RESEARCH

Accepted 23 September 2000
Revised 10 September 2000
Received 2 February 2000
Indian J. Pharm. Sci. 2001, 63(1) 24-29

Formulation of Controlled Release Matrix Tablets of Isosorbide Dinitrate

I. HARIRIAN*, A. GHAFFARI, AND M. MOHAMMAD-POUR
Department of Pharmaceutics, School of Pharmacy
Medical Science University of Tehran, Tehran-14, Iran

Different retardant polymers including Carbopol® 934P, HydroxyPropyl Methyl Cellulose (HPMC) (Methocel® K4M) and Eudragit® NE30D, RL30D and RS30D as release controlling materials were evaluated. The drug release medium consisted of hydrochloric acid buffer, pH-1.2, for the first two hours and phosphate buffer, pH-6.8, for the remaining period of time during the experiments. The influence of variables including polymer type, drug:polymer ratio, tablet filler type and tablet hardness on isosorbide dinitrate (ISDN) release profile was discussed. From the retardant polymers investigated, Eudragit NE30D exhibited proper release characteristics. The pattern of drug release from formulation prepared from Eudragit NE30D was shown to correspond to the Higuchi equation. According to the equation, $M_t/M_\infty=k.t^n$, ISDN release mechanism from Eudragit NE30D matrix tablets (40 mg) was based on non-Ficklan-Diffusion process. It was also realized that, matrix preparation was a suitable method for the formulation of ISDN-CR tablets.

The need for controlled release (CR) formulation of isosorbide dinitrate (ISDN) tablet, is well recognized. The purpose of this study was to develop a method, using a laboratory scale to formulate and evaluate the release kinetics of ISDN-CR tablets. ISDN, 1,4:3,6-dianhydro-D-glucitol-2,5-initrate, is widely used as an antianginal drug, readily absorbed from the gastrointestinal tract. The biological half-life of the parent compound (ISDN) is short (about one hour)[1] and depends on the route of administration.. The short biological half-life and increased need of patient compliance, especially in the management of angina pectoris, suggests the need for oral controlled release formulations of the drug. Various methods including, ion-exchange resin complexes, matrix tablet, osmotic pump, co-precipitation as well as microencapsulation process have been utilized to prepare the controlled release products[2,3]. The matrix tablet preparation appears to be a most attractive approach, from the process development and scale-up points of view[4].

* For correspondence
Fax: 0093-21-6461178

Pelletization of ISDN as the active agent with polyvinyl acetate[5], controlling of ISDN release with xanthan-based hydrogels[6], utilization of some release-regulators e.g. ethyl cellulose, acrylic copolymer, hydrogenated oil and wax[7] formulation of osmotic retard tablet of ISDN by gum acacia and polyvinyl pyrolidone (PVP)[8] were studied by the other investigators. Various polymers such as carbomers, cellulose derivatives and polymethacrylates (Eudragits) have been used as retarding agents. Carbomers are high molecular weight polymers of acrylic acid cross-linked with ally ethers of sucrose or pentaerythritol. Cellulose derivatives have been widely used in the formulation of hydrogel matrices for controlled drug delivery. Among them, HPMC is the most extensively utilized, because of its ease of use, availability and very low toxicity. Carbomers and HPMC are hydrophilic polymers with high gelling capacities. When these polymers meet water there is a rapid hydration of the macromolecules in the solid-liquid interface followed by formation of a viscous layer. The matrix system produced as a result of this process can pass along the gastrointestinal

tract without breaking up and releasing the active agent progressively[4].

Eudragits are polymers belonging to the family of polymethacrylates and can be used to produce inert and plastic matrix tablets. In such matrices, the drug is embedded in a spongy network of insoluble polymer, which controls the diffusion of dissolved drug through the pores, channels and capillaries of matrix tablet. The release of drug from this matrix can be described by the following equation[9]:

$$Q = [D.\varepsilon/\tau\ (2A - \varepsilon C_s)\ C_s\ .t]^{1/2} \qquad \text{Eq. 1}$$

Where, Q is the amount of drug released, t and D are time and diffusion coefficient, respectively. ε is the porosity factor and t is the tortousity factor of the matrix. A, the amount of drug in matrix and C_s is the solubility of drug. In the present investigation, the formulation and evaluation of controlled release tablets of ISDN using various polymeric retarding materials by matrix tablet preparation were performed.

