Original Article

Evaluation of *in vitro* dissolution profile comparison methods of sustained release tramadol hydrochloride liquisolid compact formulations with marketed sustained release tablets

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ABSTRACT: The aim of the present work was to prepare and evaluate sustained release liquisolid compact formulations of tramadol hydrochloride. The dissolution profile of the prepared compacts was also compared to that of a marketed preparation. Liquisolid sustained release formulations were prepared by using HPMC K4M as a sustained release agent. Precompression studies of characteristics such as flow properties were also carried out. Liquisolid compacts were evaluated by hardness, friability, and *in vitro* dissolution studies. Comparison of dissolution profiles was carried out by using a model-independent, model-dependent, and statistical approach. The prepared liquisolid compacts are new dosage forms with better sustained release behavior compared to a marketed sustained formulation. The dissolution profile followed the Peppas model as "best fit" model. Two-way ANOVA results revealed a significant difference in dissolution profiles. This systematic approach to producing a formulation was found to help with analyzing the sustained release of tramadol hydrochloride. The use and evaluation of model-dependent methods is more complicated. These methods provide an acceptable model approach that indicates the true relationship between percent drug release and time variables, including statistical assumptions.

Keywords: Liquisolid compacts, tramadol hydrochloride, dissolution, ANOVA

1. Introduction

A sustained release dosage form is mainly designed to maintain therapeutic blood or tissue levels of a drug for an extended period of time with minimized local or systemic adverse effects. Economy and greater patient compliance are other advantages (*1*). In recent years, clinical studies on tramadol hydrochloride have demonstrated that this drug is an effective agent for moderate to severe chronic pain (*2-5*). The half-life of the drug is about 5.5 h and the usual oral dosage regimen is 50 to 100 mg every 4 to 6 h, with a maximum dosage of 400 mg/day (*6*). A sustained-release formulation tramadol would prove beneficial in reducing the frequent administration of this dosage form and improving patient compliance. The drug is freely water-soluble and hence judicious selection of release-retarding excipients is necessary to achieve a constant *in vivo* input rate of the drug. Various approaches have been used by researchers to sustain drug release in the form of tablets (*7-9*).

A liquisolid system is a novel technique developed by Spireas *et al*. (*10,11*). "Liquisolid systems" involve conversion of liquid lipophilic drugs or water-insoluble solid drugs dissolved in non-volatile solvent, and this liquid medication can be converted into free-flowing, non adherent, dry, and readily compressible powders through the use of carrier and coating materials. With water-soluble drugs, sustained release can be obtained (*12*). The term "liquisolid compacts" as described by Spireas *et al*. refers to immediate or sustained release tablets or capsules that are prepared using the "liquisolid system" technique in combination with inclusion of appropriate adjuvants required for tabletting or encapsulation, *e.g.* lubricants, and for rapid or sustained release action, *e.g.* disintegrants and binders (*10*). Advantages of this technique are its low cost, simplicity of formulation, and applicability to industrial production (*13*).

In the present study, hydroxy propyl methyl cellulose (HPMC) K4M was used as an adjuvant to sustain drug release from liquisolid compacts. The term "adjuvant" as a sustained release agent is cited by Spireas *et al*. (*10,11*). Avicel PH 102 and Aerosil 200 were used as carrier and coating materials, respectively. Precompression studies such as determination of the angle of repose, Hausner's ratio, and Carr's index were carried out and stereomicroscopic analysis was also

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performed. Differences in release profiles to those of marketed tablets of tramadol hydrochloride were determined using a model-independent method f_2 and a statistical approach in the form of two-way repeated-measures ANOVA. Model fitting was also done for different models such as zero-order, first-order, Hixon-Crowell, Peppas, and Matrix models. A new mathematical model for formulation design as described by Spireas *et al*. (*10*) was used to calculate appropriate amounts of carrier and coating materials based on new fundamental properties of a powder called the flowable liquid retention potential (Φ value) and compressible liquid retention potential (Ψ number) of powder ingredients (previously determined by Spireas *et al*.) (*10*,*11*).

2. Materials and Methods

2.1. *Materials*

Tramadol was generously provided by Panacea Biotec (India). HPMC K4M, Avicel PH 102 and Aerosil 200 were generously provided by Okasa Pharmaceuticals (India). Propylene glycol was purchased from Loba Chemie (India). All other reagents and chemicals were of analytical grade.

