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Development of a simple spectrophotometric method for propylene glycol detection in tablets[1]

Rakesh Grover [a], Spiro Spireas [a,*], Cesar Lau-Cam [b]

[a] *Division of Pharmaceutics and Industrial Pharmacy, Arnold & Marie Schwartz College of Pharmacy and Health Sciences, Long Island University, 75 DeKalb Avenue at University Plaza, Brooklyn, NY 11201, USA*
[b] *Department of Pharmaceutical Sciences, College of Pharmacy and Allied Health Professions, St. John's University, Jamaica, NY 11439, USA*

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Abstract

A simple spectrophotometric procedure was developed and validated to indirectly assess the quantities of propylene glycol (PG) remaining in compressed liquid/powder admixtures. Such simplified quantitation may facilitate several testing procedures related to various aspects of formulation development and material testing of pharmaceutical powder excipients using various nonvolatile liquids as the diluents. In the present study, this new and simple approach for PG quantitation was developed as an integral part of a new method termed the liquisolid compressibility (LSC) test, used to characterize the compaction behavior of powder excipients. According to LSC testing, several admixtures of a nonvolatile liquid (in this case PG) and a powder, differing in their PG/powder weight ratio, are compressed in order to assess their compactabilities. The PG content of such compacts may then be directly quantitated by the USP gas chromatographic method or, indirectly, by this new simple spectrophotometric procedure. The new approach involves the addition of a dye marker to the PG prior to its incorporation into the powder. After compression, the PG amount remaining in the compacts may be determined by simply extracting the dye from the tablets and analyzing the extracts spectrophotometrically. In this manner, the dye content thus obtained may be extrapolated to the respective net amount of PG originally added as a dye/PG solution to the powder. Statistical comparison of the results obtained from both methods revealed almost absolute correlation.

Keywords: Propylene glycol; Simple spectrophotometric quantitation; Dye marker; Validation by comparison to gas chromatography; Liquid/powder admixtures; Liquisolid compressibility test for compaction evaluation

1. Introduction

Addition of nonvolatile liquids, such as propylene glycol, polyethylene glycol 400, glycerin, polysorbate 80 and oily substances, is quite common during several pharmaceutical operations.

* Corresponding author. Tel.: +1 718 4881631; fax: +1 718 7804586.

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During material testing and formulation development, such liquids may be added in increasing quantities to a powder excipient to obtain information about its porosity, polarity, liquid uptake and retention potentials, absorption and adsorption capacities, interparticulate friction and bonding, deterioration levels of flow and compaction, mixing characteristics, and granulation endpoints. In practice however, although the amount of added liquid diluent is a known value, its actual and accurate determination in that portion of the liquid/powder admixture subjected to testing is a quite tedious experimental endeavor.

In the field of material testing, a new procedure, termed liquisolid compressibility (LSC) test, has been recently developed [1,2] and used to evaluate the compactability of different grades of pharmaceutical powder excipients. As, in a typical dilution potential compression test in which the degree of a powder's deterioration in compactability due to blending with increased drug quantities is evaluated, the LSC test assesses such dilution effects on powder compression by mixing various amounts of propylene glycol (PG), or other nonvolatile liquids, with the powder excipient and compressing the liquid/powder admixtures into tablets using different compression loads. These studies are of interest because several linear relationships between certain compaction properties of such admixtures and their liquid/powder weight ratios have been observed [1,2] and will be reported in future papers.

A very important step in LSC testing is the quantitation of the amounts of the liquid diluent (e.g. PG) which remain in the compacts after compression since some of the liquid might have been squeezed out of the systems during compaction. The USP method for the detection and quantitation of PG involves a lengthy gas chromatographic procedure [3]. The purpose of this work was to develop and validate an indirect and simpler procedure for measuring PG by a spectrophotometric approach using a reference dye marker. Such a method may be a more convenient alternative to gas chromatography not only during LSC testing but also in other physicochemical tests for the characterization of powder materials.

The basic concept of this indirect approach is to include a readily measurable dye, such as FD&C Red # 40, in PG prior to its incorporation into the powder excipient under investigation. After compression of the liquid/powder blends, the amounts of PG remaining in the compacts may be assessed by simply extracting the dye from the tablets with a suitable solvent and analyzing the extracts for their dye contents spectrophotometrically. The results thus obtained may then be extrapolated to determine the actual PG amounts remaining in the compacts based on the original dye concentration of the dye/PG solution added to the powders.

