Zag. J. Pharm. Sci., Vol. 2, No. 1, June 1993.

SUSTAINED-RELEASE FORMULATIONS FOR NIFEDIPINE

Mohamed I. Fetouh
Department of Pharmaceutics, Faculty of Pharmacy,
Al-Azhar University, Egypt.

ABSTRACT:

Three formulae of nifedipine sustained release granules were tried, each containing 10% of the drug. The former one was composed of nifedipine, lactose and PVP 40000, and prepared adopting moist granulation technique. In the second formula, the drug, PEG 6000 and HMPC were coprecipitated into microcrystalline cellulose. While the latter one was composed of nifedipine, and three components which are; HMPC; ethyl cellulose as binders; and corn starch as a filler. These granules and the plain nifedipine powder were investigated in vitro as well as in healthy subjects. The third formula showed pronounced dissolution rate compared to the other tested ones. The granules of the second and the third formulae were administered orally to healthy subjects and the plasma levels of nifedipine were compared with those after administration of nifedipine powder. Plasma levels following the administration of the granules were prolonged but a reduced level was observed. This indicates the sustained release of the drug from the granules in vivo. The plasma profiles of nifedipine indicated that the latter formula granules were superior to that with the second formula granules with respect to prolonging the effective plasma levels and to minimizing the intersubject variations.

INTRODUCTION

Nifedipine is a calcium channel antagonist originally introduced for the treatment of angina pectoris and more recently for hypertension[1]. Nifedipine is a slightly water-soluble drug whose bioavailability is very low when it is orally administered in crystalline form[2]. Its biological half-life is very short[3] sustaining its anti-hypertensive effect for only few hours. Several water-soluble formulations have been developed in order to enhance its bioavailability[4] and to prolong the duration of its action[5-8]. But the elimination half-life of nifedipine after administartion of these formulations is only 3.43 h [9].

One method to prolong the plasma drug level in order to maintain the clinical effect, is to employ a sustained-release formulation[10]. In preparing sustained-release products, it is desirable to avoid the use of special aparatus such as coating pan or a fluidized bed coating machines.

Techniques such as microencapsulation are also not desirable on grounds of convenience and expense[11].

The purpose of the present study is to develop a sustained release and highly available nifedipine formulation.

EXPERIMENTAL

All experiments were carried out in a dark room because of the light sensitivity of the drug[12].

Materials :

Nifedipine (Nobel Chemicals, Sweden), anhydrous lactose (Scheffield Chemical Union, USA), ethyl cellulose and polyethlene glycol 6000 PEG (BDH Chemical Ltd., Poole, England), polyvinylpyrrolidone 40000 PVP (Sigma Chemical Co., USA), hydroxypropyl methyl cellulose HPMC, cellulose acetate phthalate CAP and ethanol (Prolabo, France), and Avicel pH 105, N.F., microcrystalline cellulose, average particle size 20 μ (FMC, USA). All other chemicals were of reagent grade.

Methods :

Three brands of nifedipine granules were prepared using the following formulae:

Formula A : Nifedipine; 10 parts, lactose; 85 parts and PVP 40000; 5 parts[13].

The microcrystalline particles of nifedipine were incorporated with PVP by mixing thoroughly for 15 min in a drum mixer, then lactose was added as finely-divided particles of water-soluble diluent. The mixture is kneaded with ethanol.

Formula B : Nifedipine; 10 parts, PEG 6000; 10 parts, HPMC; 10 parts, and Avicel; 70 parts[14].

Nifedipine, PEG and HPMC were dissolved in hot ethanol-dichloromethane (1:1). The solution was then poured directly onto the avicel with thorough mixing.

Formula C : Nifedipine; 10 parts, HPMC; 30 parts, ethyl cellulose; 10 parts, and corn starch; 50 parts[6].

Nifedipine, HPMC and ethyl cellulose were dissolved in ethanol-dichloromethane (1:1, v/v), then corn starch was added with agitation. A slurry was obtained by evaporating the solvent on a water-bath.

The wet mass in each formula was forced through sieve No. 8 (B.P.) and dried for 12 hours in a hot drying oven at 40°C. The dried granules were forced through sieve No. 10 (B.P.) and then dried again for 2 h at 40°C.

Determination of Nifedipine in the Prepared Granules :

An appropriate amount of the powdered granules was accurately weighed and dissolved in 20 mL of ethanol-dichloromethane (1:1, v/v) by shaking for 30 min, then centrifuged at 1500 rpm for 5 min. The supernant was appropriately diluted with the mixed solvent and spectrophotometrically analyzed against a blank at 340 nm.

