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In vitro dissolution of sparingly water-soluble drug dosage forms

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Abstract

An in vitro procedure for the evaluation of sparingly water-soluble drug products has been developed and tested. The data on several sparingly water-soluble drug products, such as danazol capsules, megestrol acetate tablets, prazosin HCl capsules, and quinestrol tablets is presented. The procedure allows a systematic approach to evaluate the dissolution profiles of sparingly water-soluble drug products using various aqueous media including those containing a surfactant such as sodium lauryl sulfate. This approach assists the analyst in developing a sensitive and specific dissolution methodology to characterize the in vitro release pattern of sparingly water-soluble drug products.

1. Introduction

In the last decade, the dissolution test has emerged as a valuable quality control tool to assess batch-to-batch product release performance and to assure the physiological availability of the drug. The in vitro dissolution test is also used to guide formulation development and to monitor manufacturing process. As a regulatory test, it is used to approve minor changes in formulation, changes in the site of manufacturing for immediate-release products and also to assess the scale-up of the bio-batch to the production batch. Generally aqueous media such as simulated gastric fluid without enzymes (SGF), simulated intestinal fluid without enzymes (SIF), water and buffers, have been employed to study the dissolution of solid oral dosage forms. For sparingly water-soluble drugs (so called water-insoluble drugs), where commonly used aqueous media are not suitable, surfactants, bile acids, bile salts, and lecithin have been shown to increase the rate of dissolution for these products (Gantt et al.,

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1961; Bates et al., 1966a,b,1967; Singh et al., 1968 Shah et al., 1989). Lecithin, a major phospholipid component of human bile, is instrumental in the formation of mixed micelles in vivo. It is implied that lecithin enhances the dissolution and absorption of poorly soluble compounds administered orally (Naylor et al., 1993). In vitro, it was found that dissolution media containing low levels of surfactants solubilize sparingly water-soluble drug substances in a manner similar to the micelles of bile salts and lecithin. The biological relevance for the use of surfactants in the dissolution medium was discussed by Bates et al. (1996a), and Shah et al. (1989). Synthetic surfactants such as sodium lauryl sulfate (SLS), have also been shown to be interchangeable in vitro with natural surfactants such as sodium cholate and sodium taurocholate (Buri and Humbert-Droz, 1983). The addition of low levels of surfactants to the dissolution medium facilitates in vitro characterization of sparingly water-soluble drug products (Bates et al., 1966b,1967; Abdou, 1985; Shah et al., 1989).

2. Experimental

A number of currently marketed sparingly water-soluble drug products such as danazol capsules, megestrol acetate tablets, prazosin HCl capsules, and quinestrol tablets lack a relevant and reproducible dissolution test or specification. The purpose of this communication is to present a systematic approach for determining the dissolution of sparingly water-soluble drug products and to arrive at a suitable in vitro dissolution test method for these products.

The procedure presented here consists of several steps:

1. The preliminary method development for each drug was carried out using two tablets/capsules of the brand name product.
2. Standard dissolution testing equipment such as the basket method at 100 rpm or paddle method at 50 or 75 rpm (US Pharmacopeia, 1995) was used.
3. 500–1000 ml of the commonly employed media such as water, SGF without enzymes, SIF without enzymes, buffer solutions, and gradually increasing amounts of SLS, 0.1, 0.25, 0.5, 0.75 and 1.0% SLS in water or 0.1 N HCl was used.
4. Samples were collected at 15 min time intervals and analyzed using UV or HPLC methods to obtain product dissolution profiles.
5. The data was analyzed to determine the influence of the media on the dissolution (and solubility) of the drug product and to ascertain the lowest amount of SLS needed to solubilize the dosage form to achieve greater than 75–80% dissolution in a reasonable amount of time.
6. Once a suitable method was developed using the brand name product, six units of all available marketed products in the USA were studied by the new procedure.
7. In addition, where a USP dissolution method was available, products were also tested by this method for comparative purposes. All results reported are the mean of six dosage unit determinations.

3. Results

The approach for developing dissolution profiles for water-insoluble drugs is illustrated with the examples of danazol, megestrol acetate, prazosin, and quinestrol drug products.

