International Journal of Drug Delivery 4 (2012) 492-497

http://www.arjournals.org/index.php/ijdd/index

Original Research Article

ISSN: 0975-0215

An approach to determine crystalline content of Granisetron in transdermal patches using X-ray diffraction technique

Pavan K V*[1], Arthanareeswari M[1], Ravikiran A[1], Kamaraj P[1], Praveen Ch[1], Rajendar B[1]

*Corresponding author:

Pavan K V

[1]Department of Chemistry, SRM University, SRM Nagar, Kattankulathur-603203,Kancheepuram District, Tamilnadu, India

Abstract

Granisetron is a drug used to treat nausea and vomiting after chemotherapy. Crystallization of drug is always a major concern in the transdermal drug delivery system. In view of consistent biopharmaceutical performance, monitoring and controlling the crystallization during product development and shelf life is very important. The need was felt to have an accurate method for determination of crystallinity in transdermal patches.

The present study is about development and validation of a quantitative X-ray diffraction method for the determination of the extent of crystallization of the drug in transdermal formulation of Granisetron. Specimens of different physically spiked concentrations were carefully prepared accurately by weighing and distributing crystalline active pharmaceutical ingredient (API) onto placebo liner patches, pasted on Silicon low background sample holder (diameter of 24.5 mm, made up of Si crystal). All the specimens thus prepared were scanned using optimized instrumental parameters while enabling specimen rotation during the diffraction analysis to ensure homogeneous exposure to the incident X-rays.

Using this novel approach, limit of detection of about 2% (weight/weight) was achieved for the drug crystalline content. The validation results indicated excellent linearity between diffracted peaks response (net area) and spiked concentration of crystalline drug with a correlation value of 0.9991, Accuracy with the recovery values well within the range of 95% to 110% and precision having RSD values lesser that 2% (at limit of quantification). The method can be adopted by any quality control lab for its intended purpose.

Keywords: Crystallinity, Amorphous, X-Ray Diffraction, Placebo, Transdermal.

Introduction

Transdermal drug delivery systems (TDS) are polymeric patches containing dissolved or dispersed drug that can deliver a drug at relatively constant rate to human body. TDS offers several important advantages over traditional approaches, which includes longer duration of action resulting in reduced dosing frequency, improved bioavailability and flexibility of terminating the drug administration by simply removing the patch from the skin and improved patient compliance and comfort via non-invasive, painless and simple application [1]. Some of the disadvantages of TDS are like local irritation at the site of application, itching, local edema and erythema can be caused by the drug, the adhesive, or other excipients in the patch formulation [2, 3]. One of the most successful advancements in TDS, is crystal reservoir technology has resulted in smaller patches with a more controlled and sustained drug release. This efficient drug delivery technology may minimize the amount of active pharmaceutical ingredient (API) required. This efficient way of releasing a drug is based on the over saturation of an adhesive polymer with medication, thus forcing a partial crystallization of the drug. The presence of both molecular solute and solid crystal forms allow for a considerably higher concentration and consistent supply of drug in each patch. As the skin absorbs the molecular solute, crystals re-dissolve to maintain maximum thermodynamic activity at the site of contact [4-6].

Drug crystallization has been reported in many Transdermal matrix systems [7-10] as well as other types of drug delivery systems [11-17]. An illustration was represented in Figure-1. The presence of crystals in a transdermal patch might significantly affect the permeation of the drug through the patch, if dissolution of drug is the rate controlling step in the mass transfer process compared to the diffusion rate. Examples of decreased bioavailability were reported in the crystallization of Nifedipine co-

precipitated with Polyvinylpyrrolidine (PVP) [14], Indomethacin dispersed in polyacrylate adhesives stored over a period of a period of six months at room temperature with moderate relative humidity [1,10]. In the present work, Granisetron transdermal patches, contains API in amorphous state were considered. Drug is often used in amorphous state especially in transdermal patches because the amorphous solid state has a higher dissolution rate, higher chemical reactivity and higher water vapor sorption than the crystalline state. This is due to increased free volume, molecular mobility and the enthalpy of the amorphous state [18]. These properties can have benefits. For example, rapid formation of solution is sometimes desirable to achieve a high efficacy and a rapid absorption rate that may increase the bioavailability of the drug [19].

