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Research Article

DISSOLUTION ENHANCEMENT OF SEROQUEL BY SOLID DISPERSION TECHNIQUES

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ABSTRACT

Objective: Seroquel is an antipsychotic drug with plasma half-life of 6 hrs and poor oral bioavailability (9%) due to extensive first-pass metabolism. A present work is an attempt to improve oral bioavailability of seroquel by solid dispersions (SDs) (to improve the aqueous solubility and dissolution rate) so as to facilitate faster onset of action. Seroquel is a biopharmaceutical classification system Class II drug having low solubility (1.28 µg/ml).

Methods: In the present investigation, an attempt was made to prepare SD with water-soluble carriers like polyethylene glycol (PEG 6000) PEG 6000 and PEG 4000. The SDs were prepared by melting method and physical mixing method by using PEG 6000 and PEG 4000 in the ratio 1:1, 1:3 and 1:5 respectfully. The prepared dispersions were evaluated for their physicochemical and dissolution characteristics. All the dispersions were easy to prepare, and the powder mass obtained in various formulations were free flowing under dry conditions. Physicochemical properties of the products were characterized by Fourier infrared spectroscopy which reveals that there is no interaction between drug and polymer. *In vitro* dissolution profiles of Seroquel formulations of physical mixtures (PMs) and melting methods were studied using Lab India Disso 2000 dissolution apparatus employing paddle method. 500 ml of 6.2 phosphate buffer was used as dissolution medium maintained at 37±0.50°C, and the stirrer rotation was kept at 50 rpm. Aliquots were withdrawn at different time intervals and measured for the absorbance for Seroquel at 244 nm using ultra violet-visible spectrophotometer with a reference to suitably constructed standard plot.

Results and Discussions: Mixture of drug:PEG 6000 in (1:3) ratio prepared by melting method gives the highest drug release (93.55%) than PM (88.12%) and pure drug (39.75%) in 60 minutes. The dissolution of all the preparation follows Higuchi order kinetics.

Conclusion: It is concluded that in melting method, due to the fineness, amorphous state of the drug, particle size reduction and absence of aggregation, dissolution rate increases but in PMs only a marginal increase in dissolution rate because the size reduction process is not effective.

Keywords: Dissolution, Solid dispersion, Seroquel.

INTRODUCTION

The term "solid dispersion (SD)" has been utilized usually with a view to enhance oral bioavailability and solubility of poorly water-soluble drugs [1], which remains one of the most challenging aspects of drug development. The pharmaceutical industry is experimenting with various techniques for improving the solubility of the drug oral administration. The techniques used for improving the solubility characteristics of a drug can be very broadly classified as either physical or chemical processes [2].

The methods include particle size reduction by micronization using either a ball mill [3], fluidized energy micronization [4], ultrasonic size reduction techniques [5], or by making a nanosuspension [6-10]. Other methods include the use of polymorphic or pseudo polymorphic forms [11], complexations [12,13], and the use of surfactants [14]. The use of pH adjustment, salt formation [15], use of solubilizing agents [16], nanotechnology [17,18], and SDs [19] can also be considered. Most of these techniques have disadvantages and suffer from limitations like size reduction by micronization, form surface charges which show poor flow property [20]. Some methods give products that have improved solubility but the solubility decreases over time, or the methods are complicated and expensive.

These problems require better technologies in processing, new technologies in processing new drug delivery systems, and this led to the development of solid disperse systems. SD technology is the science of dispersing one or more active ingredients in an inert matrix in the solid state so as to achieve increased dissolution rate, sustained release of drugs, altered solid state properties, and enhanced release of drugs. In 1961, Sekiguchi and obi first introduced the concept of SDs to improve the bioavailability of poorly water-soluble drugs. They demonstrated that the eutectic mixture of sulfathiazole and the physiologically inert water-soluble carrier urea exhibited higher absorption and excretion after oral administration when compared with sulphathiazole alone. The improved drug dissolution rate from SDs is explained by the reduced particle size, reduced agglomeration, changes in the physical state of the drug, increased surface area and wet ability, and higher degree of porosity [20]. SD is a useful method to disperse drugs in the molecular state in a carrier matrix [21,22]. Various methods have been reported for the preparation of SD such as physical mixture (PM), kneading method, spray drying, solvent wetting, and modified solvent evaporation method [23]. Most of these methods are amenable only to research laboratory set up, with the exception of spray drying, which can be scaled up industrially [24]. SDs by spray drying technique have been reported for a wide variety of poorly aqueous soluble drug such as glibenclamide [25], curcumin [26], albendazole [27], tolbutamide [28], loperamide [29].