2.2. *Use of a mathematical model to design liquisolid compacts*

The formulation design of liquisolid systems was done in accordance with the new mathematical model described by Spireas *et al*. (*10*). In this study, propylene glycol was used as a liquid vehicle, and Avicel PH 102 and Aerosil 200 were used as the carrier and coating materials, respectively. The concentration of the drug in propylene glycol was 10, 20, and 30 g% and the carrier: coat ratio ranged from 30 to 40 and 50. According to new theories, the carrier and coating powder materials can retain only certain amounts of liquid while maintaining acceptable flowability and compressibility.

The excipient ratio *R* of the powder is defined as

$$R = Q / q \qquad \text{----- Eq. 1}$$

where *R* is the ratio of the weight of carrier (Q) and coating (*q*) materials present in the formulation.

The liquid load factor (L_f) is defined as the ratio of the weight of liquid medication (W) to the weight of the carrier powder (Q) in the system, which should be present in an acceptably flowing and compressible liquisolid system, *i.e.*

$$L_f = W / Q \qquad \text{----- Eq. 2}$$

The flowable liquid retention potential (Φ value) of powder excipients was used to calculate the required ingredient quantities. Therefore, powder excipients ratios *R* and liquid load factors L_f of the formulations are related as follows:

$$L_f = \mathbf{\Phi} + \Phi\,(1 / R) \qquad \text{----- Eq. 3}$$

where, $\mathbf{\Phi}$ and Φ are the Φ values of carrier and coating materials, respectively.

Hence, to calculate the required weights of the excipients used $\mathbf{\Phi}$ and Φ from Eq. 3 are constants, and thus L_f was calculated according to the ratio of carrier: coating materials (*R*).

Using the above mathematical model, liquisolid compacts were formulated as summarized in Table 1.

2.3. *Determination of solubility*

Saturated solutions were prepared by adding excess tramadol to the propylene glycol and shaking on a shaker for 48 h at 25°C with constant vibration. The solutions were filtered through a 0.45 micron filter, diluted with water, and analyzed with a Shimadzu 1700 UV-Vis spectrophotometer at 271.5 nm with respect to a blank sample (the blank sample was a solution containing the same concentration used without the drug). Determination was carried out in triplicate for each sample to calculate the solubility of tramadol.

2.4. *Preparation of liquisolid compacts*

Calculated quantities of tramadol hydrochloride and propylene glycol were accurately weighed in a 20-mL

Table 1. Formulation design of liquisolid compacts

Formulation batch code	Drug concentration in Propylene glycol (%, w/w)	*R*	L_f	Avicel PH 102 (mg) ($Q = W/L_f$)	Aerosil 200 (mg) ($q = Q/R$)	HPMC K4M (mg)
F1		30	0.270	197.5	6.58	100
F2	10	40	0.243	219.46	5.48	150
F3		50	0.226	235.97	4.71	200
F4		30	0.270	395.03	13.10	100
F5	20	40	0.243	438.93	10.97	150
F6		50	0.226	471.94	9.43	200
F7		30	0.270	592.59	19.75	100
F8	30	40	0.243	658.43	16.46	150
F9		50	0.226	707.96	14.15	200

glass beaker and then heated to 180°C. The resulting hot medication was incorporated into calculated quantities of carrier and coating materials. The mixing process was carried out in three steps as described by Spireas *et al*. (*10*). In the first, the system was blended at an approximate mixing rate of one rotation per second for approximately one minute in order to evenly distribute liquid medication in the powder. In the second, the liquid/powder admixture was evenly spread as a uniform layer on the surface of a mortar and left standing for approximately 5 min to allow the drug solution to be absorbed inside powder particles. In the third, the powder was scraped off the mortar surface using an aluminum spatula. Then HPMC K4M was added to this mixture and blended in a mortar. This provided the final formulation that was compressed into tablets using a single punch tablet compression machine.

2.5. *Precompression studies: Flow properties*

Flow properties of liquisolid formulation were studied by angle of repose, Carr's index, and Hausner's ratio (*14*). Each analysis was carried out in triplicate. Bulk density measurements were carried by placing a fixed weight of powder in a graduated cylinder, and the volume occupied was measured and the initial bulk density was calculated. The cylinder was then tapped at a constant velocity until a constant volume was obtained. The tapped density was then calculated. The angle of repose was calculated by the fixed-height cone method. All studies were done in triplicate.