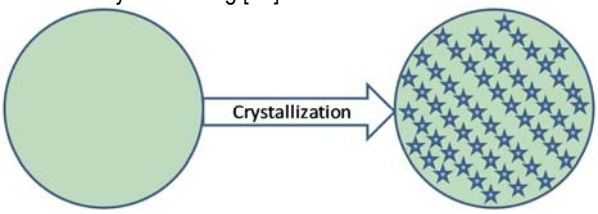

Figure 1: An illustration demonstrating crystallization in Transdermal patches.

The biopharmaceutical classification system (BCS) divides drugs into four classes depending on drug product in vitro dissolution properties and in vivo bioavailability [20]. Poor dissolution of drug may be the rate limiting step to absorption and hence to bioavailability of drug. More than 40% of potent new APIs suffer from poor solubility and thus pharmaceutical companies are interested in the amorphous state [21]. So, determination of degree of Crystallinity in a converted amorphous transdermal patch is crucial and plays a key role in the stability studies and controlling the factors affecting the conversion. To the best of our knowledge, none of the reported procedures describe method for the determination of degree of crystallinity in converted transdermal patches. Thus, an attempt was made to develop and validated a new method for the determination of degree of crystallinity in converted transdermal patches. Granisetron Transdermal patches are used for this exertion.

The API used for the study is Granisetron Hydrochloride. Intravenous chemotherapy in patients suffering from cancer requires the co-administration of several medications to prevent severe side effects that are enough to deter patients from continuing therapy [22]. Granisetron Hydrochloride is a selective 5-HT_3 receptor antagonist. It is also an effective and post-operative nausea and vomiting in adults and children. The chemical name of Granisetron Hydrochloride (Molecular structure represented in Figure-2) is 1-Methyl-N-[(3-endo)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-1H-indazole-3-carboxamide hydrochloride. Molecular Formula is C18H24N4O.HCl; C18H25ClN4O and molecular weight is 348.87 [23].

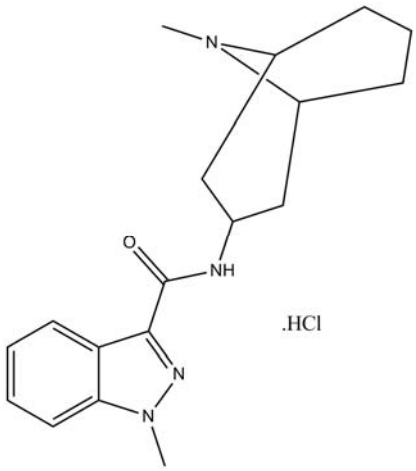

Figure 2: Molecular structure of Granisetron HCl.

Materials and Methods

Materials

Crystalline Granisetron Hydrochloride API, Amorphous Granisetron Patch (6.99cm^2) and Placebo patch (6.99cm^2). Silicon low background sample holder (External diameter 51.5 mm, internal diameter 24.5 mm, made-up of Si crystal) sample holders were used for this study.

Methods

Specimen preparation (Spiked standards)

High Sensitive Microbalance (Mettler Toledo XP2U, Maximum 2.1g and Minimum-1μg) was used to prepare all the required spiked concentrations. The different Spiked Concentrations were prepared by accurately weighing required amount of crystalline API of Granisetron Hydrochloride followed by spreading uniformly on to the Silicon Low background sample holder and pasted Placebo patch after removing liner. In the Transdermal Patches formulation, each patch of area 6.99cm^2 contains 3.5mg of the API. So the required concentrations were prepared accordingly. The weights of the API taken for the required concentration preparations are listed in the below Table 1.