The dissolution of 200 mg danazol capsules (Danocrine®, Sterling Drug) in different dissolu-

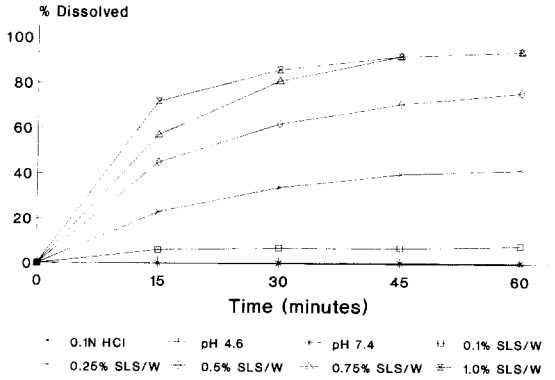


Fig. 1. Danazol capsules: Dissolution of 200 mg Danocrine® (Sterling drug) tested using the paddle method at 75 rpm and 900 ml of media.

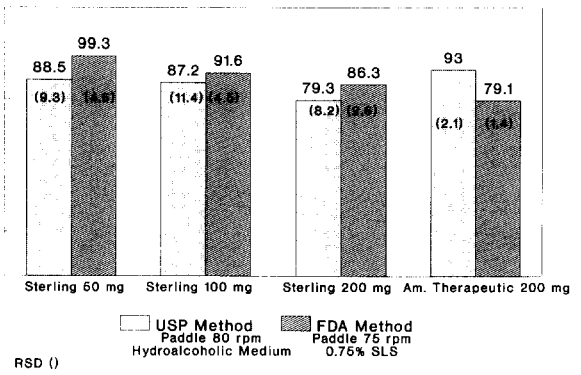


Fig. 2. Danazol capsules: Comparison at 30 min of all products tested by the USP Method (Apparatus 2, paddle method; 80 rpm; 900 ml of isopropyl alcohol-0.1 N HCl (4:10) and by the FDA method, Paddle method at 75 rpm in 0.75% SLS. RSD given in parentheses.

tion media using the paddle method at 75 rpm is shown in Fig. 1. The preliminary results indicated that the product dissolved less than 1% of the active ingredient in 105 min in water, acid and other buffers. A significantly higher dissolution was obtained in the presence of SLS. Fig. 2 shows comparative dissolution using the paddle method, 75 rpm, with 0.75% SLS in water as the medium and the USP method which uses isopropyl alcohol in acid as the medium. All dissolution aliquots were assayed by UV spectrophotometry (287 nm). The use of a surfactant in the dissolution medium provides dissolution rates comparable to the hydroalcoholic medium without the use of alcohol. The difference in the effect of the different dissolution media on the formulations can be seen when comparing the Sterling 200 mg product with the 200 mg product manufactured by American Therapeutics. Relative standard deviations (RSD) are given in parentheses.

The dissolution profiles of all megestrol acetate tablets in different dissolution media, including SLS, were determined using the paddle method at 75 rpm. The dissolution aliquots were filtered using a 0.45 μm Duraporel membrane filter and analyzed by UV spectrophotometry at 292 nm. The dissolution profiles using 1.0% SLS in water at 75 and 100 rpm were found to be nearly the same indicating that 75 rpm provides adequate agitation for dissolution, and there is no need to increase the agitation to 100 rpm (Fig. 3). All products dissolved greater than 80% in 45 min using an agitation of 75 rpm. In most cases, the RSD on six units were slightly less with 100 rpm (1.0, 0.4 Mead Johnson 20 mg, 1.5, 0.7 Mead Johnson 40 mg, 1.4, 0.7 PBI 20 mg, 1.2, 2.3 PBI 40 mg) than with 75 rpm (5.1, 0.4 Mead Johnson 20 mg, 2.4, 1.2 Mead Johnson 40 mg, 1.2, 1.2 PBI 20 mg, 1.8, 1.2 PBI 40 mg).

The dissolution profiles of prazosin HCl capsules were determined using the basket method at 100 rpm. Fig. 4 shows the dissolution profiles of the Pfizer product in several media. Samples were analyzed using the HPLC procedure found in the US Pharmacopeia (1995). An increase in