MATERIALS AND METHODS

ISDN (80 mesh powder) was obtained from SOHA3 pharmaceutical Co. (Tehran, Iran). Carbomer (Carbopol®) 934P and HPMC (Methocel® K4M) with nominal viscosity of 2% in water 4000 cps, were gift samples from B.F. Goodrich Co. (Ohio, USA) and Colorcon Co. (Orpington, UK), respectively. Eudragits (NE30D, RL30D and RS30D) were obtained from Rohm Co. (Germany). Lactose monohydrate of DMC (Netherlands), Microcrystalline cellulose (Avicel® PH101) of FMC corp., USA and Dibasic calcium phosphate (Emcompress®) from Mendel Co. (Finland) were used.

A single punch tabletting machine (Korsch, Germany) was used for compression. Breaking strength of tablets was measured on a hardness tester (Erweka, Germany). A fluid-bed (Uni-Glatt) apparatus was used for granulation. The USP XXIII dissolution test apparatus No. II (Labindia, India) and a HPLC unit (Waters, USA) were utilized for the drug release study and analysis. A pH meter (Corning, UK) for dissolution media pH adjustment and a cubic blender (Erweka, Germany) for powder mixing were also used.

Preparation of Tablets:

The matrix tablets (40 mg) with Carbopol 934P and Methocel K4M were prepared by compressing a blend of ISDN powder (#80 mesh) and polymer in ratio of 1:0.4 and lactose monohydrate as filler. These materials were thoroughly mixed in a cubic blender for 10 min. After blending with lubricating agent (1% w/w magnesium stearate) for 5 min, the direct compression of tablets was performed. By considering that Eudragits used in this study are commercially available in aqueous dispersion form, matrix tablets were prepared through wet granulation. For this purpose, a Uni-Glatt top spray granulator was utilized and the technical and process data is presented in Table 1. Tablets of 250 mg were compressed with one set of 9.0 mm round standard flat tools.

The dissolution test was performed using the USP paddle system (apparatus No. II) at 75 rpm and 1000 ml of dissolution medium at 37±0.5°. Six tablets from each formulation were tested individually in simulated gastric fluid (SGF, pH 1.2) for the first 2 h and in simulated intestinal fluid (SIF, pH 6.8) for the remaining period of time. At appropriate intervals, 5 ml samples were removed with

TABLE 1: GRANULATION PROCESS USING A TOP SPRAY UNI-GLATT

Process data	Preheating	Spraying	Drying
Duration	5 min	15 min	25 min
Inlet air quantity	7.3 m^3/min	9.2 m^3/min	7.3m^3/min
Inlet air temp.	38°	30°	50°
Outlet air temp.	32°	25°	35°
Atomizing pressure	3.5 bar	2 bar	2 bar

Top Spray Uni-Glatt was composed of a feed pump attached with a peristaltic pump of silicone tube with internal diameter of 4 mm and a nozzle diameter of 1.8 mm. The distance between nozzle and product was 120 mm and spraying process was continuous.

replacement by the fresh dissolution medium. The total drug release was evaluated until 8 or 12 h. Samples were filtered and the amount of drug released was analyzed by HPLC method[10]. The HPLC (Waters, USA) consisted of a pump set at a constant flow rate of 1.0 ml/min, a variable UV detector set at 220 nm, a Bondapak L1, 4.6 mm 5 cm reversed phase column, and automatic integrating system. The eluant solution consisted of a mixture of 0.1M ammonium sulfate and methanol (50:50).