Powder X-ray diffraction analysis

The diffraction patterns of the spiked concentrations and of crystalline API were collected using Bruker Axs-D8 ADVANCE with Cu Anode and Lynx Eye detector. Each sample was scanned from 13 to 22 2theta, with step size of 0.01 and time per step of 3 seconds. The Instrument was operated at 40kV Generator Voltage and 40mA Generator current. Variable divergent slit and Anti scattering slit were used of V20mm; Nickel filter was used in secondary beam path as K-beta filter. Eva Software was used for data processing and evaluation.

Table 1: Preparation of spiked concentrations: actual weights of crystalline API transferred and corresponding crystallity value calculated against 3.5mg of the API per patch.

Sl. No	Weight of Crystalline API transferred (mg)	Actual concentration (% Weight/Weight)
1	0.075	2.1
2	0.145	4.1
3	0.271	7.6
4	0.357	10.1
5	0.529	14.9
6	0.707	19.9

Results and discussions

The diffraction pattern of crystalline API and overlaid diffracted patterns of spiked concentrations are represented in Figure-3 and Figure-4 respectively. The sum of net area values (in cps x degree) of characteristic diffraction peaks (at about 13.9 , 14.3 , 15.3 , 16.1 , 17.3 , 18.2 and 18.9 2theta) of crystalline API for different spiked concentration were listed in Table-1. A linear graph was obtained by plotting concentrations versus net area. The linear equation was supported by high correlation value (R^2 value is 0.9991).

Validation results

The limit of detection (LOD) for was determined by signal to noise ratio and the value found to be about 2.0% (weight/weight) for crystalline API in patches. To check accuracy and precision of the method, the spiked concentrations were prepared at the concentrations of 2% and 5% (weight/weight) in triplicate, the same were analyzed and data evaluated, the results are compiled in Table-3 and Table-4 along with the mean and percent relative standard deviation (% RSD). The overlaid diffractograms at Limit of Detection Level and Limit of Quantification Level are shown in the Figure-5 and Figure-6 respectively. It was observed that the calculated wt% values predicted by X-ray diffraction are in good agreement with the actual wt%. The low %RSD indicates that the method is precise and reproducible

Table 2: Prepared spiked concentrations and sum of the net area values

Sl.No	Concentration of the spiked standard (weight/weight)	Sum of the net area values of the characteristic peaks of crystalline API (cps x degree)
1	2.1	0.65
2	4.0	0.913
3	7.7	1.494
4	10.1	1.786
5	14.9	2.593
6	19.9	3.29

Table 3: Accuracy and reproducibility in quantitative measurement at limit of detection (LOD)

Actual wt% (calculated from weight of API spiked)	Calculated wt%	Net Area (Cps x deg)	%Recovery
2.11	2.08	0.635	101
2.19	1.99	0.622	110
1.93	1.77	0.588	109
Mean	1.95	0.615	
Standard deviation	0.162	0.024	
%RSD	8.3	3.9	

Table 4: Accuracy and reproducibility in quantitative measurement at limit of quantification (LOQ) Level

Actual wt% (calculated from weight of API spiked)	Calculated wt%	Net Area (Cps x deg)	%Recovery
5.13	5.06	1.081	101
5.93	5.15	1.095	96
5.08	4.97	1.067	102
Mean	5.06	1.081	
Standard deviation	0.094	0.014	
%RSD	1.8	1.3	