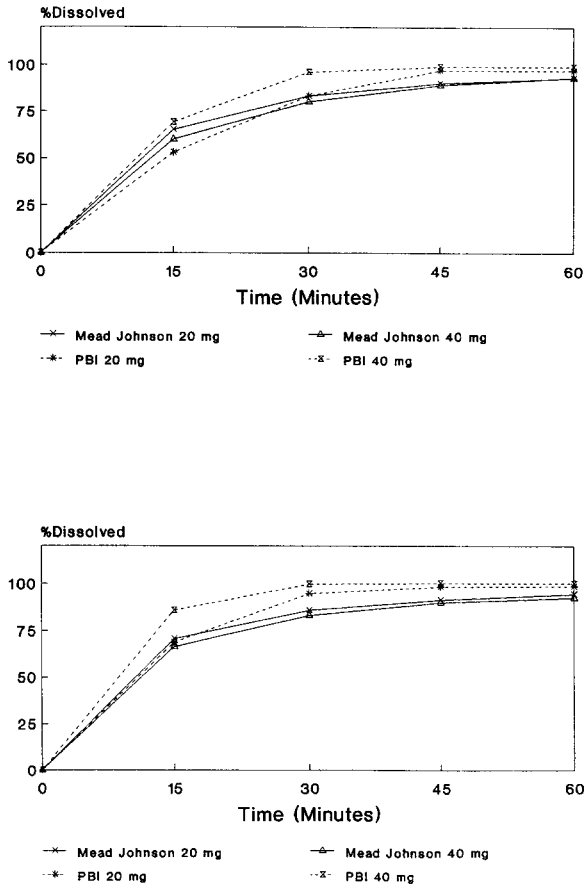


Fig. 3. Megestrol acetate tablets: Dissolution profiles of 20 mg tablets using the paddle method, 75 rpm and 1% SLS in water as the dissolution medium (top) compared to the USP method (paddle method, 100 rpm, 1% SLS in water) (bottom).

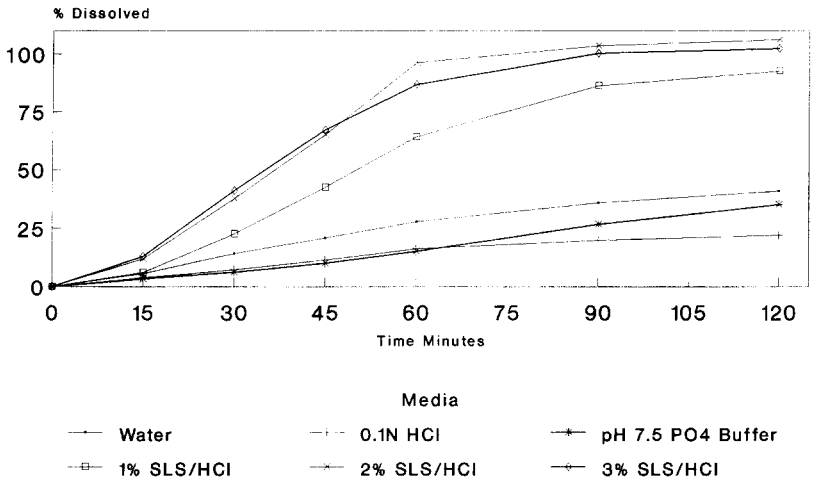


Fig. 4. Prazosin hydrochloride capsules: Dissolution profiles of 5 mg capsules (Pfizer) using the basket method, 100 rpm and 900 ml of media.

the rate and extent of dissolution was seen with an increase in the SLS concentration in most cases. However, the increase was minimal when the SLS concentration was increased from 2.0 to 3.0%. The results of the market survey using the basket method at 100 rpm and 2% SLS in water are shown in Table 1. The results indicate that most of the products dissolve greater than 80% in

Table 1
Dissolution of prazosin HCl capsules (2% SLS in water; 900 ml; basket method; 100 rpm)