Seroquel is a psychotropic agent belonging to a chemical class of dibenzothiazepine derivatives, used for the treatment of schizophrenia and bipolar disorder. It is a white to off-white crystalline powder with molecular weight of 883.11. Seroquel is moderately soluble in water-soluble in N,N-dimethylformamide, glacial acetic acid, sparingly soluble in methanol. The drug exhibits low bioavailability related to its poor water solubility. The Seroquel is a Class II compound, i.e., water-insoluble, lipophilic, and highly permeable according to biopharmaceutical classification system. In this study, polyethylene glycol 6000 (PEG 6000) and PEG 4000 were selected in different ratios (1:1, 1:3 and 1:5), and SD was prepared by the method of solvent evaporation [30,31].

METHODS

Seroquel was received as a gift sample from Alkem Laboratories Limited, India. PEG 6000 from Central Drug House (P) Ltd., New Delhi, India. PEG 4000 from Himedia Laboratories Limited, Mumbai. Potassium dihydrogen phosphate procured from Finar Chemical Ltd., Ahmedabad India. Sodium hydroxide from Merck Ltd., Mumbai.

Pre-formulation studies

Bulk density (D_b)

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve #20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. From this, the bulk density is calculated according to the formula mentioned below. It is expressed in g/ml and is given by $D_b=M/V_b$, Where, M is the mass of powder and V_b is the bulk volume of the powder.

Tapped density (D_t)

It is the ratio of total mass of the powder to the tapped volume of the powder. The volume was measured by tapping the powder for 750 times (Macro scientific works, India) and the tapped volume was noted. Tapping was continued until the difference between successive volumes was <2%. It is expressed in g/mL and is given by $D_t=M/V_t$, Where, M is the mass of powder and V_t is the tapped volume of the powder.

Angle of repose (θ)

The frictional forces in a loose powder blend were measured by the angle of repose (θ). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

$\tan(\theta) = h/r$

$\theta=\tan^{-1}(h/r)$

Where, θ is the angle of repose, h is the height in cm, and r is the radius in cm.

The powder blend was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed. Care was taken to see that the powder particles slip and roll over each other through the sides of the funnel.

Carr's index (I) % compressibility
It indicates powder flow properties. It is expressed in percentage and is given by,

$I=[(D_t-D_b)/D_t]\times100$

Where, D_t is the tapped density of the powder and D_b is the bulk density of the powder.

Hausner ratio
Hausner ratio is an indirect index of ease of the powder flow.

It is calculated by the following formula:

$\text{Hausner ratio}=D_t/D_b$

Where, D_t is the tapped density, D_b is the bulk density.

Lower Hausner ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Spectroscopic study

Spectroscopy study result given in Table 2.

Preparation of SDs of seroquel

Water soluble carrier used: PEG 6000, PEG 4000 (Table 2)

Preparation of SD:

1. Melting or fusion method - PEG 6000, PEG 4000
2. Physical mixing method - PEG 6000, PEG 4000.

Melting or fusion method

Accurately weighed polymers and **S**eroquel were taken in a China dish and are directly heated until they melt. Then, the melted mixture was then cooled, solidified rapidly by immersing vessel in an ice bath. The mass obtained by this method was dried in desiccators. Then, the product was crushed, pulverized, and sieved through mesh no.80 and stored in desiccators.

Preparation of PMs

PM was prepared by thoroughly mixing accurately weighed quantities of Seroquel and the polymer in a mortar. The powders were then sifted through 80 no meshes and stored in desiccators. Different mixtures of drug:polymers (SDs) which were prepared in the following ratios:

Compatibility study

The drug excipient compatibility study was performed by subjecting the drug excipient blend to Fourier transform infrared (FT-IR) analysis (Elico SL-159).

RESULTS

Evaluation of SDs for seroquel

Yeild

Yeild % is in Table-4.

