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Research Article

INFLUENCE OF pH, SURFACTANTS, AND SINK CONDITION ON DISSOLUTION RATE OF BCS CLASS II DRUGS SERTRALINE HCL AND INDOMETHACIN

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ABSTRACT

Surfactants are commonly used in molecular biology, as well as in the formulation of new and advanced pharmaceutical preparations. Surfactants execute cellular membrane features, emulsification, solubilization, and transport of substances that are otherwise insoluble in living tissues to some extent. In the present study, the influence of pH, surfactant, and sink condition on the Dissolution Rate of BCS class II drugs was studied. BCS class II drugs like Indomethacin and Sertraline HCl can be used to study the effect of pH, sink condition, and surfactants on dissolution rate. The rationale behind this study is that the drug should be dissolved appropriately within the gastrointestinal tract (GIT) to get absorbed into the body system. On the other hand, dissolution has become the most significant parameter to determine drug release behaviour and also to determine product quality. The results showed that by the addition of surfactants, dissolution rate was increased to a greater extent. The comparative study was done at different pH and also at different surfactant concentrations.

Keywords: Dissolution Rate, Surfactants, Indomethacin, Sertraline HCl.

1. INTRODUCTION

For solid oral dosage types, the dissolution test was first implemented in the United States Pharmacopeia (USP) [1]. The dissolution study is particularly important for insoluble or low soluble drugs whose absorption is constrained by the rate of dissolution. The study aims that the drug must be dissolved properly in the gastrointestinal tract (GIT) to be absorbed into the body system. Dissolution, on the other hand, has emerged as the most important parameter in determining drug release performance as well as product quality [2].

Dissolution is characterized as the rate of mass transfer from a solid surface or solid system into the dissolution medium in pharmaceutical terms, and it primarily consists of two steps: drug release from the dosage form and drug transport within the dissolution medium.

The following are some of the factors that affect substance dissolution [3]:

- The drug's physicochemical properties (*e.g.*, Solubility, crystalline forms, particle size, molecular structure, diffusivity in the dissolution medium)
- Features of the formulation (*e.g.,* additives, coatings, manufacturing parameters)
- Dissolution process (volume, surface tension, ionic pressure, viscosity, and pH of the medium, as well as hydrodynamic conditions).

As mentioned in USP, the dissolution medium must provide sink conditions where the mean saturation solubility is at least three times greater than the drug concentration in the dissolution medium [1]. To provide sink conditions, the drug concentration in the dissolution medium should not exceed 15% to 20% of saturation solubility, according to several other sources. In the absence of sink conditions, release kinetics can be unpredictable, and release profiles may be suppressed [4]. The role of formulation changes in the selection of candidate formulations can easily be overshadowed by the generation of drug dissolution data under non-sink conditions. Scientists have used a variety of strategies to increase solubility and ensure sink conditions, including the use of a two-phase solvent system or the addition of organic solvents, the use of a broad dissolution volume,

the use of surfactants, and pH modifications (or their combinations) [5]. It should be noted that any changes made should closely resemble real GI conditions. pH adjustment and surfactant addition appear to be the easiest of these methods, and they can be tailored to mimic the GI fluid environment [6, 7]. Sertraline is an SSRI (selective serotonin reuptake inhibitor) that is used to treat depression, anxiety, and obsessive-compulsive disorder. Sertraline therapy has been linked to sporadic cases of clinically evident acute liver damage and has been linked to intermittent asymptomatic elevations in serum aminotransferase levels [8]. Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) that reduces inflammation, pain, and fever. Indomethacin works by reducing prostaglandin production. Prostaglandins are chemicals produced by the body and are responsible for the fever and pain associated with inflammation. Indomethacin prevents the enzymes that produce prostaglandins (cyclooxygenase 1 and 2), lowering prostaglandin levels. Fever, discomfort, and inflammation are eliminated as a result [9]. The effect of pH, sink state, and surfactants on dissolution rate can be studied using BCS class 2 drugs including Indomethacin and Sertraline HCl.