Manufacturer	Strength	% dissolved (RSD) in stated minutes				
	(mg)	15	30	45	60	90
Pfizer	1	77.3 (10.4)	97.5 (2.7)	95.7 (0.8)	97.5 (2.1)	102.2 (4.2)
	2	46.3 (10.6)	81.2 (7.3)	98.7 (2.8)	98.7 (3.2)	100.7 (4.2)
	5	43.8 (6.6)	69.8 (10.6)	91.2 (10.9)	97.5 (5.2)	101.0 (4.7)
Lederle	1	12.8 (15.8)	27.8 (19.1)	44.9 (19.5)	56.6 (15.8)	68.7 (14.6)
	2	9.4 (4.3)	22.8 (7.0)	43.3 (12.3)	62.1 (11.7)	87.7 (6.4)
	5	25.1 (10.5)	54.0 (13.8)	85.9 (10.8)	97.3 (9.8)	99.5 (2.2)
American Therapeutics	1	69.8 (15.2)	97.5 (2.4)	98.6 (0.3)	100.3 (0.9)	100.7 (2.0)
	2	71.5 (9.0)	98.0 (1.5)	100.0 (0.8)	99.9 (1.0)	100.0 (0.2)
	5	62.5 (10.2)	75.1 (8.2)	88.8 (7.9)	95.7 (3.3)	96.3 (0.7)
Cord	1	68.4 (5.8)	98.6 (2.1)	104.5 (4.0)	108.2 (4.7)	
	2	44.2 (7.2)	75.7 (6.5)	93.0 (3.4)	95.1 (3.0)	97.4 (3.1)
	5	46.5 (8.1)	77.1 (12.7)	94.9 (7.5)	101.7 (4.0)	102.7 (2.0)
Danbury	1	65.5 (21.8)	89.0 (12.1)	95.8 (4.6)	103.2 (5.0)	111.6 (1.6)
	2	69.7 (17.2)	90.1 (4.4)	94.6 (1.2)	93.8 (2.5)	93.8 (1.8)
	5	55.6 (11.1)	72.2 (4.6)	87.2 (4.3)	96.5 (8.2)	95.9 (3.6)
Purepac	1	54.1 (10.2)	88.1 (1.9)	95.7 (2.3)	96.9 (2.7)	95.8 (2.0)
	2	32.4 (2.6)	61.8 (8.9)	92.0 (4.9)	95.9 (1.0)	96.6 (3.9)
	5	13.1 (1.5)	41.4 (5.2)	66.8 (9.6)	90.1 (8.7)	95.8 (3.4)
Mylan	1	16.7 (2.6)	26.3 (2.5)	36.1 (2.8)	47.8 (4.3)	80.1 (7.0)
	2	9.4 (3.7)	19.1 (4.8)	29.0 (6.0)	42.5 (6.8)	61.0 (7.2)
	5	6.3 (2.9)	13.1 (4.2)	21.5 (5.8)	29.3 (7.1)	46.0(9.3)

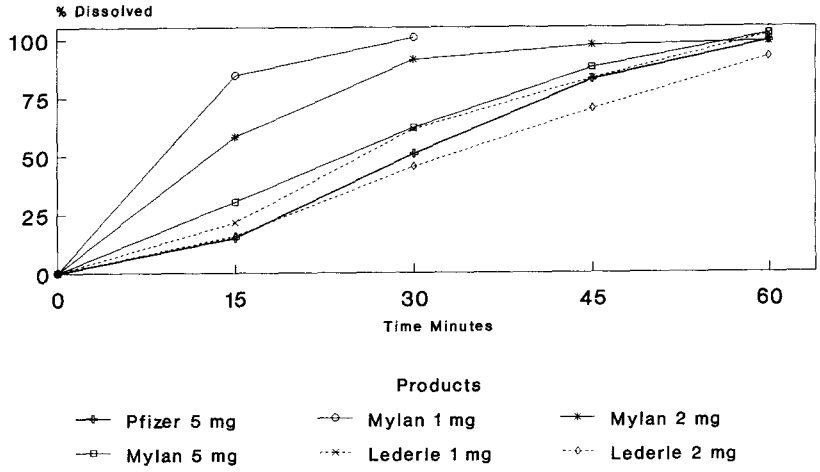


Fig. 5. Prazosin hydrochloride capsules: Dissolution profiles of Pfizer 5 mg capsule, Mylan 1, 2, and 5 mg capsules and Lederle 1 and 2 mg capsules using the basket method, 100 rpm and 900 ml of 2% SLS in 0.1 N HCl.

60 min using the water/SLS system. Lederle's 1 and 2 mg capsules showed wide inter-lot variability in dissolution, ranging between 44 and 87% for the 1 mg capsules, and between 48 and 83% for 2 mg capsules in 60 min. Also, products manufactured by Mylan showed poor dissolution in the water/SLS system, between 29 and 48% in 60 min. These products were tested in a 0.1 N HCl/2% SLS system and showed an increase in dissolution, 86–95% in 60 min (Fig. 5). RSDs at 60 min were 1.4, 1.0, 1.3, 2.4, 5.3, and 3.3 for the Pfizer 5 mg, Mylan 1, 2 and 5 mg, and the Lederle 1 and 2 mg products, respectively. These differences in dissolution profile between water/SLS and acid/SLS media may be attributed to the differences in formulation excipients, rather than the active drug.