RESULTS AND DISCUSSION

Fig. 1 depicts the drug release profiles from commercial brands such as Isoket retard 40 mg (Schwarz Pharma AG, Germany), and ISDN sustained release tablets 40 mg (Arya Pharmaceutical Co., Iran). The formulations prepared in laboratory scale contained different retarding polymers (1:0.4) in various media. The figure shows that Eudragit NE30D polymer had excellent retarding property. As the formulations containing Carbopol 934P and Methocel K4M (two pH-independent polymers), dissolved completely after about 4 h, it became clear that these formulations were not successful in retarding the drug release. It could also be due to the hydrophobicity of ISDN powder. Generally, in contact with an aqueous environment, the matrix hydrates and a viscous gel barrier is formed. But in this case, the fine and hydrophobic ISDN powder does not permit free water penetration into the matrix tablet and gelling of the polymer does not take place[11].

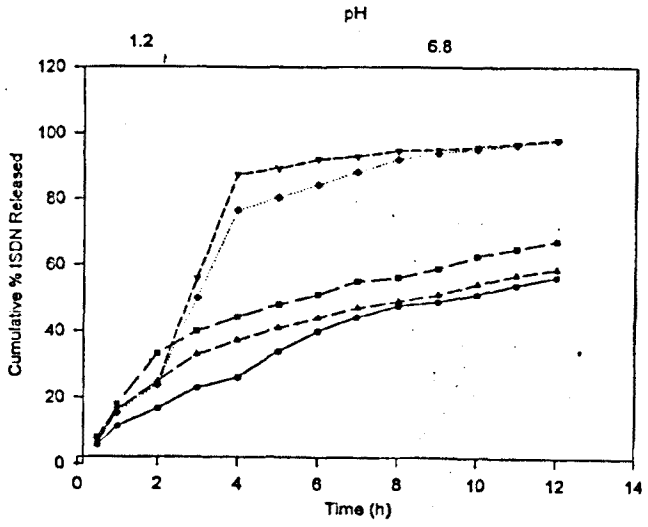

Fig. 1: Drug release profiles of controlledrelease ISDN tablets

ISDN tablets were prepared from different polymers such as Eudragit NE30D, formulation 1 (—▲—) Carbopol 934P polymer, formulation 2 (—▼—) and Methocel K4M polymer, formulation 3 (—◆—) and the release profiles of these formulations were compared with two marketed products Isoket retard tablet (—●—) and Arya product (—□—). Each point represents mean of 6 observations.

Fig. 2 shows the release profile of ISDN matrix tablets prepared from various Eudragit types. The release rate of tablets could be ranked as Eudragit NE30D>Eudragit RL30D>Eudragit RS30D. This observation may be due to the fact that Eudragit RL has greater permeability in comparison with Eudragit RS. Eudragit RL and RS referred to as amoniomethacrylate copolymers in the USPNF monograph. Those polymers are aqueous dispersions of copolymers of acrylic acid and methacrylic acid esters with quaternary ammonium groups. The quaternary groups occur as salts and are responsible for the permeability of those polymers. Because of the greater amount of quaternary groups in the chemical structure of Eudragit RL than Eudragit RS, the above rank order was obtained. Eudragit NE30D is an aqueous dispersion of a neutral copolymer consisting of polymethacrylic acid esters. Matrix tablet prepared from

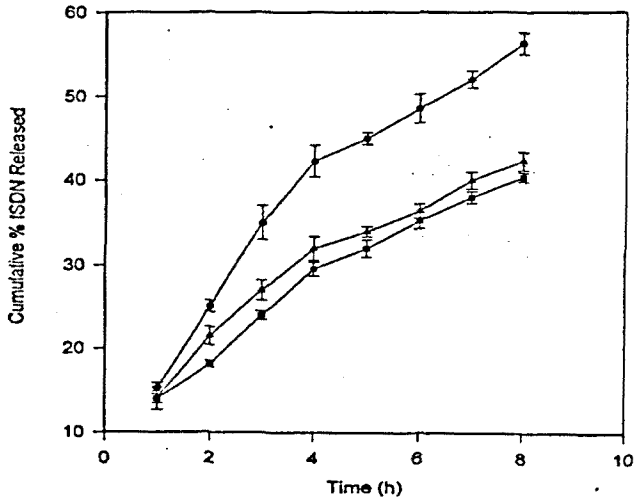

Fig. 2: The effect of various types of Eudragit on ISDN tablets release profile

Symbol (—●—) represents the ISDN tablets prepared from Eudragit NE30D, symbol (—□—) indicates the tablets prepared from Eudragit RS30D, and the symbol (—▲—) represents the tablets of Eudragit RL30D polymer. Vertical bars indicate ±SD of 6 observations