2. MATERIAL AND METHOD

2.1. Material

Indomethacin, Sertraline HCl, Sodium Lauryl Sulfate (SLS), and Cetyl Trimethyl Ammonium Bromide (CTAB) were obtained from SVKM's NMIMS SPTM Shirpur Campus. Marketed preparations of Indomethacin Capsules and Sertraline HCl Tablets were purchased from a nearby pharmacy and all other chemicals were of reagent grade or above and were used without further purification. Glassware used for each procedure was rinsed thoroughly with double distilled water. These were then dried in a hot air oven at a suitable temperature.

2.2. Reagents and Buffers

De-ionized water: Deionized water was prepared by passing double distilled water through the deionizer distillation assembly while monitoring the conductance of the effluent.

Preparation of 0.1 N hydrochloric acid (pH 1.2): 9.1 ml hydrochloric acid of analytical grade (36%; 11 N) was taken in a litre volumetric flask and the volume was made up to the mark with de-ionized water.

Preparation of Buffer of pH 4.5 (Acetate Buffer): 27.20 g of Sodium Acetate Trihydrate was dissolved in one liter volumetric flask. 800 mL of deionized water was added. Mixed and dissolved. The pH of the solution was maintained at 4.5 with Glacial Acetic Acid.

Preparation of Buffer of pH 6.8 (Phosphate Buffer): 13.872 g of potassium dihydrogen phosphate and 35.084 g of disodium hydrogen phosphate was dissolved in sufficient water to produce 1000 ml. Stored in a cold place till further use.

2.3. Equipments/ Instruments

Analytical balance (Shimadzu, Model AUX220), pH meter (Lab India Model PICO+), UV spectrophotometer (Perkin Elmer, Model Alpha), Sonicator (Oscar, Model Micro Clear 103), Water Purification System (Millipore, Model Elix-10), Dissolution Test Apparatus (Electrolab, Model TDT-08L), Junior Shaker (Scigrnics Bio tech, Model Orbittek- LJE) were used.

2.4. Studies on Saturation Solubility

Saturation solubility of Indomethacin as shown in table 1 and Sertraline HCl as shown in table 2 was determined following a standard approach by stirring an excess amount of the active pharmaceutical ingredient (API) in the respective medium in 100-mL volumetric flasks at room temperature (37°C) for 24 hours. Samples were then filtered through Whatman filter paper 42 pore size. The UV absorbance of the solutions after appropriate dilution was determined at 320 nm and 274 nm for Indomethacin and Sertraline HCl respectively by UV spectrophotometry (UV- Perkin Elmer) and the amount of drug dissolved was calculated using a respective calibration curve [10].

Saturation solubility of Indomethacin and Sertraline HCl was calculated at three different pH (1.2, 4.5, and 6.8). Saturation solubility was calculated using various mediums like 0.5% SLS, 0.1% SLS in deionized water, and 0.1% and 0.5% CTAB in deionized water.

Saturation solubility of Indomethacin and Sertraline HCl was determined and sink condition was calculated accordingly as mentioned in table numbers 2 and 3.

3. RESULTS AND DISCUSSION

3.1. Dissolution study of Indomethacin

Indomethacin is a BCS Class II drug *i.e.,* low solubility, High Permeability and is practically insoluble in water. As a result, modifying the dissolution medium to increase solubility and studying the effect of pH and surfactant on dissolution rate are needed for dissolution studies of indomethacin dosage forms.

To evaluate the effects of surfactants on drug dissolution

rates SLS, or CTAB was dissolved in medium, and an aliquot of the medium was withdrawn at various time intervals and an equivalent amount of fresh medium was added to maintain sink condition. Drug concentrations were measured by UV spectrophotometry (UV- Perkin Elmer).

Blank solution: Blank solution was used during analysis as dissolution media.

3.1.1. Dissolution conditions for Indomethacin Capsule

Apparatus used for dissolution study was Dissolution Test Apparatus (DTA- Electrolab), Dissolution medium was phosphate buffer pH 7.4, 0.1% and 0.5% SLS in Deionized water, deionized water, 0.1% and 0.5% CTAB in Deionized water. Volume was 750 ml, with rotation speed 100 rpm and temperature 37°C±0.5°C [11, 12]. The drug release of Indomethacin Capsule is shown in Table 3.

The dissolution rate was calculated by using different mediums in which dissolution medium as per IP 2007 [13] showed highest drug release, while by increasing concentration of surfactants drug release was also increased to a greater extent.