Dissolution Studies :

The dissolution characteristics of nifedipine plain crystalline powder and nifedipine prepared granules were determined adopting the USP XXI padle method. The paddle was immersed such that a distance of 2.5 ± 0.2 cm was allowed between the blade and the inside bottom of the vessel and rotated at 100 rpm. The dissolution medium was 900 ml deaerated distilled water equilibrated at 37 ± 0.5°C. At suitable intervals, an aliquot was withdrawn by a pipet through a 0.45 µm millipore filter and analyzed spectrophotometrically against a blank at 340 nm. Equal amount of deaerated distilled water was added back to the dissolution vessel immediately after each sampling to maintain the orginal volume. Triplicate runs were made in each test.

Bioavailability Studies :

Drug Administration :

Six healthy male volunteers weighing 60-80 kg (age range 30-40 years), were selected to participate in the present study. The study was designed in a randomized crossover fashion with at least 14 days interval between doses. All volunteers were fasting with the exception of water, 12 h prior to dosing. Informed consent was obtained. The subjects remained supine for the first 2 h. They were only allowed to take food at 4 and 10 h post-dosing. Each subject received orally 10 mg of the nifedipine crystalline powder as reference or 20 mg of nifedipine in sustained-release granules of brand B or of brand C in a soft gelatin capsule, followed by 200 ml of water. Blood samples were collected from a forearm vein at the following times relative to drug administration; 0.5, 1,2,3,4,6,9 and 12 h post-dosing. Blood specimens were centrifuged and the separated plasma samples were stored at 20°C with protection from light until assayed.

Estimation of Nifedipine in Plasma :

The method adopted was that described by ***Miyazaki, et al.*** [15]. It is a specific and sensitive method utilizing HPLC. A one ml of plasma was put in a brown test tube 100 µL methanol and 3 ml acetonitrile were added. The tube wa vortexed for 60 seconds and centrifuged for 5 min. at 1500 rpm 3 ml of the supernant were transferred into a brown test tube containing 1 ml of distilled water, then 4.5 mL of acetone-chloroform (1:1) were added. The mixture was shaken for 10 min. and then centrifuged at 1500 rpm for 5 min. The aqueous phase was aspirated and discarded, 5 ml of the organic phase was transfered into a brown test tube then evaporated in a water bath at 60°C. The residue was reconstituted with 100 µl of the mobile phase containing butamfen as an internal standard (2 µg/mL), and 20 µL) of the solution was injected onto the column.

Statistical Analysis:

Equality of variances and significant differences in the peak plasma levels (C_{max}). The times to the peak plasma levels (t_{max}) and areas under

the concentration-time curves (AUC 0-12 h) between powder and granules were tested by means of F test.

RESULTS AND DISCUSSION

The transit time of single-unit formulations is highly variable. However, as the subunits of multiple-unit formulations are allowed to pass freely through the gastro-intestinal tract, they offer a possibility of achieving a longer-lasting and more reliable source of drug[16]. Therefore, a granular formulation was chosen as a sustained-release dosage form in this work.

Dissolution Studies :

The rate limiting step in the absorption process, for orally administered water-insoluble drugs, is usually the dissolution rate of the drug in GIT fluids[17]. The significance of this on the transport and absorption processes is well recognized and has been the subject of several detailed discussions[18]. Table 1, shows great difference in the rate and extent of nifedipine release. The plain powder of the drug exhibited the slowest dissolution rate and extent of nifedipine released in comparison to the prepared granules. This may be ascribed to the following (a) nifedipine was more easily wetted in the medium due to the addition of binders of fillers in the granules; (b) nifedipine was dispersed as fine particles in the granules, since nifedipine powder was dissolved in the mixed solvent in the preparation of the granules of brands B and C, (c) crystalline nifedipine was transformed to an amorphous form in the granules by using HPMC in the second and third formulae[19].

TABLE 1 : DISSOLUTION RATE OF NIFEDIPINE IN DISTILLED WATER AT 37°C.