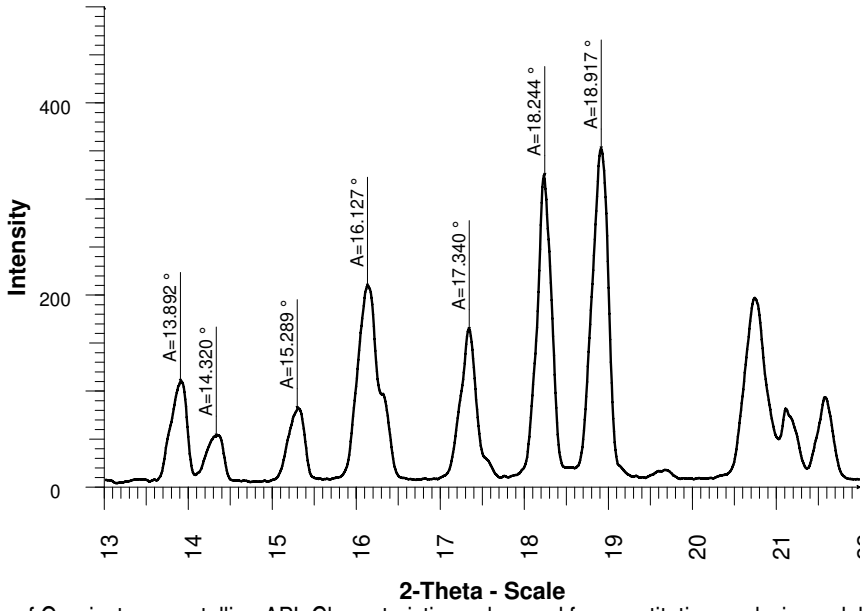

Figure 3: Diffraction pattern of Granisetron crystalline API: Characteristic peaks used for quantitative analysis are labeled with respective peak position values.

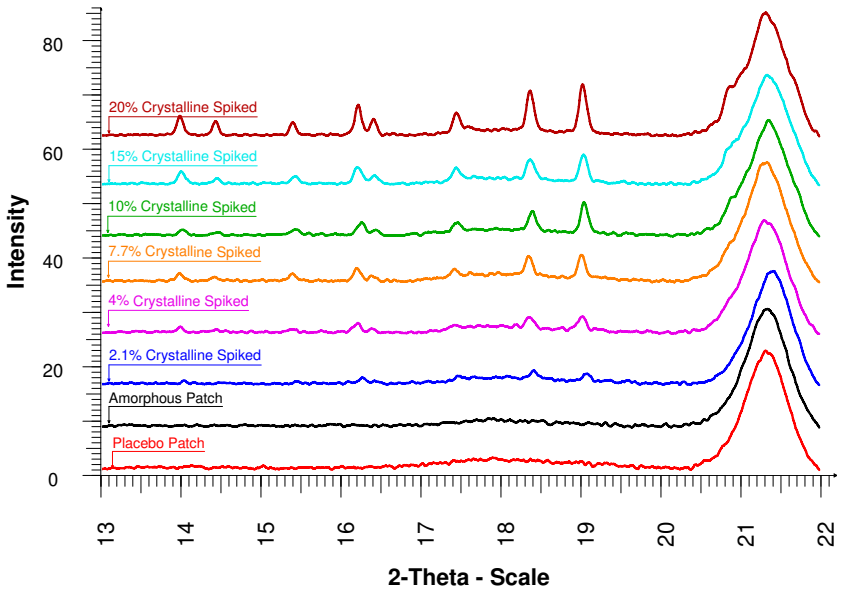

Figure 4: Overlaid diffraction pattern of different spiked concentrations of crystalline API in Placebo patch: Incremental change can be seen at the characteristic peak positions.