Following preliminary studies, the dissolution profile of quinestrol tablets was determined using the paddle method, at 50 rpm in 500 ml of 0.29% SLS in water. Sample aliquots were filtered through a 0.8 μm membrane filter and analyzed using an HPLC assay procedure consisting of a 4.6 mm × 30 cm column packed with octadecylsilane bonded to 3 μm spherical particles, and acetonitrile and water (3:1) as the mobile phase with detection at 205 nm. The results of the preliminary study indicated that the dissolution of quinestrol in water or 0.1 N HCl, was between 5 and 15% in 90 min. Addition of a small amount of SLS in water, 0.1 M (0.29%) resulted in a rapid and complete dissolution of the product, more than 80% in 15 min (Fig. 6). RSDs of 0.5–0.75 were seen for the two runs.

Dissolution profiles of spironolactone (SPIRO) and hydrochlorothiazide (HCTZ) combination products were determined using the paddle method at 50 and 75 rpm in 0.1% SLS in water and 0.1% SLS in 0.1 N HCl. Sample aliquots were filtered through straw filters and analyzed by HPLC using a 3.9 mm × 30 cm column packed with octadecylsilane (Waters μBondapack), and acetonitrile and water (6:4) as the mobile phase with detection at 254 nm. The results show that

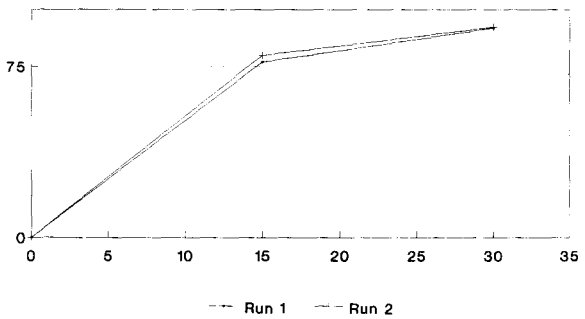
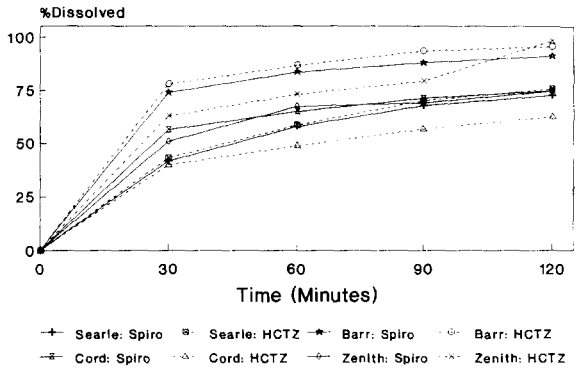


Fig. 6. Quinestrol tablets: Dissolution profiles (two runs) using the paddle method, 50 rpm and 500 ml of 0.29% SLS in water.



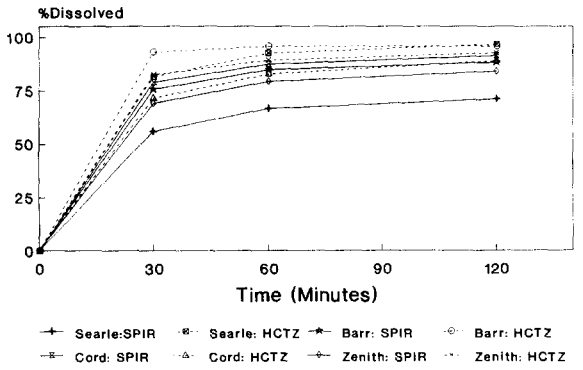


Fig. 7. Spironolactone/hydrochlorothiazide: Dissolution profiles using paddle method, 50 rpm (a) and 75 rpm (b) in water.

the release rate of both components increased with the addition of SLS. The USP has now accepted 0.1% SLS in 0.1 N HCl as the dissolution medium of this product. A comparison of four products is shown in Fig. 7. RSDs ranged from 1.0 to 4.9 at the 60 min time point.