TEST	Percent Released (Min.)									
	5	10	15	30	45	60	75	90	105	120
Plain Powder	4.9	8.5	11.0	18.3	24.2	28.8	34.1	37.6	40.1	42.0
Formula A	7.8	12.0	15.9	24.4	33.5	39.1	44.0	47.7	51.4	56.1
Formula B	9.5	14.0	18.3	28.0	35.9	41.3	46.5	51.1	54.9	58.8
Formula C	11.5	17.1	23.1	36.2	44.4	51.5	56.4	61.2	65.4	68.0

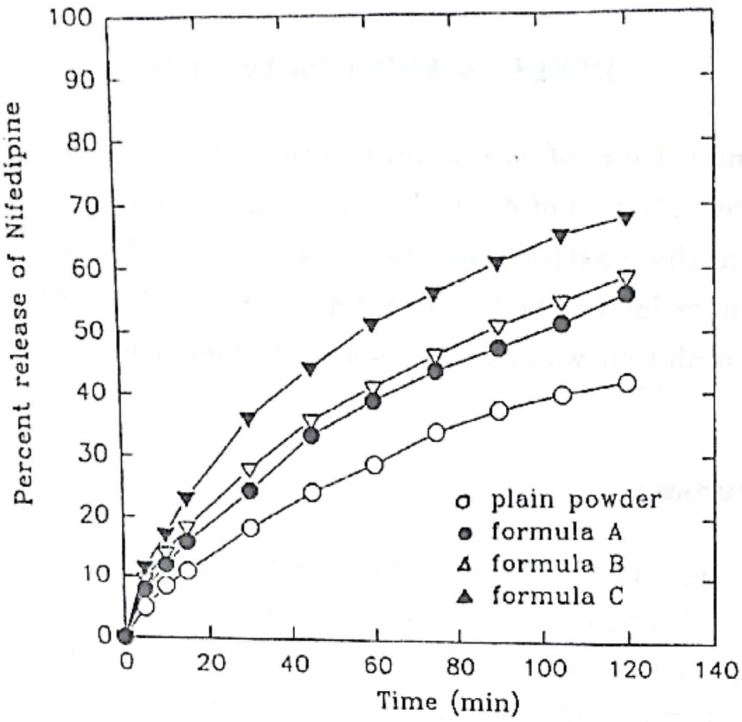

Fig.1. Disolution Profile of Nifedipine in Distilled Water at 37°c.

As seen in Fig. 1, the prepared granules of brand C gave significantly higher release rate of nifedipine. The granules of brand A and that of brand B are nearly similar in the dissolution rate of nifedipine.

The granules of brand A comprises particles of finely-divided water-soluble diluent as lactose coated with microcrystalline particles of nifedipine in the presence of PVP. The incorporation of PVP in an amount less than that of the drug slows the dissolution of nifedipine from the finished solid dosage form.

The increase in the dissolution rate of the granules of brand B may be explained, on one hand, by the increase in the surface area of nifedipine as a result of its depostion on microcrystalline cellulose by the coprecipitation technique. On the other hand, by the fact that PEG being a water-soluble polymer, will dissolve readily in the dissolution medium, hence, encircles the crystallites of medicament causing its wettability, thus, enhances its dissolution[20,21]. The addition of HPMC, as a swellable polymer, to the solid dispersion of the drug in PEG, a water-soluble system, might also enahnce its dissolution.

The mechanism of drug release from the granules of brand C presumably involves the formation of a hydrated zone of HPMC on the surface of the granular matrix[22-23]. This would be the first step in the formulation of a transport channel. Part of the drug would be diffused through the hydrated zone and be released into the medium while the remainder would be liberated when the hydrated zone dissolved.

It is clear that, the release rate decreased with the increment of ethyl cellulose and increased with the increment of HPMC. Therefore, if the polymer variation in the formulations, as well as their ratio per unit of mass of granules are chosen carefully, it should be possible to obtain drug delivery systems which exhibit constant release of the drug at a desired rate[24].

Bioavailability Studies :

The mean plasma nifedipine levels following single administration of the crystalline powder as reference and formulated granules of brands B and C are shown in Table 2 and depicted in Figure 2. The concentrations exhibit in all cases a substantial intersubject variation. These differences may be attributed to the variability in the rate of drug absorption[25] and/or the extent of first-pass hepatic extraction and metabolism[26-30]. The pharmacokinetic parameters for the two formulations and the reference powder are not directly comparable since the dose of nifedipine administered as granules was double the dose in the powder. However, dose proportionality studies of nifedipine established linear kinetics[31]. Thus, after correcting the dose by multiplying C_{max} and AUC_{0-12} h by to for the powder, these parameters were analyzed statistically (Table 2). The parameters C_{max} and t_{max} describe the rate of absorption and the value of AUC indicate the relative extent of absorption. The mean nifedipine plasma levels of the sustained-release granules were significantly higher over the 2-12 h period than those in the case of the powder, though the dose of nifedipine adminstered as granules was double the dose in the powder. Both granules showed lower peak plasma levels (C_{max}) and more prolonged plasma levels. These prolonged plasma levels were more significantly observed for granules brands B and C. Both the reduction of