Table 1: Physicochemical properties of pure drug (micromeritic study)

Parameters	Pure drug	Melting method	PM
Bulk density	0.240 g/ml	0.52 g/ml	0.23 g/ml
Tapped density	0.304 g/ml	0.547 g/ml	0.34 g/ml
Compressibility index	24.23	7.56	18.64
Angle of repose	24.56°C	26°C	29°C
Hausner's ratio	1.311	1.08	1.24

PM: Physical mixtures

Table 2: Maximum wavelength in solvents

Solvent	Maximum wavelength (in nm)
6.2 phosphate buffer	244
Distilled water	247

Table 3: Formulations of seroquel SD

Sl. no	Formulation code	Name of the polymer	Drug: polymer	Followed method
1	F1	PEG 6000	1:1	Melting method
2	F2	PEG 6000	1:3	Melting method
3	F3	PEG 6000	1:5	Melting method
4	F4	PEG 4000	1:1	Melting method
5	F5	PEG 4000	1:3	Melting method
6	F6	PEG 4000	1:5	Melting method
7	F7	PEG 6000	1:1	Physical method
8	F8	PEG 6000	1:3	Physical method
9	F9	PEG 6000	1:5	Physical method
10	F10	PEG 4000	1:1	Physical method
11	F11	PEG 4000	1:3	Physical method
12	F12	PEG 4000	1:5	Physical method

PEG: Polyethylene glycol

Estimation of seroquel content of SD

The quantities of 100 mg SD was accurately weighed and dissolved in distilled water. Then, the volume was made up to the mark and further diluted suitably with water and the absorbance was measured at 244 nm against blank. Then, the drug content was calculated using calibration curve and the results are given in Table 4.

FT-IR study of pure drug and final formulation

For final formulation (F2), PEG 6000 and Seroquel the pellets were prepared using potassium bromide for FT-IR study. The pellets were subjected to FT-IR instrument Elico SL-159, FT-IR spectrometer, spectrum 1000 Germany for the collection of IR spectra which are illustrated in Figs. 1-5. It represents the IR graphs.

***In vitro* dissolution study**

Dissolution parameters:

Apparatus: USP XXVI Apparatus-II (Paddle type)

Dissolution medium: 500 ml of water

RPM: 100

Temperature: 37±0.50 c

Sample collection volume: 2 ml

Replacement: 2 ml of respective medium at 37±0.50 c

Sampling interval: 0, 5, 15, 30, 45, 60 minutes.

DISCUSSION

Organoleptic characteristics of pure drug (Seroquel) show that the drug is white colored, odorless and crystalline in nature. The spectroscopy study using ultraviolet-visible spectrophotometer of pure drug with a different medium like 0.1N HCL and distilled water showed that the maximum wavelength was found to be 244 mm and 247 nm. *In vitro* dissolution studies of pure drug (Seroquel) were carried out with water using paddle at 100 rpm which shows that 39.75% drug release in 60 minutes. SD of Seroquel was prepared using water-soluble polymers such as polyethylene glycol (PEG 6000) and (PEG 4000) with an attempt to increase the dissolution rate of drug, which is a practically insoluble drug (BSC-II). Various formulations of Seroquel SDs were prepared in the ratio of (drug:polymer) 1:1, 1:3, 1:5 with the melting method and PM method (Table 3). All the dispersion was easy to prepare and the powder mass obtained in various formulations were found to be free flowing under dry conditions (Table 1). The drug content was estimated in the prepared dispersion and found to be uniform. All the polymers with different methods used for the preparation of SD have some direct effect on the solubility which reveals that increase in the dissolution of Seroquel. With melting method, the increase in the dissolution rate is probably due to the fineness and amorphous state of the drug, particle size reduction and absence of aggregation. Whereas PM of the drug and polymer produces only marginal increases in the

Table 4: Percentage drug content and % yield of formulations

Sl. no	Formulation code	Name of the polymer	Ratio of drug: polymer	Yeild (in %)	Drug content (in %)
1	F1	PEG 6000	1:1	56.97	74
2	F2	PEG 6000	1:3	78.23	96.67
3	F3	PEG 6000	1:5	49.76	26.71
4	F4	PEG 4000	1:1	62.02	63.79
5	F5	PEG 4000	1:3	64.24	38.62
6	F6	PEG 4000	1:5	63.11	23.27
7	F7	PEG 6000	1:1	68.52	41.65
8	F8	PEG 6000	1:3	68.02	50.23
9	F9	PEG 6000	1:5	62.04	35.61
10	F10	PEG 4000	1:1	46.42	65.62
11	F11	PEG 4000	1:3	53.67	32.72
12	F12	PEG 4000	1:5	47.78	26.11