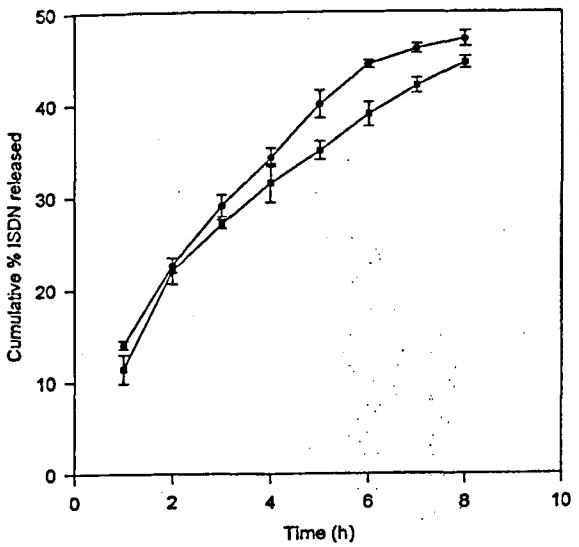

Fig. 3: The effect of tablet hardness on drug release from matrix tablets of ISDN.

Effect of tablet hardness on drug release from ISDN matrix tablets prepared using Eudragit NE30D. The 5-6 kp tablet hardness is represented by the symbol (—O—) and 10-12 kp tablet hardness is represented by the symbol (—□—).

this polymer swells in water, to which they become permeable. Eudragit RL and RS do not swell in water as Eudragit NE, so penetration of dissolution medium into the matrix tablet prepared from Eudragit NE30D is greater than matrix tablets made from Eudragit RL and RS30D[12]. Fig. 3 demonstrates the effect of hardness on drug release from matrix tablets containing Eudragit NE30D as a retardant. By increasing tablet hardness, the porosity decreased, so according to equation 1, the drug release induced to diminish.

The effect of filler type (Lactose monohydrate, Avicel PH101 and Emcompress) on drug release from matrix tablets of Eudragit NE30D is shown in fig. 4. As realized, Lactose monohydrate showed the greatest release rate and Emcompress the lowest one. This event may be due to the fact that as lactose monohydrate is a water-soluble filler, it dissolves easily, by penetrating water into the matrix tablet; the tortousity decreases, and therefore ISDN release rate increases. This process does not occur in the case of water insoluble fillers such as Avicel PH101 and Emcompress. By considering the fact that Avicel PH101 as a filler, tends to swell in water, produces a porous network within matrix tablet hence its release rate would be higher than Emcompress.

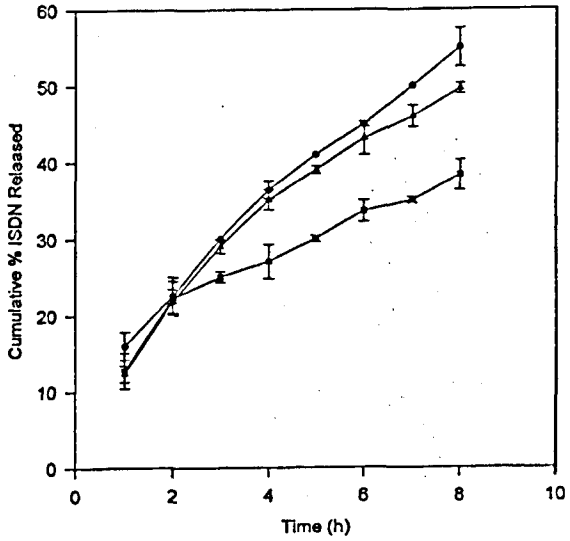

Fig. 4: Drug release profiles from ISDN controlled release tablets

The ISDN controlled release tablets were prepared using different fillers such as lactose monohydrate (—O—), Emcompress (—□—) and Avicel PH101 (—Δ—).