Table 1: Saturation Solubility and Relative Sink Conditions of Indomethacin

Medium	Saturation solubility (mg/ml)	C_S*/C_D**
Deionized water - Buffer pH 1.2	0.0005	0.000015
Deionized water - Buffer pH 4.5	0.0041	0.000125
Deionized water - Buffer pH 6.8	0.0686	0.00209
0.5% SLS in deionized water	0.407	0.01241
0.1% SLS in deionized water	0.0814	0.00249
0.1% CTAB in deionized water	0.1666	0.005082
0.5% CTAB in deionized water	0.833	0.025411

* C_S: *Saturation solubility of Indomethacin*

** C_D: *Concentration of Indomethacin after complete capsule dissolution in 750ml medium.*

Table 2: Saturation Solubility and Relative Sink Conditions of Sertraline HCl

Medium	Saturation solubility (mg/ml)	C_S*/C_D**
Deionized water - Buffer pH 1.2	3.2	61.185
Deionized water - Buffer pH 4.5	2.08	39.77
Deionized water - Buffer pH 6.8	1.24	23.70

* C_S: *Saturation solubility of Sertraline HCl*

** C_D: *Concentration of Sertraline HCl after complete Tablet dissolution in 900ml medium*

Table 3: Drug Release Profile of Indomethacin Capsule

Dissolution medium(s)	% Drug Release (±SD)					
	Minutes					
	0	5	10	15	20	30
As per IP	0	42.85 ±0.87	77.93 ±1.11	84.42 ±1.07	90.38 ±1.87	94.24 ±1.49
0.1% SLS in Deionized water	0	28.42 ±1.19	46.46 ±1.91	65.45 ±1.17	69.12 ±1.99	74.19 ±1.04
0.5% SLS in Deionized water	0	11.23 ±1.78	42.49 ±1.77	66.90 ±1.89	74.99 ±1.48	81.98 ±1.19
Phosphate Buffer pH 7.4	0	24.48 ±1.14	59.24 ±1.74	65.46 ±1.72	75.92 ±1.46	83.96 ±0.72
0.1% CTAB in Deionized water	0	7.75 ±0.88	48.91 ±1.44	67.70 ±1.37	70.74 ±1.88	70.87 ±1.76
0.5% CTAB in Deionized water	0	4.73 ±1.47	29.60 ±1.86	54.01 ±1.44	61.69 ±0.91	73.58 ±1.44

Each reading is a mean of 6 readings

3.2. Dissolution study of Sertraline HCl

Sertraline hydrochloride belongs to the class of antidepressants and known as selective serotonin reuptake inhibitors (SSRIs). It is poorly water-soluble drug having only 46% oral bioavailability. As a result, modifying the dissolution medium to increase solubility and studying the effect of pH and surfactant on dissolution rate are needed for dissolution studies of Sertraline HCl dosage forms.

To evaluate the effects of surfactants on drug dissolution rates SLS, or CTAB was dissolved in medium, and an aliquot of the medium was withdrawn at various time

intervals and an equivalent amount of fresh medium was added to maintain sink condition. Drug concentrations were measured by UV spectrophotometry (UV- Perkin Elmer).

Blank solution: Blank solution was used during analysis as dissolution media.

3.2.1. Dissolution conditions for Sertraline Tablet

Apparatus used for dissolution study was Dissolution Test Apparatus (DTA- Electrolab), Dissolution medium was acetate buffer pH 4.5,7.4, 0.1% and 0.5% SLS in Deionized water, deionized water, 0.1% and 0.5% CTAB in Deionized water and 01% and 0.5% CTAB in Acetate buffer. Volume was 900 ml, with rotation speed 100 rpm and temperature 37°C±0.5°C [11, 12]. The drug release profile of Sertraline HCl Tablets is shown in Table 4.

The dissolution rate was calculated by using different mediums in which dissolution medium 0.5% SLS in deionized water showed the highest drug release this may be due to increased wettability [14, 15]. The dissolution rate of Sertraline HCl was enhanced significantly by all surfactants with minimal differences. The results show that the dissolution profiles of BCS class II (low soluble) acidic drug are influenced by the class of surfactant added to the dissolution medium. The surfactant CTAB is cationic; it efficiently enhanced the dissolution rate of the acidic drug. Since the solubility of an acidic drug in a medium containing cationic surfactant was increased to a greater extent. Hoping that this comparative study will provide pharmaceutical researchers involved in the development of new dissolution mediums, data to take under consideration for selecting appropriate dissolution conditions [16, 17].