2.6. *Evaluation of liquisolid compacts*

The *hardness* of liquisolid compacts was determined using a Pfizer hardness tester (Pfizer). The mean hardness of each formula was determined. The *friability* of prepared liquisolid compacts was determined using a digital tablet friability tester (Roche).

2.7. *In vitro drug release studies*

Studies were done on a six-station USP dissolution apparatus I (LabIndia). All batches of tablets were evaluated (n = 3) using 900 mL of sequential gastrointestinal release medium, *i.e.,* 0.1 N hydrochloric acid (pH 1.2) for the first 2 h, acetate buffer of pH 4.5 for the next 2 h, and then phosphate buffer of pH 7.4 for the remaining 6 h. Temperature was maintained at 37 ± 0.5°C throughout the study and stirring was done at 50 rpm. Samples were periodically collected, filtered through a 0.45 micron filter, and replaced with dissolution medium. After filtration through Whatman filter paper 41, the concentration of Tramadol hydrochloride was determined spectrophotometrically at 271.5 nm (Shimadzu 1700 UV-Vis Spectrophotometer). The actual amount of released drug was determined from the calibration curve (n = 3).

2.7.1. *Model-independent approach*

According to US FDA guidance for dissolution data equivalence, a model-independent approach is recommended. This involves use of the similarity factor (f_2), which provides a simple means of comparing data. The similarity factor (f_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) dissolution between the two curves.

$$f_2 = 50 \times \log\{[1 + (1/n)\sum_{t=1}^{n}(R_t - T_t)^2]^{-0.5} \times 100\} \quad \text{----- Eq. 4}$$

where n is the number of time points, R is the dissolution value of the reference at time t, and T is the dissolution value of the test at time t.

2.7.2. *Model-dependent methods*

The drug release from liquisolid compacts was analyzed by various mathematical models such as zero-order, first-order, Hixon-Crowell, Peppas, Hixon-Crowell, and Matrix models.

2.7.3. *Statistical methods*

Repeated-measures two-way ANOVA was used to determine how dissolution was affected by two factors. The percentage dissolved was the dependent variable and time was a repeated factor.

3. Results and Discussion

3.1. *Use of a new mathematical model to design liquisolid systems*

Tramadol hydrochloride was selected as model drug for this study as a suitable candidate for sustained release. The liquisolid hypothesis of Spireas *et al*. (*18*) states that a drug candidate dissolved in a liquid nonvolatile vehicle and incorporated into a carrier material with a porous structure and closely matted fibers in its interior will exhibit both adsorption and absorption. A drug in the form of liquid medication will initially be absorbed in the interior of particles of the carrier and after saturation will be adsorbed into internal and external surfaces of the carrier. Coating materials such as Aerosil 200 that have high adsorptivity and greater surface area allow liquisolid systems to provide desirable flow properties (*18*).

The mathematical model equation for Avicel PH 102 and Aerosil 200 in propylene glycol is given according to values of Phi (Φ) as cited by Spireas *et al*. (*10,11*).

$$L_f = 0.16 + 3.31\ (1 / R) \quad \text{----- Eq. 5}$$

Based on this equation, L_f is calculated using different *R* values.

3.2. *Solubility of tramadol hydrochloride in propylene glycol*

Determination of solubility is most important aspect in formulating liquisolid systems. Solubility may contribute to molecular dispersion of the drug in a non-volatile solvent such as propylene glycol. The solubility of tramadol in propylene glycol was found to be 6.254 ± 0.44 g/10 mL.

3.3. *Precompression studies for liquisolid systems: Flow properties*

Flow properties are the important aspect of formulation and industrial production of tablet dosage forms. Results of measurements such as the angle of repose, Carr's index, and Hausner's ratio are shown in the Table 2. The angle of repose is characteristic to the flow rate of the powder. In general, an angle of repose ≥ 40° indicates a powder with poor flowability (*14*). The current results were in accordance with that principle. Results of Carr's index and Hausner's ratio also revealed good flow behavior.