PEG: Polyethylene glycol

Table 5: Formulations having R^2 values

Formulation code	Zero order	First order	Higuchi order	Hixon crowell order
F1	0.528	0.650	0.775	0.613
F2	0.568	0.759	0.905	0.667
F3	0.611	0.780	0.838	0.734
F4	0.527	0.618	0.768	0.576
F5	0.614	0.836	0.857	0.776
F6	0.637	0.854	0.876	0.792
F7	0.658	0.868	0.885	0.838
F8	0.539	0.766	0.802	0.718
F9	0.478	0.615	0.749	0.577
F10	0.679	0.828	0.842	0.786
F11	0.622	0.789	0.853	0.728
F12	0.606	0.735	0.851	0.697

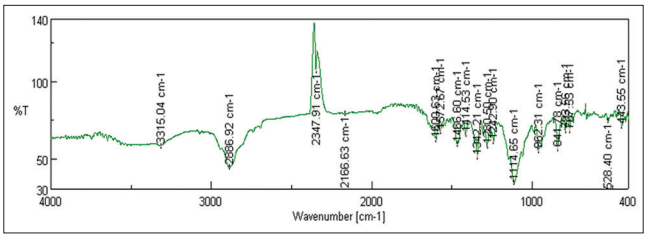

Fig. 1: Melting method

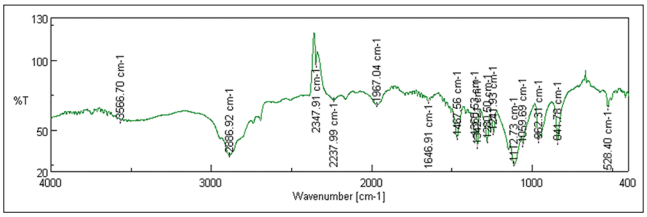

Fig. 2: Polyethylene glycol 6000

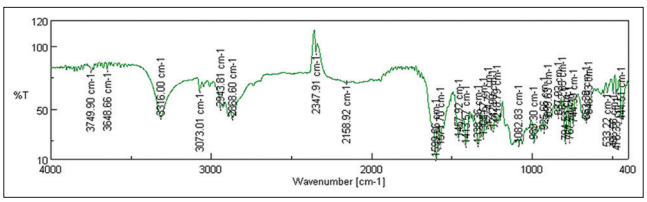

Fig. 3: Physical mixure

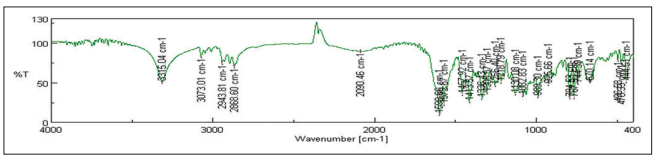

Fig. 4: Seroquel

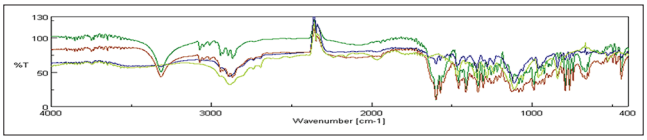

Fig. 5: Overlay

dissolution rate because the size reduction process is not effective. The dissolution rate of Seroquel in SD was strongly dependent on the relative concentration of the drug:polymer ratio. Among the various solid mixtures prepared maximum improvement in dissolution rate of Seroquel was observed with 1:3 (drug:PEG 6000). The dissolution rates increased with the increment in polymer proportion up to the drug:polymer in 1:3 and then decreased may be due to the distortion of molecular dispersion structure, which leaves an insoluble base particle and increased accumulation of polymer in the bulk to cause a saturation by which further solubility of drug is retarded. It was observed that the dispersions with PEG 6000 (F2) showed highest dissolution rates compared with the PEG 4000 (F5).

PEG 6000 >PEG 4000.

Among the various solid mixtures prepared maximum improvement in dissolution rate of Seroquel was observed with 1:2 (drug:PEG 6000). The order of the increment in the dissolution rate of dispersion was melting method>physical mixing. The dissolution of Seroquel from SD systems followed Higuchi order kinetics (Table 5).

CONCLUSION

All the SD prepared was found to be fine and free flowing. The drug content was estimated in the prepared SD were found to be uniform. The dissolution rate of Seroquel is strongly dependent on the concentration of drug:polymer ratio and methods by which is done. Melting method was found to be better than physical mixing. 1:3 ratio of drug:polymer was found to be best. The order of increment in dissolution rate was

PEG 6000 > PEG 4000 > Pure drug

1:3 ratio of drug:polymer was found to be the best. The melting method was found to be better than physical mixing.

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