The present paper describes the validation and application of this new, simple and indirect spectrophotometric procedure to the measurement of PG in tablets made from several common powder excipients, such as microcrystalline cellulose, lactose and silica, and various levels of PG to which two fixed amounts of dye have been added as a marker. All compacts were analyzed for their PG content by the proposed spectrophotometric method and the results were compared and correlated with those obtained by gas chromatography.

2. Experimental

2.1. Materials

The following materials were used as received: granular Avicel® PH-102 (MCC-1) and coarse granular Avicel® PH-200 (MCC-2) microcrystalline celluloses (FMC, Princeton, NJ); Cab-O-Sil® M5 nm-sized colloidal silicon dioxide (silica) (Spectrum, Gardena, CA); lactose monohydrate standard (LM) (EM Industries, Hawthorne, NY); FD&C Red # 40 Dye (dye) (Purdue Frederick, Norwalk, CT); and propylene glycol (PG) (Ruger, Irvington, NJ).

2.2. Dye/PG solutions

To prepare dye/PG solutions, with 2.5 and 5 mg ml^{-1} concentrations of dye, accurately weighed 250 and 500 mg quantities of FD&C Red # 40 dye were transferred to 100 ml volumetric

flasks, dissolved and diluted to volume with PG. The densities of these dye/PG solutions were measured in triplicate with a pycnometer at room temperature (25°C). Such densities (ρ) were used to calculate the extrapolation factors (e_f) required in the spectrophotometric analysis (see Eq. (2)).

2.3. Liquid/powder admixtures

A 2 g quantity of a powder (i.e. MCC-1, MCC-2) or a powder blend (i.e., MCC-2:LM 9:1 w/w, MCC-2:silica 9:1 w/w) was placed in a 25 ml glass bottle and mixed with various quantities of the 5 mg ml^{-1} dye/PG solution to obtain liquid/powder weight ratios ranging from 0.025 to 0.25. The process was repeated by adding the 2.5 mg ml^{-1} dye/PG solution to the MCC-1 and MCC-2 powders. The glass bottles were attached to a Turbula mixer (Glen Mills, Maywood, NJ) and their contents were mixed for 10 min.

2.4. Compression

A semi-automatic Carver system (Fred S. Carver, Wabash, IN) consisting of a Model-C hydraulic laboratory press connected to a Motor-Pak motorized unit with automatic time and pressure release, was used for tablet compression. By using an 8/32 in. S-7 flat cylindrical tooling (Advance Engineering and Manufacturing, O'Fallon, MO) and applying compression loads ranging from 2000 to 3000 lb., 100 mg compacts were obtained from each of the liquid/powder admixtures.

2.5. Extraction of dye and PG

After compression, the dye and PG contents of the resulting tablets were extracted by placing each compact in a 25 ml volumetric flask, diluting to volume with purified water, and sonicating until the tablet had entirely disintegrated. After centrifugation, a portion of the supernatant was filtered through a 0.45 μm, type HA, nylon membrane filter (Millipore, Bedford, MA).

2.6. Quantitation of dye and PG

The above extracts were analyzed for their PG content using a modified version of the gas chromatographic procedure described in the USP [3] (direct method). In addition, the same extracts were analyzed spectrophotometrically for their dye content which was then used to calculate their PG content based on the concentration of the dye originally present in the dye/PG solution (i.e. 2.5 or 5 mg ml^{-1}) which was added to the powders prior to compression (indirect method).

2.7. Gas chromatographic (GC) method

A Model 3920 B gas chromatograph equipped with a flame ionization detector and an off-column injection port (Perkin-Elmer, Norwalk, CT) was used for the gas chromatographic analyses. Separations were achieved on a 1 m × 4 mm glass column packed with 5% CW on 40–60 mesh Chrom-T. The chromatographic conditions were: column temperature, programmed to increase at the rate of 4°C min^{-1} from 120°C (initial) to 150°C (final); injection port temperature, 240°C; detector block temperature, 250°C; carrier gas and flow rate, helium at 23 ml min^{-1}. A standard curve for PG was prepared by serially diluting a stock solution of PG in water to obtain concentrations ranging from 0.05 to 0.3 mg ml^{-1}. Each dilution was injected three times. The concentrations of PG in the tablet extracts were obtained by reference to the calibration curve.