3.4. *Evaluation of liquisolid compacts*

Results of hardness, friability, and disintegration time are shown in Table 3. Tablets should have a certain amount of strength or hardness and resistance to friability so that they do not break during handling. However, these characteristics also affect drug dissolution. The average *hardness* of a liquisolid tablet ranged from 5.11 ± 0.25 to 6.44 ± 0.42 kg/cm^2. The compactness of tablets may be due to hydrogen bonding between Avicel PH 102 molecules (*16*). As propylene glycol is an alcoholic compound, it might have hydrogen bonding due to the presence of hydroxyl groups and may contribute to the compactness of compacts. *Friability* of liquisolid compacts was in the range of 0.133% to 0.278%. This indicates that liquisolid compacts had acceptable ability to withstand handling.

3.5. *In vitro dissolution studies*

In the preparation of liquisolid compacts, liquid medications containing the drug were adsorbed on the surface of carrier materials. When this system is exposed to dissolution medium, the drug on the surface of the compact dissolves quickly and diffuses into the dissolution medium. This can be assumed to be the cause of the burst release effect observed. The concentration of drug in liquid medication is an important aspect as it affects drug release. As was previously proven, an increase in drug concentration in liquid medication leads to a lower drug release rate. This is due to fact that at a higher drug concentration the drug tends to precipitate within silica (Aerosil 200) pores. This finding was also corroborated by Javadzadeh *et al*. (*17*). A higher amount of Aerosil 200 (Batch F9) was found to result in retarded drug release in comparison to other batches. An increase in the concentration of HPMC K4M might be responsible for the sustained effect. This is reflected in batches F3, F6, and F9. However, the marketed sustained release tablets had faster release than liquisolid sustained release formulations (Figure 1).

3.5.1. *Model-independent methods*

A model-independent method such as the similarity factor (f_2) provides a simple way to compare dissolution data. US FDA guidance proposes that f_2 values of 50-100 indicate equivalence in dissolution profiles. Table 4

Table 3. Results of hardness and friability tests of sustained release liquisolid tablet formulations

Formulation batch code	Average *hardness* (kg/cm^2) ± SD	Percentage *friability* obtained during friability test (%)
F1	5.11 ± 0.25	0.174
F2	5.78 ± 0.15	0.210
F3	6.14 ± 0.38	0.256
F4	5.74 ± 0.20	0.192
F5	5.96 ± 0.37	0.244
F6	6.26 ± 0.15	0.278
F7	6.32 ± 0.34	0.143
F8	6.44 ± 0.42	0.267
F9	6.29 ± 0.29	0.133

Table 2. Results of flowability parameters of liquisolid powder systems for different formulation batches

Formulation batch code	Average angle of repose (θ) ± SD	Average Carr's index (%) ± SD	Average Hausner's ratio ± SD
F1	40.61 ± 0.54	19.29 ± 0.15	1.23 ± 0.01
F2	38.97 ± 0.57	19.63 ± 0.24	1.26 ± 0.01
F3	38.76 ± 0.24	21.31 ± 0.19	1.28 ± 0.01
F4	39.62 ± 0.52	20.21 ± 0.18	1.24 ± 0.01
F5	38.49 ± 0.97	22.40 ± 0.80	1.27 ± 0.01
F6	38.02 ± 0.12	25.40 ± 0.31	1.30 ± 0.01
F7	39.19 ± 0.46	21.47 ± 0.23	1.27 ± 0.02
F8	38.56 ± 0.11	23.80 ± 0.15	1.32 ± 0.01
F9	37.40 ± 0.32	25.30 ± 0.16	1.34 ± 0.01

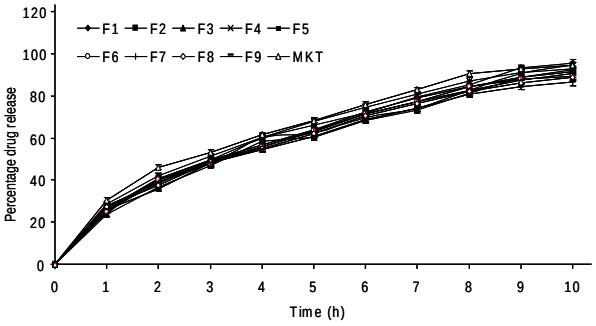

Figure 1. *In vitro* dissolution profile of sustained release tramadol hydrochloride liquisolid compacts (F1-F9) in comparison to a marketed formulation (MKT).