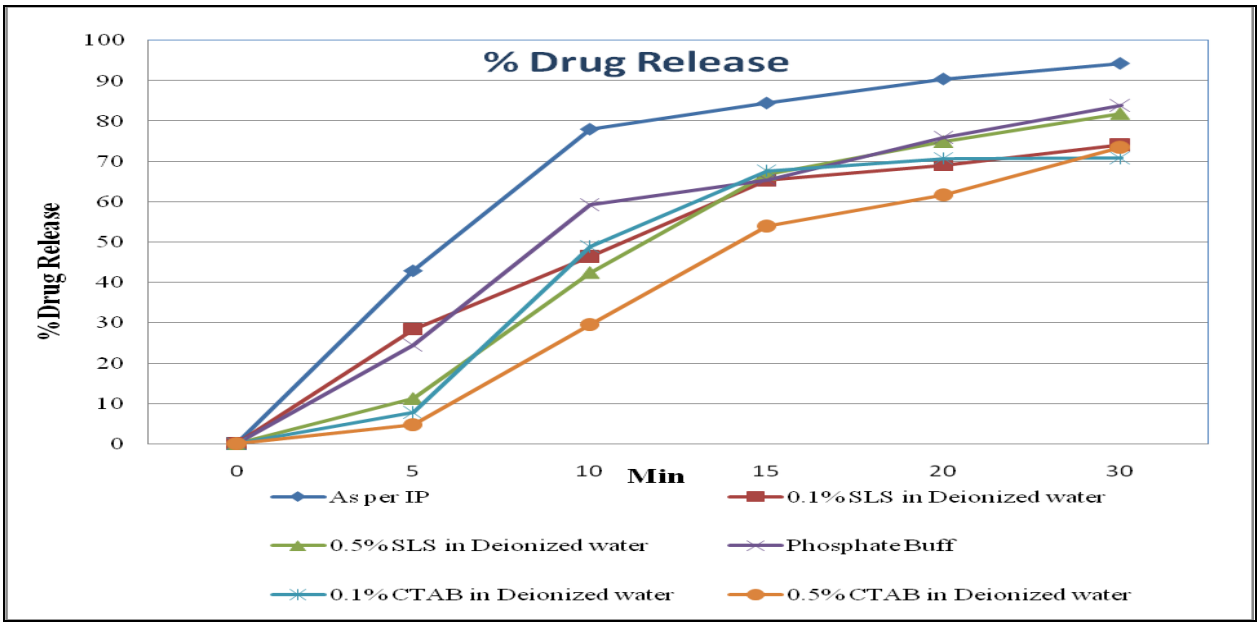

Fig. 1: Drug Release Profile of Indomethacin Capsule

Table 4: Drug Release Profile of Sertraline HCl Tablets

Dissolution medium(s)	% Drug Release (±SD)					
	Minutes					
	0	5	10	15	20	30
As per IP	0	59.85±1.17	68.72±1.19	71.72±1.00	82.83±1.11	92.90±0.97
0.1% CTAB in Deionized water	0	44.08±1.87	65.00±1.11	65.45±1.74	69.12±1.72	74.19±1.84
0.5% CTAB in Deionized water	0	73.77±1.83	81.74±0.74	84.68±1.47	82.00±1.63	86.47±1.32
Deionized water	0	44.60±1.99	68.60±0.97	73.44±1.81	73.70±1.58	76.26±1.24
0.1% CTAB in acetate buffer	0	44.08± 0.84	65.92±1.43	74.59±1.31	74.98±1.94	78.36±1.27
0.5% CTAB in acetate buffer	0	11.20±1.74	42.40±1.97	66.90±1.97	74.88±1.33	81.90±1.74
0.1% SLS in Deionized water	0	28.40±1.08	46.44±1.44	65.38±1.42	69.10±1.29	74.10±1.33
0.5% SLS in Deionized water	0	63.23±1.17	81.05±1.07	86.66±1.84	96.30±1.72	96.60±1.68