2.8. Spectrophotometric (dye) method

A Model DU-50 spectrophotometer (Beckman Instruments, Fullerton, CA) was used for the spectrophotometric analysis of FD&C Red # 40 dye at a wavelength of 506 nm. A standard curve for the dye was constructed by serially diluting an aqueous stock solution of the dye to obtain concentrations in the range 1–8 μg ml^{-1}. Each concentration was analyzed in triplicate. The unknown concentration of the dye in a tablet extract was derived from this calibration curve. Then, from the amount of dye (W_{dye}) found in the tablet extract, the amount of PG (W_{PG}) remaining in the tablet was calculated by:

$$W_{PG} = e_f \times W_{dye} \quad (1)$$

where e_f is an extrapolation factor characteristic for each of the dye/PG solutions used, calculated by taking into account the densities (ρ in g ml^{-1}) and dye concentrations ($c = 2.5$ or 5 mg ml^{-1}) of the stock dye/PG solutions added to the powders before compression, as follows:

$$e_f = \frac{(\rho \times 10^3) - c}{c} \quad (2)$$

where ρ is multiplied by 10^3 mg g^{-1} for unit conversion. It should be noted, here, that e_f is only an empirical conversion factor and must not be confused with a theoretical physical attribute of the system. Furthermore, due to the size of the experimentally measured density (i.e., $\rho \approx 1$) and the relatively small value of the dye concentration (c) in the numerator, the extrapolation factor in the Eq. (2) may be more conveniently calculated by approximation, as follows:

$$e_f \approx \frac{1000}{c} \quad (2A)$$

2.9. Intermethod difference

The amounts of PG found in tablets of different powder substrates by the two methods were compared. For each compact analyzed, the intermethod difference (Δ in mg) was calculated from:

$$\Delta = A_{GC} - A_{dye} \quad (3)$$

where A_{GC} and A_{dye} are the amounts (in mg) of PG found in the tablet by gas chromatography and spectrophotometry (dye), respectively. Finally, the relative intermethod difference (Δ_{rel}%) with reference to the results obtained from gas chromatography was determined from:

$$\Delta_{rel} = \left(\frac{\Delta}{A_{GC}}\right) \times 100 \quad (4)$$

2.10. Statistical analysis

Statistical analysis of the means of Δ_{rel} was performed using a two-tailed one-sample t-test and a null hypothesis of $\Delta_{rel} = 0\%$ for non significant intermethod difference. Furthermore, the amounts of PG found in the compacts using the proposed spectrophotometric method were plotted against those found in the same samples by gas chromatography and their correlation coefficients and slopes were determined by linear regression analysis.

3. Results and discussion

In the present study, the USP gas chromatographic method for PG analysis [3] was modified by using a flame ionization detector in place of the thermal conductivity detector and a different temperature setting and programming rate for the column. In this case, the retention time of PG was about 4 min. This modified GC method yielded a linear relationship between peak heights (in mm) and concentrations of PG ranging from 0.05 to 0.3 mg ml^{-1} ($Y = 230.86X - 1.61$, $r = 0.998$) with the R.S.D. for each set of triplicate injections not exceeding 2%.

The dye (FD&C Red # 40), used as the reference marker in this study, was selected on the basis of its ready availability, good solubility in PG, easy extractability in water, and strong absorbance in the visible spectral range. The calibration curve for the spectrophotometric analysis of this dye was linear for concentrations of dye ranging from 1 to 8 μg ml^{-1} ($Y = 0.045X + 0.667$, $r = 0.999$). The R.S.D. values for absorbance readings of each set ($n = 3$) did not exceed 2%.

The densities of the 5 and 2.5 mg ml^{-1} dye/PG solutions, determined pycnometrically, were 1.027 ± 0.012 and 1.021 ± 0.009 g ml^{-1}, respectively. Based on Eq. (2), the extrapolation factors (e_f) of the 5 and 2.5 mg ml^{-1} dye/PG solutions were calculated to be 204.4 and 407.4, respectively. These extrapolation factors were in turn used to calculate the amounts of PG remaining in each tablet according to Eq. (1).

The possibility that this indirect spectrophotometric assay for measuring PG based on the amounts of dye, might yield inaccurate analytical results due to disproportional squeezing of the dye/PG solution through the powder substrate during compression, was considered. In other words, because of differences in the affinities of

the dye and PG for the carrier powders, it was theorized that the dye/PG solution which might have been squeezed out of the admixtures during compaction, would contain a dye concentration which is different from that of the originally incorporated dye/PG solution, thereby leading to erroneous PG assessments.

