F3, F4 and F5 contain propylene glycol 1, 2, 3, 4 and 5 ml, respectively.

1 ml of propylene glycol had 96% drug release at 3.5 h, however, $T_{100\%}$ could not be attained in other formulations. Increase in the amount of propylene glycol significantly ($P < 0.05$) delayed the release of pyridoxine hydrochloride as shown in Figure 1 a to c. The results of *in vitro* drug release in SGF (pH, 1.2) showed that the release of pyridoxine hydrochloride was significantly ($P < 0.05$) lower than the release in 0.1 N HCl and in SIF (pH, 7.2), respectively. Generally, batch F5 formulated with 5 ml of propylene glycol had 46.87 and 54.42% drug release at T_{120} and T_{180} (120 and 180 min), respectively in 0.1 N HCl, also F5 had 15.04 and 13.96% drug release at T_{120} and T_{180}, respectively in SGF (pH, 1.2) and 69.87 and 66.6% drug release at T_{120} and T_{180}, respectively in SIF (pH, 7.2). Therefore, pyridoxine hydrochloride sustained release capsule formulated exhibited higher drug release in SIF (pH, 7.2).

In vitro release kinetics

From the results of drug release kinetics shown in Table 4, the regression coefficients had r^2 of ≈ 0.9. Also, the release exponent in the Ritger-Peppas model (n) for all the batches suggested that the mechanism that led to the release of pyridoxine hydrochloride from the capsule was

by diffusion with release rate adequate for a sustained release dosage form. Higuchi's kinetics seconds the Ritger–Peppas in the linearity of their plot with r^2 of ≈ 0.9. The linearity of Higuchi's kinetic explains why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred to as square root kinetics (or Higuchi's kinetics) (Rawat et al., 2011; Singh et al., 2011). The linearity of the plot indicates that the release of pyridoxine hydrochloride from the samples followed diffusion mechanism. The results of first order kinetics showed that drug release was not dissolution controlled ($r^2 \neq 0.9$) in most of the formulations, however, batches F2 and F4 showed some level of linearity ($r^2 = 0.9$). This suggested that the release of drug from these batches followed mixed mechanism of drug release (Rawat et al., 2011; Singh et al., 2011).

Conclusion

Pyridoxine hydrochloride sustained release capsules with fixed concentrations of binder-disintegrants, diluents and equal load of active pharmaceutical ingredient were successfully formulated using propylene glycol co-solvent as the moistening agent. The results showed that free flowing spherical particles were produced. The capsules complied with BP (2009) specifications for capsule weight uniformity and drug content. The *in vitro* release properties of the pyridoxine capsules showed that increase in the amount of propylene glycol increased the time of drug release. Therefore, pyridoxine hydrochloride sustained release capsules could be formulated with kaolin as the diluent and propylene glycol co-solvent as the moistening agent in order to reduce the frequency of administration of this drug and improve patient compliance.

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