Table 4. Similarity factor (f_2) values of liquisolid compacts in comparison to marketed tablets

Comparison	f_2	Dissolution profile
F1 and MKT	24.52	Dissimilar
F2 and MKT	25.96	Dissimilar
F3 and MKT	11.90	Dissimilar
F4 and MKT	63.30	Similar
F5 and MKT	60.11	Similar
F6 and MKT	56.11	Similar
F7 and MKT	83.12	Similar
F8 and MKT	69.33	Similar
F9 and MKT	64.79	Similar

shows f_2 values of all of the batches. Although the dissolution profile seems to be equivalent to that of the marketed tablets, differences in f_2 values of batches F1 to F3 might be due to a lower concentration of drug present in the formulations. Other batches had f_2 values > 50, which indicates a similarity in the dissolution profile.

3.5.2. *Model-dependent methods*

Although model-independent methods are simple and easy to use, they lack scientific justification (*18-20*). Different models of dissolution profile comparison were used (Tables 5 and 6). The results of these models indicate that all liquisolid compacts followed the Peppas model as "best fit model". This is due to the previously proven R^2 value obtained from model fitting (*21*). The T_{50}% of all of the formulations was also determined and indicated that batches F3 and F9 retarded release more. The T_{50}% value was thus found to increase as the concentration of HPMC K4M increases. The Korsmeyer-Peppas release exponent (n) values of all liquisolid compacts were greater than 0.5, indicating non-Fickian diffusion, *i.e.,* a rapid release initially, the reason for which was previously explained. Different models were characterized based on the plots shown in Figures 2-5.

Table 5. Parameters and determination coefficients of the release profile from sustained release liquisolid compacts (F1-F5)

Model	Parameter	F1	F2	F3	F4	F5
Zero-order	R^2	0.9121	0.9196	0.9223	0.8782	0.8969
	k	11.129	10.788	10.567	11.177	10.843
First-order	R^2	0.9684	0.9655	0.9764	0.9930	0.9933
	k	- 0.262	- 0.240	- 0.223	- 0.252	- 0.232
Matrix	R^2	0.9975	0.9954	0.9953	0.9991	0.9986
	k	29.885	28.931	28.325	30.155	29.182
Peppas	R^2	0.9990	0.9973	0.9977	0.9991	0.9988
	k	26.469	25.031	24.307	29.121	27.061
Hixon-Crowell	R^2	0.9923	0.9889	0.9908	0.9909	0.9921
	k	- 0.062	- 0.058	- 0.055	- 0.061	- 0.057
Korsmeyer-Peppas release exponent (n)	n	0.5660	0.5784	0.5828	0.5197	0.5413
T_{50}% (h)		3.1	3.3	3.4	2.8	3.1

Table 6. Parameters and determination coefficients of the release profile from sustained release liquisolid compacts (F6-F9) and marketed sustained release tablets

Model	Parameter	F6	F7	F8	F9	MKT
Zero-order	R^2	0.9004	0.8936	0.8964	0.8967	0.8636
	k	10.679	10.680	10.513	10.297	11.452
First-order	R^2	0.9959	0.9941	0.9960	0.9967	0.9867
	k	- 0.221	- 0.222	- 0.212	- 0.200	- 0.274
Matrix	R^2	0.9976	0.9991	0.9986	0.9982	0.9983
	k	28.725	28.756	28.293	27.712	30.941
Peppas	R^2	0.9978	0.9994	0.9989	0.9983	0.9976
	k	26.042	27.512	26.685	25.797	31.230
Hixon-Crowell	R^2	0.9902	0.9904	0.9891	0.9864	0.9892
	k	- 0.056	- 0.056	- 0.054	- 0.052	- 0.065
Korsmeyer-Peppas release exponent (n)	n	0.5538	0.5235	0.5314	0.5388	0.4954
T_{50}% (h)		3.2	3.1	3.3	3.4	2.6

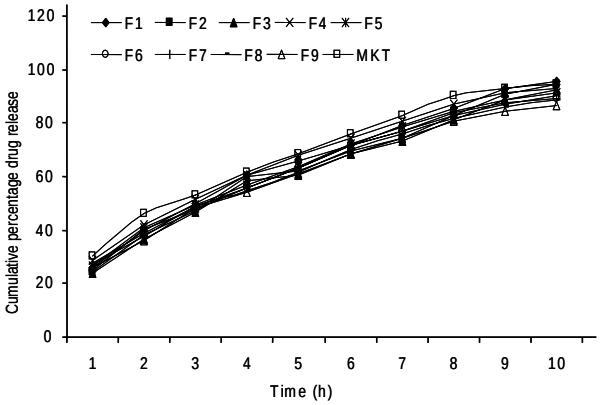

Figure 2. Zero-order plot for liquisolid compacts in comparison to a marketed formulation.