4. Discussion

Orally administered drugs must be in solution, or be solubilized before they can be absorbed. Drugs which are sparingly water-soluble are solubilized in the body by endogenous surfactants such as bile acids, bile salts, lecithin, etc. before the drug molecules are absorbed. In vitro dissolution studies using bile acids/bile salts showed increased dissolution rate profiles with increasing concentrations (Kwan et al., 1977; Shah et al., 1989). However, because of the expense of these natural surfactants, it is not practical to use bile acids, bile salts, and lecithin for routine dissolution testing purposes. Synthetic surfactant, such as sodium lauryl sulfate, can be used as a surrogate in routine dissolution studies. Other surfactant such as Polysorbate 80^{TM} have also been utilized in dissolution studies (Gantt et al., 1961; Singh et al., 1968). Surfactant, when present at levels below the critical micelle concentration, enhances the dissolution rate of sparingly water-soluble drug products, probably by increasing the wetting and lowering the interfacial tension. Using the examples cited here, the systematic procedure developed for determining the dissolution of sparingly water-soluble drug products is illustrated. Initially, the dissolution should be studied in common aqueous media, such as water, buffers, SGF and SIF, under mild agitation conditions. Failing to achieve complete dissolution profiles, increasing amounts of surfactant, such as SLS, should be added to the medium. The lowest amount of surfactant necessary to achieve 75–80% drug release in a reasonable amount of time (60–90 min) was determined to be the adequate concentration of SLS for all further dissolution studies of the product. In all of the cases studied, the rate and extent of the dissolution increased with an increase in the concentration of the surfactant. Higher concentrations of surfactant may be less discriminatory towards the formulation and may also cause problems in automation of the dissolution test procedure due to foaming. Therefore, it is essential to use a minimum amount of SLS in the dissolution test procedure. A time period of 60–90 min was selected as a reasonable time for complete dissolution, based on compendial dissolution requirements for other immediate release dosage forms.

The dissolution methodology for the sparingly water-soluble drug, carbamazepine, using SLS was developed earlier (Shah et al., 1989). The solubility of carbamazepine is significantly increased due to micelle-facilitated solubilization of the drug in dissolution media containing SLS. As a

further extension of this, the mechanism of micelle-facilitated drug solubilization and mathematical models describing the process has been extensively studied to further rationalize the use of surfactants in the dissolution medium (Crison et al., 1995). In a bioequivalence study, four carbamazepine products with different dissolution characteristics in water/SLS, were evaluated for in vivo performance in a four-way cross-over study design in 24 subjects. All four products resulted in different bioavailability profiles. The faster and complete dissolving products had higher bioavailability and the least and incomplete dissolving products had the lowest bioavailability. The C_{max} and AUC parameters were well correlated with in vitro dissolution data, thus giving a good in vitro-in vivo correlation (Meyer et al., 1992). These data support the use of surfactant, SLS, in the dissolution test, at least in the case of carbamazepine.

It is also recognized that the use of surfactant such as SLS may not be the universal answer for all sparingly water-soluble drug products, as observed with the dissolution method development for dicumarol tablets. In the case of dicumarol, the compendial dissolution procedure requires a Tris pH 9.0 buffer. Studies in dissolution media such as water, and water containing SLS showed that, in 2 h, the dissolution increased from 5% in water to about 50% in water containing 4% SLS. On the other hand, dicumarol tablets dissolved about 70% in 2 h in pH 7.4 phosphate buffer and almost 100% in 15 min in pH 9.0 Tris buffer. Similarly, it was found that the SLS had no effect on the rate and extent of dissolution of one brand of conjugated estrogen tablets. This obviously is due to the formulation of conjugated estrogen tablets rather than solubilizing property of the surfactant, since the active ingredient, conjugated estrogens, are water soluble.

Complete dissolution of sparingly water-soluble drug products such as griseofulvin, carbamazepine, medroxyprogesterone acetate, clofibrate, cortisone acetate, danazol, megestrol acetate, prazosin, quinestrol and spironolactone/hydrochlorothiazide has been achieved in 500–1000 ml of the dissolution media, employing mild agitation (paddle 50–75 rpm or basket 50–100 rpm) in a reasonable time period using SLS as a solubilizing agent. These results show that solutions with micellar surfactant concentrations are realistic alternatives to the use of the disintegration test and/or other dissolution media such as hydroalcoholic or organic media which are presently used for sparingly water-soluble drugs. Use of surfactant in the dissolution medium may also be used as an alternative method to the use of a flow-through apparatus for sparingly water-soluble drug products.

5. Conclusion

In conclusion, a systematic approach to study the dissolution profile of sparingly water-soluble drug products using media containing a surfactant such as sodium lauryl sulfate has been described here. This allows the analyst to develop a sensitive and specific dissolution methodology to characterize the in vitro release pattern of sparingly water-soluble drug products. This approach provides a reliable quality control procedure to assure batch-to-batch product consistency, in vitro performance and bioequivalence of the product.

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