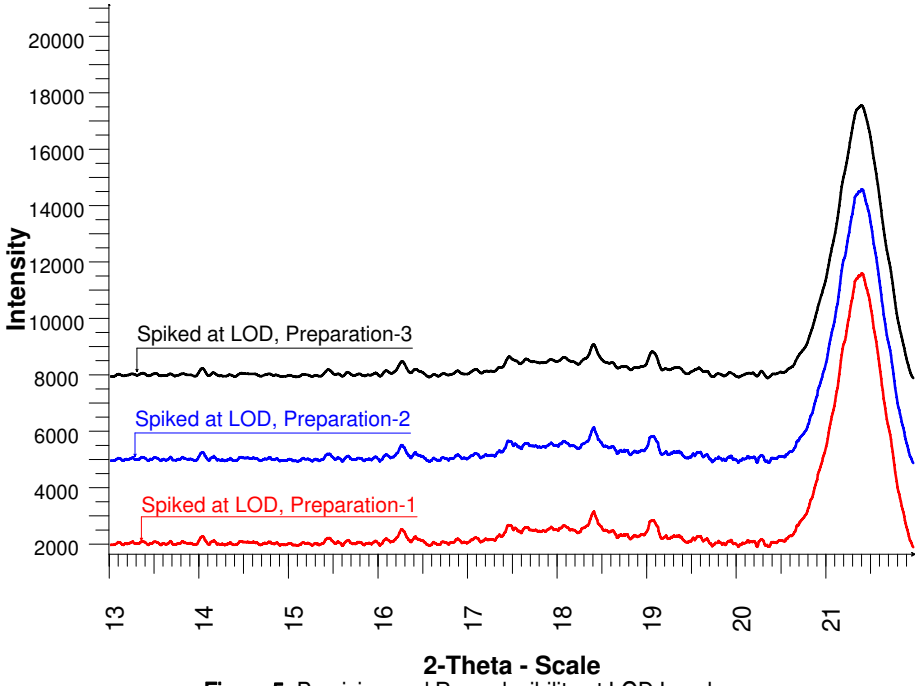

Figure 5: Precision and Reproducibility at LOD Level

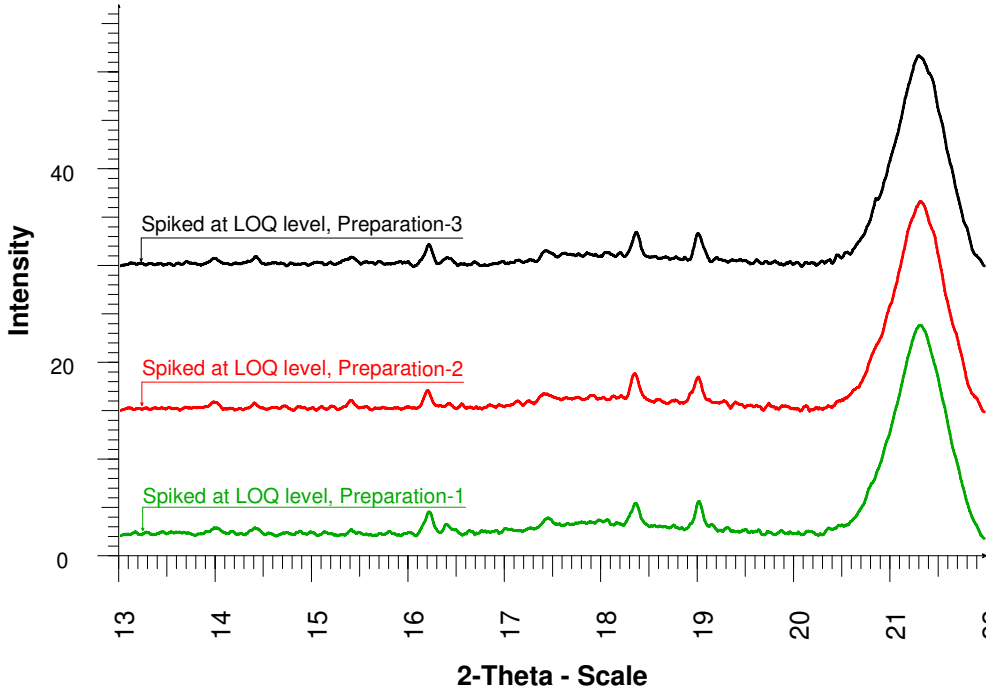

Figure 6: Precision and Reproducibility at LOQ Level

Conclusion

In this work, we have reported a method to determine degree of crystallinity in converted amorphous transdermal Patches using X-ray diffraction technique. The results obtained in this study clearly demonstrate the potential of X-ray diffraction technique, which proves to be relatively simpler and better technique for the crystallinity determination in transdermal patches. The method can be adopted by any quality control laboratory for its intended purpose without any major changes

Acknowledgements

The author wish to thank Department of Chemistry, SRM University for their excellent guidance and support.

References

[1]. Robinson JR, Lee HL. In: Controlled Drug Delivery Fundamentals and applications. Marcel Dekker, New York, 1987; 2nd Ed:524-552.