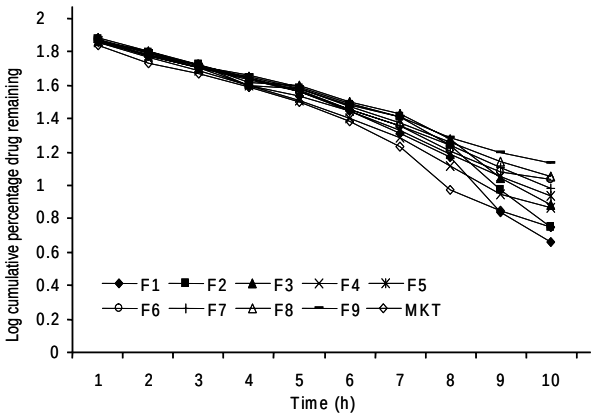

Figure 3. First-order plot for liquisolid compacts in comparison to a marketed formulation.

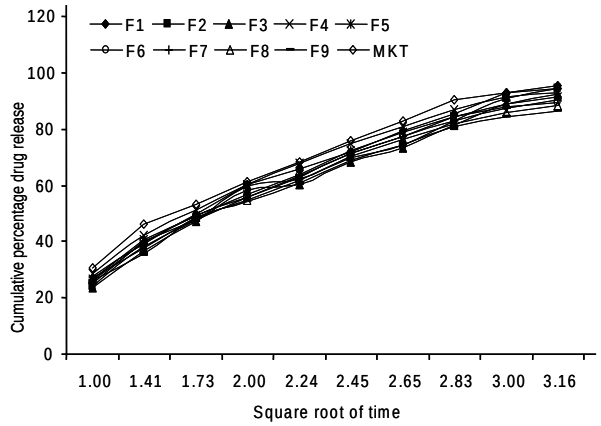

Figure 4. Higuchi plot for liquisolid compacts in comparison to a marketed formulation.

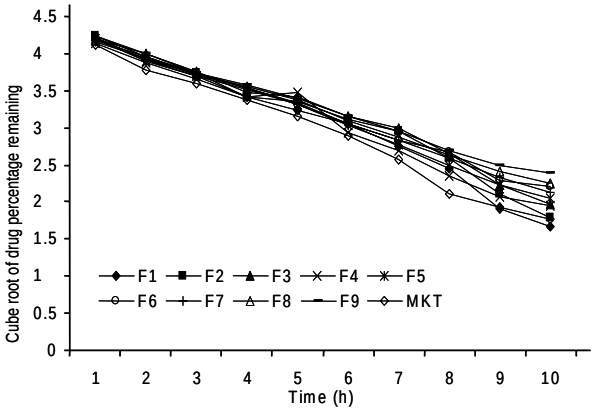

Figure 5. Hixon-Crowell plot for liquisolid compacts in comparison to a marketed formulation.

Table 7. Results of two-way ANOVA

Source of variation	Degrees of freedom	Sum of squares	Mean squares	F value
Column factor	9	441.4	49.05	21.58
Row factor	10	81150	8115	3570.52
Residual (error)	90	204.6	2.273	
Total	109	81800		

3.5.3. *Statistical methods*

Statistical methods based on ANOVA are the simplest way to determine differences in dissolution profiles. A statistically significant difference was observed in two-way ANOVA (Table 7). This was confirmed by a p value of < 0.0001.

4. Conclusion

The present work showed that the liquisolid compact technique can be effectively used to prepare sustained release matrices of water-soluble drugs such as tramadol hydrochloride. Propylene glycol was used as a liquid vehicle. Drug release profiles in model fitting follow the Peppas model as the best-fit model, which indicates drug release from sustained release dosage forms. Model-independent methods were found to be the simplest way to compare dissolution profiles, but differences in dissolution profiles were noted using a model-dependent approach.

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