the peak plasma levels and the prolongation of the plasma levels observed in the two formulations may be attributed to the retardation of the rapid release of the drug from the granules at the early stage. The extent of bioavailability of the granules of brands B and C were about 57% and 66% of the powder respectively. The t_{max} values for the two formulations were larger than that of the reference, but there was no statistically significant difference (at $P > 0.05$) in AUC_{0-12} h or t_{max} values between the two types of granules.

Table 2: PHARMACOKINETIC PARAMETERS OF NIFEDIPINE FOLLOWING SINGLE ORAL ADMINISTRATION OF POWDER, FORMULATIONS B AND C GRANULES,

TEST	AUC (μg/ml. h)	C_{max} (μg/ml)	T_{max} (h)	HALF-LIFE** (h)
Plain Powder	565.72 ± 97.25* (440.20 - 698.63)	218.3 ± 26.15* (187.1 - 253.6)	1.1 ± 0.39* (0.5 - 2.0)	3.46 ± 0.01* (3.26-3.86)
Formula B	321.12 ± 23.65 (294.32 - 354.31)	60.3 ± 2.44 (56.8 - 63.1)	2.5 ± 0.68 (1.5 - 4)	2.99 ± 0.02 (2.73-3.47)
Formula C	374.02 ± 25.72 (339.2 - 405.74)	56.0 ± 2.31 (52.8 - 59.1)	2.6 ± 0.93 (1.5 - 4)	2.87 ± 0.02 (2.60-3.14)

* Corrected for the dose by multiplying by 2.

** Half-life comparison is determined from linear regression of log conc 6-12 h.

The hypotensive effect of nifedipine in hypersensitive patients was related to the plasma level[32,33] and the minimum nifedipine level required for the effect was 10-15 μg/ml[34]. Thus, the patients should receive one dose every 6 h (total: 40 mg/d). However, the granular formulation of brand C would be expected to be effective even if the patients receive it every 12 h (total: 40 mg/d). If two doses of nifedipine powder (equal to the dose of the sustained-release granules) are administered to the subjects, high peak plasma levels might produce severe side effects. The slower release of nifedipine from the granules may minimize the side effects, which are a result of high plasma levels[35].

In conclusion, the granules of formula C are expected to improve the compliance of patients. Twice-daily dosing should be sufficient for therapeutic effectiveness and minimization of intersubject variation.