[2]. Aquil M, Sultana Y, Ali A. Matrix type Transdermal systems of metoprolol tartrate: In vitro characterization. Acta Pharm. 2003;53(2):199-125.

[3]. Sing J, Tripathi KP, Sakia TR. Effect of penetration enhancers on the in vitro transport of ephedrine through rat skin and human epidermis from matrix based transdermal formulation. Drug Dev. Ind. Pharm. 1993;19(13):1623-1628.

[4]. Valenta C, Almasi-Szabo I. Invitro diffusion studies of ketoprofen transdermal therapeutic system. Drug Dev.Ind. Pharm. 1995;21(15):1799-1805.

[5]. Shin S, Lee H. Enhanced transdermal delivery of triprolidine from the ethylene-vinyl acetate matrix. Eur. J. Pharm. Biopharm. 2002;54(3):161-164.

[6]. Sweetman SC. Martindale – The Complete Drug Reference, 34th edi, Pharmaceutical Press, London (U.K), 2005; 34th Ed:1055.

[7]. [Miranda J, Sablotsky S, WIPO Patent # WO 95/18603, Noven Pharmaceuticals (1995).

[8]. Miranda, J. and Sablotsky, S., US Patent PCT US95/00022, Noven Pharmaceuticals (1995).

[9]. Ma X, Taw J, Chiang CM. Inhibition of crystallization of steroid drug in transdermal patches. Proc. Int Symp controlled Release Bioact Mater. 1995;22:712-713.

[10]. Ma X, Taw J, Chiang CM. Control of drug crystallization in transdermal matrix system. Int.J.Pharm. 1996;142(1):115-119.

[11]. Simonelli AP, Mehta SC, Higuchi WI, Inhibition of sulfathiazole crystal growth by polyvinylpyrrolidone. J Pharm Sci. 1970;59(5):633–638.

[12]. Ziller KH, Rupprecht HH. Control of Crystal growth in Drug Suspensions. Pharm.Ind. 1990;52(8):1017-1022.

[13]. Sugimoto I, Kuchiki A, Nakagawa H. Polyvinylpyrrolidone Excipients for Pharmaceuticals. Chem.Pharm.Bull. 1981;29:6.

[14]. Yoshioka M, Hancock BC, Zografi G. Inhibition of indomethacin Crystallization in poly(vinylpyrrolidone) coprecipitates. J.Pharm.Sci. 1995;84(8):983-986.

[15]. Uekama K, Ikegamiu K, Wang Z, Horiuchi Y. Hirayama F. Inhibitory effect of 2-hydroxypropyl-beta-cyclodextrine on crystal growth of nifidipine during storage: superior oral bioavailability compared with polyvinylpyrrolidone k-30. J.Pharm.Pharmacol. 1992;44 (2):73-78.

[16]. Toddywala R, Ulman K, Walters P, Chien YW. Effect of physicochemical properties of adhesive-type transdermal drug delivery systems (a-TDD) containing silicone-based pressure-sensitive adhesives. Int.J Pharm. 1991;76 (1-2):77-89.

[17]. Stefano F, Bioali F. Inhibition of crystallization in Transdermal devices. Int, I Symp.Control.Rel.Bioact.Mater. 1997;24:703-704.

[18]. Hancock BC, Zografi G. Characteristics and significance of the amorphous state in pharmaceutical systems, J. Pharm. Sci. 1997; 86(1):1-12.

[19]. Singhal D. Curatolo W. Drug polymorphism and dosage form design: a practical perspective, Adv. Drug Del. Rev. 2004;56 (3):335-347.

[20]. [20]. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: The correlation of in vitro drug product dissolution and in vivo bioavailability, Pharm. Res. 1995:12(3)413-420.

[21]. Verma RK, Garg S. Current status of drug delivery technologies and future directions, Pharm. Tech. On-line 2011;25(2):1-14.

[22]. Kirchner V, Aapro M, Terrey JP, Alberto P. Eur. J. Cancer. 1997;33(10):1605-10

[23]. Aapro M. Granisetron an update on its clinical use in management of nausea and vomiting. Oncologist. 2004; 9(6):673-686.