To address such concerns, dye/PG solutions of two different dye concentrations (i.e. 2.5 and 5 mg ml^{-1}) were added, at five levels, to four carrier powder substrates differing in chemical structure, particle size, porosity, polarity, compaction properties and liquid retention potentials. After compression of such admixtures, the amounts of PG in each compact were measured by GC and spectrophotometry (dye). Tables 1–6 summarize the results of these analyses. Each Table reports the amounts of PG found in five 100 mg compacts containing different levels of a dye/PG solution added to a given powder substrate.

Tables 1–4 report the mean amounts of PG found by the GC and dye methods along with the intermethod differences, Δ (mg) and Δ_{rel} (%) for different compacts prepared with a 5 mg ml^{-1} dye/PG solution and four different powder substrates. On the other hand, Tables 5 and 6 show the analytical findings for compacts obtained with a 2.5 mg ml^{-1} dye/PG solution and two powder substrates.

As shown in these Tables, for compacts containing the 5 mg ml^{-1} dye/PG solution and dif-

Table 1
Comparison of two methods for quantitation of PG in tablets containing MCC-1 and different levels of a 5 mg ml^{-1} dye/PG solution

Tablet No.[a]	Mean amount of PG (mg)[b]		Intermethod difference	
	GC	Dye	Δ (mg)[c]	Δ_{rel} (%)[d]
1	2.81	2.74	0.07	2.49
2	4.76	4.85	−0.09	−1.89
3	8.05	7.69	0.36	4.47
4	14.32	13.76	0.56	3.91
5	20.05	20.27	−0.22	−1.10
Mean				1.58[e]
S.D.				2.91

[a] In each tablet a different amount of PG has been originally added.
[b] Average of 3 determinations (the R.S.D. of such determinations did not exceed 2%).
[c] Δ is the difference (mg) from GC value as calculated from Eq. (3).
[d] Δ_{rel} Is the relative difference (%) from the GC method as calculated from Eq. (4).
[e] t-Test of the mean: $t = 1.21$, not significantly different from 0% ($P = 0.2923$).

Table 2
Comparison of two methods for quantitation of PG in tablets containing MCC-2 and different levels of a 5 mg ml^{-1} dye/PG solution

Tablet No.[a]	Mean amount of PG (mg)[b]		Intermethod difference	
	GC	Dye	Δ (mg)[c]	Δ_{rel} (%)[d]
1	2.47	2.44	0.03	1.21
2	4.20	4.18	0.02	0.48
3	7.17	7.04	0.13	1.81
4	11.63	12.03	−0.40	−3.44
5	17.68	17.35	0.33	1.87
Mean				0.39[e]
S.D.				2.21

[a]–[d] See footnotes, Table 1.
[e] t-Test of the mean: $t = 0.39$, not significantly different from 0% ($P = 0.7162$).

Table 3
Comparison of two methods for quantitation of PG in tablets containing MCC-2:LM (9:1 w/w) and different levels of a 5 mg ml^{-1} dye/PG solution

Tablet No.[a]	Mean amount of PG (mg)[b]		Intermethod difference	
	GC	Dye	Δ (mg)[c]	Δ_{rel} (%)[d]
1	2.47	2.45	0.02	0.81
2	4.87	4.84	0.03	0.62
3	8.68	8.67	0.01	0.12
4	14.27	14.41	−0.14	−0.98
5	18.79	19.08	−0.29	−1.54
Mean				−0.19[e]
S.D.				1.02

[a]–[d] See footnotes, Table 1.
[e] t-Test of the mean: $t = 0.42$, not significantly different from 0% ($P = 0.6938$).

Table 4
Comparison of two methods for quantitation of PG in tablets containing MCC-2:silica (9:1 w/w) and different levels of a 5 mg ml^{-1} dye/PG solution

Tablet No.[a]	Mean amount of PG (mg)[b]		Intermethod difference	
	GC	Dye	Δ (mg)[c]	Δ_{rel} (%)[d]
1	2.36	2.33	0.03	1.27
2	4.76	4.69	0.07	1.47
3	9.43	9.31	0.12	1.27
4	12.71	12.13	0.58	4.56
5	17.45	18.03	−0.58	−3.32
Mean				1.05[e]
S.D.				2.81

[a–d] See footnotes, Table 1.
[e] t-Test of the mean: $t = 0.83$, not significantly different from 0% ($P = 0.4511$).