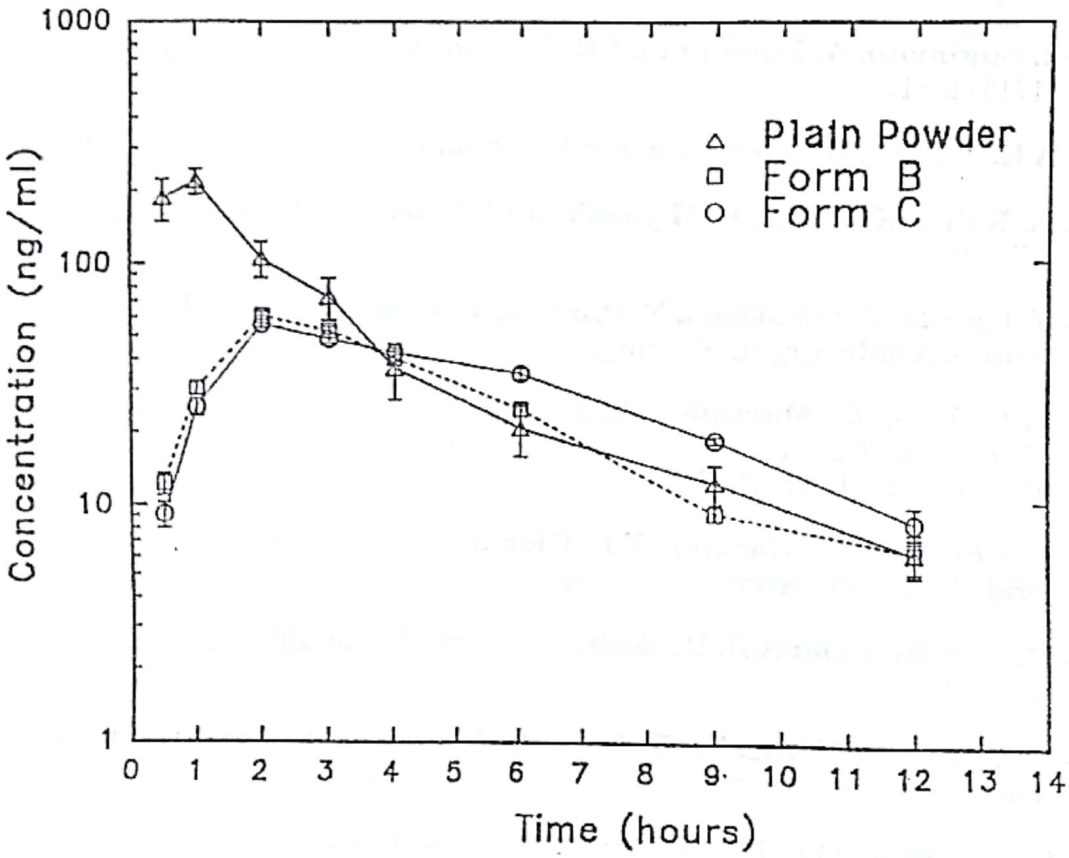

Fig. 2: Mean Plasma Profile of Nifedipine Following Single Oral Administration of Powder, Form B and C.

REFERENCES

1- **C. Remunan, A. Mrhar, S. Primozic, R. Karba, and J.L. Vila-Jato,** Drug Dev. Ind. Pharm., 18 (2), 198 (1992).

2. **I. Sugimoto, A. Kuchiki, H. Nakagawa, H. Tohgo, S. Kondo, I. Iwane, and K. Takahashi,** Ibid, 6 (2), 137 (1980).

3- **K.D. Raemsch and J. Sommer,** Calcium Antagonists Supp. II. Hypertension, 5 (4), 11 (1983).

4- **I. Sugimoto, A. Kuchiki and H. Nakagawa,** Chem. Pharm. Bull., 29 1715 (1981).

5. **A Hasegawa, H. Nakagawa and I. Sugimoto,** Ibid, 33 (4), 1615 (1985).

6. **N. Kohri, K.I. Mori, K. Miyazaki and T. Arita,** J. Pharm. Sci., 75 (1), 57 (1986).

7- **T. Umeda, T. Yokoyama, N. Ohnishi, T. Kuroda, Y. Kita, K. Kuroda and S. Asada,** Chem. Pharm. Bull., 33 (9), 3953 (1985).

8- **J.L. Vila, R. Martinez, A. Concheiro and C. Remunan.** III. European Congr. of Biopharmaceutics and Pharmacokinetics Proceddings, I. 69 (1987).

9- **T.S. Foster, S.R. Hamann, V.R. Richards, P.J. Bryant, D.A. Graves and R.G. McAllister,** J. Clin. Pharmacol., 23, 161 (1983).

10- **M. Rowland and A.H. Beckett,** J. Pharm. Pharmacol., 16, Suppl., 156 T (1964).

11- **N. Kohri, K. Miyazaki, T. Arita, H. Shimono, A. Nomura and H. Yasuda,** Chem. Pharm. Bull., 35 (6) 2504 (1987).

12- **P. Jakobsen, O.L. Pedersen and E. Mikkelsen,** J. Chromatogr., 162, 81 (1979).

13- **Rhodes, Alan,** Eur. Pat. Appl. EP, 9 (1989).

14- **S.E., Leucuta,** Pharmazie, 43 (12), 845 (1988).

15- **K. Miyazaki, N. Kohri and T. Arita,** J. Chromatogr., 310, 219 (1984).

16- **H. Bechgaard,** in "Optimization of Drug Delivery", Bundgaard, H. Hansen, A.B.; Kofod, H., Eds.; Munkagaard: Copenhagen, pp. 67 (1982).

17- **M.I. Fetouh, H.A. Swalhy and M. Radwan,** III European Congress of Biopharmaceutics and Pharmacokinetics Proceedings, I, 391 (1987).

18- **B.F. Bellard and E. Belson,** J. Pharmacol. and Exp. Therap., 135, 120 (1962).

19- **I. Sugimoto; K. Sasaki, A. Kuchiki, T. Ishihara and H. Nakagawa,** Chem. Pharm. Bull. 30, 4479 (1982).