Fig. 5 shows the effect of Eudragit NE30D content on drug release from matrix tablets. Increasing the amount of this polymer, cause increasing the tortousity factor due to the lengthening of capillary diffusion path, which ultimately decrease drug release. Drug release

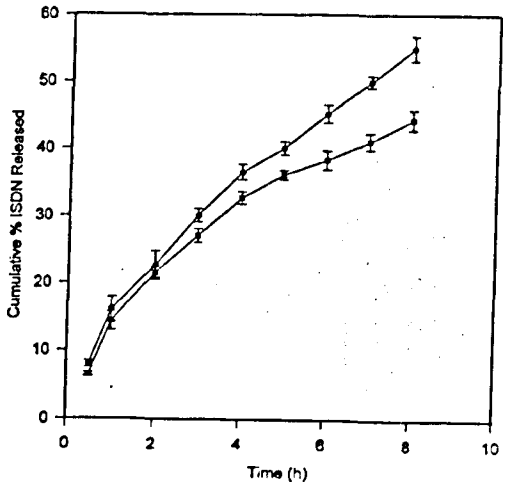

Fig. 5: The effect of drug:polymer ratio on dissolution profile of ISDN matrix tablets

Dissolution studies were carried out with ISDN tablets prepared with drug:polymer ratios of 1:0.4 (—O—) and 1:0.8 (—□—).

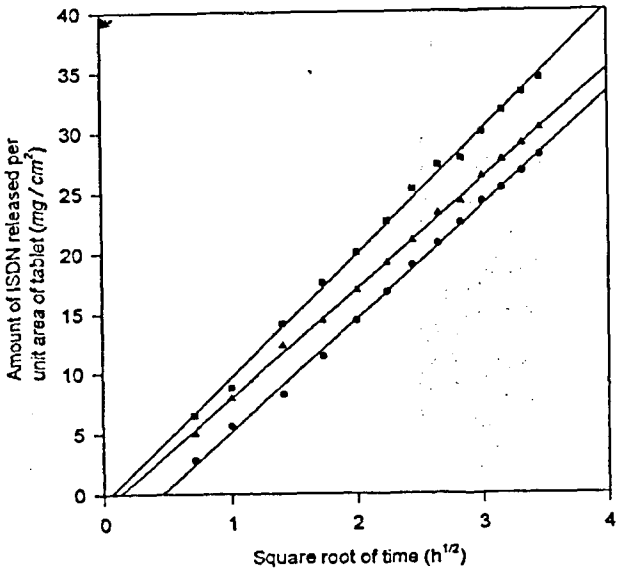

Fig. 6: Drug release kinetics from ISDN matrix tablets

Drug release expressed as a function of the square root of time, according to Higuchi equation. The symbol (—O—) represents the release kinetics from Isoket retard tablet. Similarly, the release kinetics for Arya product and Laboratory formulation containing Eudragit NE30D polymer are represented by the symbols (—□—) and (—▲—), respectively.

profile according to the Higuchi equation was demonstrated in fig 6. The relationship expressed by Higuchi equation (diffusion-controlled process) in its modified form can be written as[9]

$$Q = k_H.t^{1/2} \qquad \text{Eq. 2}$$

Where, Q is the amount of drug released after time t and k_H is the Higuchi rate constant. Release rate constant values according to zero order kinetics, and Higuchi equation for the matrix tablet containing Eudragit NE30D and brand samples were calculated and exhibited in Table 2. It was realized that the resultant data showed to fit Higuchi equation and corresponded to a diffusion-controlled mechanism.

Another equation for analyzing the mechanism of drug release from tablets is based on the Korsmeyer and Peppas model[13]. The dissolution data obtained were fitted to the empirical equation of Korsmeyer is given below:

$$M_t / M_\infty = K.t^n \qquad \text{Eq. 3}$$

Where, M_t/M_∞ and t are the fractional release of drug and the release time, respectively. K is a constant incorporative structural and geometric characteristics of the controlled device, and n is the diffusion release exponent indicative mechanism of release. They indicate that the value of n is 0.5 for Fickian transport (diffusion) and 0.5<n<1.0 for non-Fickian transport and 1.0 for zero-order (case-II transport). When the value of 'n' approaches to 1.0 it may be concluded that the release is approaching to zero-order kinetics. In Table 3, the amount of K, n and correlation coefficient were mentioned for tablets of Eudragit NE30D-based and Isoket retard 40 mg. As has been shown in this table, the drug release mechanism for tablets containing Eudragit NE30D obey non-Fickian-diffusion process.