Table 6
Comparison of two methods for quantitation of PG in tablets containing MCC-2 and different levels of a 2.5 mg ml^{-1} dye/PG solution

Tablet No.[a]	Mean amount of PG (mg)[b]		Intermethod difference	
	GC	Dye	Δ (mg)[c]	Δ_{rel} (%)[d]
1	2.34	2.31	0.03	1.28
2	4.53	4.64	−0.11	−2.43
3	8.08	7.85	0.23	2.85
4	14.21	14.03	0.18	1.27
5	19.86	19.69	0.17	0.86
Mean				0.77[e]
S.D.				1.94

[a–d] See footnotes Table 1.
[e] t-Test of the mean: $t = 0.88$, not significantly different from 0% ($P = 0.4276$).

ferent carrier powders, such as MCC-1 (Table 1), MCC-2 (Table 2), MCC-2:LM (Table 3) and MCC-2:silica (Table 4), and for compacts containing the 2.5 mg ml^{-1} dye/PG solution and MCC-1 (Table 5) and MCC-2 (Table 6) as the powder substrates, the mean relative intermethod differences with reference to GC (Δ_{rel}) ranged from −0.19 to 1.58%. The two-tailed, one sample t-test of such means performed in each Table, did not yield any significant difference between the mean Δ_{rel} of each group and 0% ($P > 0.3$).

Table 5
Comparison of two methods for quantitation of PG in tablets containing MCC-1 and different levels of a 2.5 mg ml^{-1} dye/PG solution

Tablet No.[a]	Mean amount of PG (mg)[b]		Intermethod difference	
	GC	Dye	Δ (mg)[c]	Δ_{rel} (%)[d]
1	2.73	2.75	−0.02	−0.73
2	4.66	4.58	0.08	1.72
3	7.88	7.69	0.19	2.41
4	13.57	13.81	−0.24	−1.77
5	18.58	18.12	0.46	2.48
Mean				0.82[e]
S.D.				1.95

[a–d] See footnotes, Table 1.
[e] t-Test of the mean: $t = 0.94$, not significantly different from 0% ($P = 0.3992$).

The amounts of PG found in the compacts by the GC and dye methods, reported in Tables 1–6, were used to generate the intermethod correlation curves presented in Figs. 1 and 2. Regression analysis of such linear plots revealed correlation coefficients and slopes very close to 1 ($r = 0.999$, and slopes ranging from 0.985 to 1.02), thereby indicating an absolute correlation between the two methods. The linear regression equations are included in Figs. 1 and 2.

The above findings clearly indicate that the newly developed indirect spectrophotometric method may be used in place of gas chromatography as a simpler approach for PG quantitation in tablets. Moreover, this new approach might be also proven to be conveniently applicable to the measurement of other nonvolatile water miscible liquids, occasionally added to solid dosage forms such as liquid polyethylene glycols and surfactants.

Particularly, related to our investigations of powder compactability, the new method may be employed as a convenient analytical alternative to a powder testing procedure termed the liquisolid compressibility (LSC) test, which has been recently developed [1,2] and used to evaluate vari-