20- **H.H. El-Shattawy, A.A. Kassem, A.T. Nouh and M.I. Fetouh,** Durg Dev. and Ind. Pharm., 11, 12 (1985).

21- **W.L. Chiou and S. Riegelman,** J. Pharm. Sci., 60, 1281 (1971).

22- **N.B. Shahm and B.B. Sheth,** Ibid., 61, 412 (1972).

23- **S. Borodkin and F.E. Tucker,** Ibid., 63, 1359 (1974).

24- **S.E. Leucuta,** 5th Congr. Int. Technol., Pharm. Proceedings, I 371 (1989).

25- **W. Snedden, P.G. Fernandez, A. Brenda and B.K. Kim,** Clinical and Investigative Medicine, 7 (3), 173 (1984).

26- **G.R. Brown, D.G. Fraser, J.A. Castile, P. Gaudreault, D.R. Platt and P.A. Friedman,** Int. J. Clin. Pharmacol. Ther. Toxicol., 24 (6), 283 (1986).

27- **C. Hoyo-Vadillo, G. Castaneda, J.E. Herrera, J.V. Garate, A. Moreno, F. Chavez and E. Hong,** J. Clin. Pharmacol., 29, 816 (1989).

28- **C. Kleinbloesem, P. Van Brummelen, J.A. Van De Linde, P.J. Voogd and D.D. Breimer,** Clin. Pharmacol. Ther., 35, 742 (1984).

29- **R.G. McAllister,** J. Cardiov. Pharmacol., 4, 5340 (1982).

30- **Z. Stem, E. Zylber-Katz and M. Levy,** J. Clin. Pharmacol. Ther Toxicol., 22, 198 (1984).

31- **A.M. Taburet, E. Signals, J.N. Colin, O.Banzet, M. Thibonnier and P. Corvol,** Hypertension, 5 (Suppl. II), 29 (1983).

32- **K. Aoki, K. Sato, Y. Kawaguchi and M. Yamamoto,** Eur. J. Clin. Pharmacol., 23, 197 (1982).

33- **O. banzet, J.N. Colin, M. Thibonnier, E. Singles, J.M. Alexandre and P.,** Corvol, Ibid., 24, 145 (1983).

34- **D. Lutz, G. Pabst, W. Dahmen, K.H. Molz and H. Jaeger,** Arzneim-Forsch., 35 (II), 1840 (1985).

35- **E. Zylber-Katz, G. Koren, L. Granit and M. Levy,** Biopharm. Drug Dispos., 5, 109 (1984).

صيغ ممتدة المفعول لعقار النيفيديبين

محمد إيهاب فتوح
قسم الصيدلانيات - كلية الصيدلة
جامعة الأزهر - القاهرة

إجريت تجارب علي ثلاث صيغ من حبيبات ممتدة المفعول تحتوي كل منها علي ١٠٪ من عقار النيفيديبين . وقد حضرت الصيغة الأولي بطريقة التحبيب الرطب وتحتوي علي نيفيديبين ، ولاكتوز وعديد فنيل البيروليدون ٠٠٠ ر ٤٠ . وتحتوي الصيغة الثانية علي العقار وعديد ايثلين الجليكول ٦٠٠٠ وهيدروكس ميثيل بروبيل السليولوز محضرة بالترسيب المشترك في بلورات السليولوز الدقيق . . بينما أحتوت الصيغة الأخيرة علي النيفيديبين مع إستخدام هيدروكس ميثيل بروبيل سليولوز وإيثيل سليولوز كمواد رابطة ، ونشأ الذرة كمادة مالئة . وقد أجريت التجارب علي الصيغ الثلاثة والعقار منفردا معمليا وعلي أشخاص اصحاء .

وقد أعطت الصيغة الثالثة تحسنا في معدل الاذابة بالمقارنة بالصيغ الأخري . وتمت مقارنة كمية العقار في البلازما بعد تناول الصيغة الثانية والثالثة والعقار منفردا عن طريق الفم . وقد أوضحت النتائج أنخفاض مستوي العقار لكنه ممتد لفترة أطول ، مما يثبت نجاح تحضير حبيبات ممتدة المفعول . وبأستعراض شكل منحني البلازما أثبتت تفوق الصيغة الثالثة علي الصيغة الثانية في أطالة مدة بقاء العقار في الدم مع عدم وجود اختلاف كبير بين الأشخاص .