**Each reading is a mean of 6 readings*

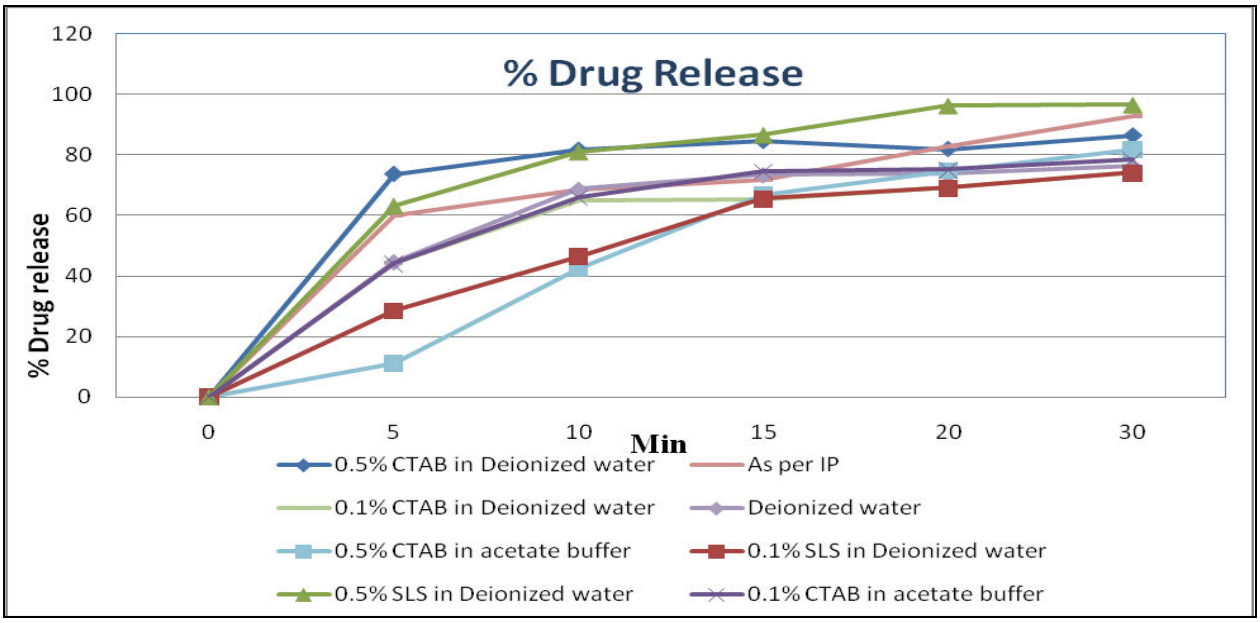

Fig. 2: Drug Release Profile of Sertraline HCl Tablets

4. SUMMARY

Dissolution test was initially introduced in United States pharmacopeia (USP) for solid oral dosage forms. The dissolution study is mainly important for insoluble drugs or low soluble drugs where absorption is dissolution rate limited. The aim of present work was to study the influence of pH, surfactant and sink condition on Dissolution rate of BCS class II drugs. BCS class II drugs like Indomethacin and Sertraline HCl can be used to study effect of pH, sink condition and surfactants on dissolution rate. The rationale behind this study is that the drug should be dissolved appropriately within gastrointestinal tract (GIT) in order to get absorbed into body system. On the other hand,dissolution has become most significant parameter to determine drug release behaviour and also to determine product quality. The results showed that by addition of surfactants dissolution rate was increased to a greater extent. Comparative study was done at different pH and also at different surfactant concentrations.

5. CONCLUSION

These results show that the dissolution profiles of BCS class II (low soluble) acidic drug are influenced by the class of surfactant added to the dissolution medium. The surfactant CTAB is cationic in nature; it efficiently enhanced the dissolution rate of acidic drug. Since the solubility of acidic drug in medium containing cationic surfactant were increased to a greater extent. Hoping that this comparative study will provide pharmaceutical researchers involved in the development of new dissolution mediums, a data to take under consideration for selecting appropriate dissolution conditions.

6. ACKNOWLEDGEMENTS

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Conflict of interest

There are no conflicts of interest.

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