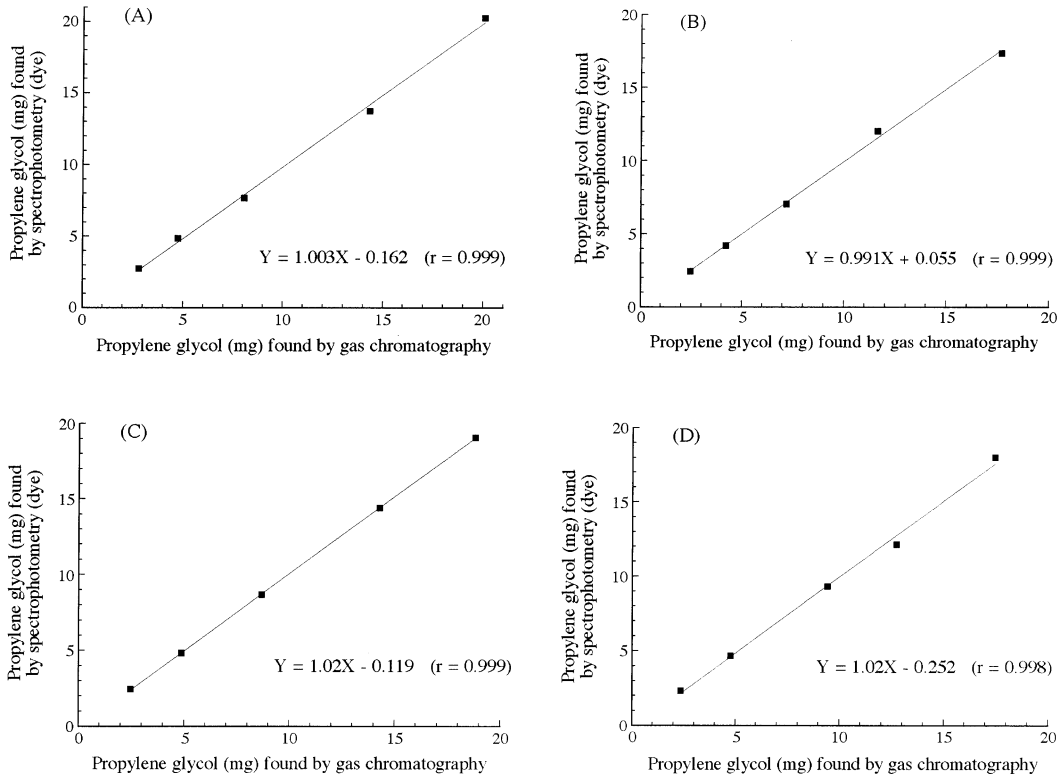

Fig. 1. Correlation and linear regression analysis of the amounts of PG found by GC and spectrophotometry in liquid/powder compacts containing various levels of a 5 mg ml^{-1} dye/PG solution and different powder substrates such as: (A), MCC-1; (B), MCC-2; (C), MCC-2:LM (9:1 w/w); and (D), MCC-2:silica (9:1 w/w).

ous compression properties of different grades of pharmaceutical powder excipients. In LSC testing, the amounts of PG squeezed out of, and/or remaining in PG/powder compacts possessing variable PG contents and compressed at different compaction loads, may be suitably determined by using the simple, indirect spectrophotometric approach presented in this paper. The effects of PG content on the deterioration profile of a powder's compactability might be highly important in the areas of excipient suitability testing, and dosage form and process validation and development. In our recent work, it has been shown that such liquisolid compressibility studies are of interest because several linear relationships between certain compaction properties of different PG/powder admixtures and their liquid/powder weight ratios have been observed [1,2] and will be reported in future papers.

4. Conclusions

The new indirect spectrophotometric method, introduced in this study, will determine in an accurate and reproducible manner the amounts of PG (propylene glycol) remaining in compacts prepared by adding various levels of the liquid to several powder substrates and compressing at different loads. Therefore, it can be used as a convenient alternative to GC. In addition, this simple spectrophotometric approach might be applicable

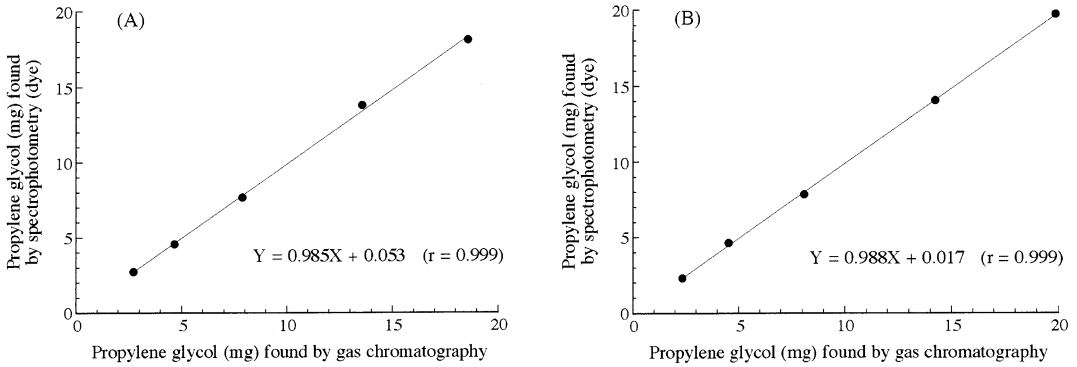

Fig. 2. Correlation and linear regression analysis of the amounts of PG found by GC and spectrophotometry in liquid/powder compacts containing various levels of a 2.5 mg ml^{-1} dye/PG solution and different powder substrates such as: (A), MCC-1; and (B), MCC-2.

to the measurement of other nonvolatile liquid excipients, similar to PG, which have been incorporated into various carrier powders.

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