ACKNOWLEDGEMENTS

We are grateful to Tolidarou Pharmaceutical Co. (Tehran, Iran) for supplying the materials and apparatus used in this study. The authors also wish to thank Dr. M. Sadat Rezaii and Dr. M. Khoshayand for their assistance.

TABLE 2: RELEASE RATE COSTANT VALUES FOR DIFFERENT FORMULATIONS

	Eudragit NE30D	Isoket retard 40 mg	Arya 40 mg product
k_0 (h^{-1})	3.71	4.25	3.59
r_0	0.978	0.990	0.989
k_H ($mg.cm^{-2}.h^{-1/2}$)	10.67	12.16	10.53
r_H	0.997	0.995	0.999

The values have been calculated according to the zero order, Higuchi equation in Simulated Gastric Fluid pH 1.2 (first 2 h), and Simulated Intestinal Fluid pH 6.8 (for remaining period of time), as measured by paddle system at 37±0.5°. r_0 is correlation coefficient and k_0 is the release constant according to zero-order kinetics. r_H is correlation coefficient and k_H is the release constant according to Higuchi equation.

TABLE 3: COMPARATIVE ANALYSIS OF RELEASE MECHANISMS.

	Kinetics constant K (h^{-n})	Kinetics exponent n	Correlation Coefficient	Release Mechanism
Euragit NE30D	16.92	0.514	0.996	Non-Fickian diffusion
Isoket retard 40 (mg)	25.82	0.45	0.992	Fickian diffusion

Analysis of release mechanism following non-linear regression of dissolution data according to the equation $M_t/M_\infty = K.t^n$

REFERENCES

1. Parfitt, K. In; Martindale, the complete drug reference, 32 Edn., Vol.1, Pharmaceutical press, London, 1999, 893.
2. Kislalioglu, M.S., Khan, M.A., Blount, C., Goettsch, R.W. and Bolton, S., **J. Pharm. Sci.**, 1991, 80, 799.
3. Rafiee-Tehrani, M. and Haddad, T., **Eur. J. Pharm. Biopharm.**, 1993, 39, 87.
4. Vazquez, M.J., Perez-Marcos, B., Gomez-Amoza, J.L., Martinez-Pacheco, R., Souto, C. and Concheiro, A., **Drug Dev. Ind. Pharm.**, 1992, 18, 1355.
5. Muench, U., Mika, H.J., Emschermann, B. Schmidt, R. and Sczepanik, B., Ger.offen.DE 4, 031, 881(Cl. A61K9/16) 1992. Through **Chem. Abstr.** 1992, 116, 221616w.
6. Dumitriu,S., Dumitriu, M. and Matian, C., **Colloid polym. Sci.**, 1991, 269, 1140.
7. Nara, T., Hatori, T., Nishiromiya, Y. and Hayashi, H., Japan patent. Jpn. Kokal Tokyo Koho JP, 61, 148, 115 (Cl. A61K9/20)1986; Through **Chem. Abstr.** 1986, 105, 178462b.
8. Janicki, S., Cichon, R., Jedras, Z. and Sawicki, W., **Pharmazie**, 1987, 42, 95.
9. Higuchi, T., **J. Pharm. Sci.**, 1961, 50, 847.
10. The United States Pharmacopoeia XXIII/ National Formulary XVIII, The USP Convention, Inc., 1995, 858.
11. Yoshida, R., Sakai, K., Okano, T. and Sakurai, Y., **Polym. J.** (Tokyo), 1991, 23, 1111.
12. Wade, A. and Weller, P.J., In; Handbook of Pharmaceutical Excipients, 2nd Edn., American Pharmaceutical Association and the Pharmaceutical Society of Great Britain, Washington, 1994, 362.
13. Korsmeyer, R.W., Gurny, R., Doelker, E., Buri, P. and Peppas, N.A., **Int. J. Pharm.**, 1983, 15, 25.