Full Length Research Paper

Dissolution rate enhancement of bicalutamide by adsorption process

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The aim of the present research was to enhance the dissolution rate of poorly water soluble drug, bicalutamide by adsorption process. Bicalutamide is an antiandrogen agent used in the treatment of prostate cancer. To improve the dissolution rate of the drug, hydrophilic carrier like povidone K30 and adsorbent like magnesium aluminum silicate were used as dissolution rate enhancers. Granules of bicalutamide were prepared by wet granulation technique by using magnesium aluminum silicate and povidone K 30 either alone or in combination at different concentrations. The granules were evaluated for packing and compression properties. The granules were compressed into tablets, and different tableting parameters were investigated. The dissolution profile of the tablets was also evaluated and compared with the marketed product. From the dissolution profile, it was observed that the carrier ratio of 3:1 of magnesium aluminum silicate to povidone K 30 exhibited higher dissolution rate than the other formulations.

Key words: Bicalutamide, magnesium aluminum silicate, adsorption, povidone K 30.

INTRODUCTION

Presently, product development scientists working in the areas of drug discovery, preformulation and formulation studies are using various solubilization techniques for solving solubility problems related to the drug in their daily work. The solubility and dissolution rate of poorly water soluble drug can be altered in many ways, such as modification of drug crystal forms, addition of co-solvents, micronisation, solubilisation by surfactants, addition of adsorbents, solid dispersion, complexation with cyclodextrins (CD), etc. (Vippagunta et al., 2002; Chiou and Riegelman, 1971; Leuner and Dressman, 2005; Kinoshita et al., 2002;

Toshiro, 2006). Some of these techniques make use of organic solvents which are expensive and hazardous to our environment. Among all the possibilities, selective adsorption on insoluble carriers is one technique that can be applied to increase the dissolution rate dramatically. In the adsorption process, a highly active adsorbent such as inorganic clays like bentonite, magnesium aluminum silicate etc. enhance the dissolution rate of poorly water-soluble drugs by maintaining the concentration gradient at its maximum. The two reasons suggested for the rapid release of drugs from the surface of clays are the weak

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Figure 1. Chemical structure of bicalutamide.

physical bonding between the adsorbate and the adsorbent, hydration and swelling of the clay in the aqueous media (Monkhouse and Lach, 1972).

Poor water-solubility of drugs is associated with slow drug absorption, leading eventually to inadequate and variable bioavailability. Bicalutamide comes under this class of poor water soluble drug for which its solubility is to be enhanced. The chemical name of the bicalutamide is (+/-)-N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-propanamide (Figure 1). It is a non-steroidal antiandrogen used for the treatment of prostate cancer (Michael et al., 2009). It competitively inhibits the action of androgens by binding to cytosol androgen receptors in the target tissue (Fuzheng, 2006). Bicalutamide blocks the growth stimulating effect of androgens on prostate cancer. The aqueous solubility of bicalutamide is low (5 µg/ml) when determined by *in vitro* method at pH 7 and 37°C (Srikanth et al., 2010a). Since the pK_a of bicalutamide is 12, hence the solubility of the drug is low at physiological pH. Thus, it is important to enhance the solubility and dissolution rate of bicalutamide to improve its oral bioavailability (Srikanth et al., 2010b).

The process of adsorption has numerous applications of diverse nature in the pharmaceutical field in formulation of various dosage forms. Surface method is one of the methods used to reduce the drug particle size by increasing the surface area available to the dissolution medium. Active adsorbents can enhance the dissolution rate of the poorly water soluble drugs by maintaining the concentration gradient at its maximum. The main reasons for the rapid release of drugs from the surface of the adsorbents are, the weak physical bonding between the adsorbate and the adsorbent, and hydration and swelling of the adsorbent in the aqueous medium (Manish et al., 2001; Harish and Madan, 2007).

In the present investigation, bicalutamide formulations were prepared by wet granulation technique using different combinational ratios of magnesium aluminum

silicate and povidone K 30. Out of these concentrations, best ratio was selected based upon their efficiency to enhance the dissolution rate of the drug.

MATERIALS AND METHODS

Bicalutamide (BC) was a generous gift sample from Dr. Reddy's Laboratories Ltd (Hyderabad, India). Povidone K 30 and sodium lauryl sulphate were obtained as gift samples from Orchid Health Care (Chennai, India). Magnesium aluminum silicate was obtained as gift samples from Unichem Laboratories Ltd (Goa, India). Bicalutamide commercially available tablet (Tabi, 50 mg, Manufactured by Dr. Reddy's Laboratories Ltd, Mumbai, India) was purchased from local market. All other reagents and chemicals used were of analytical grade.

Preparation of granules and tableting

Required quantities of bicalutamide, magnesium aluminum silicate, povidone and lactose were accurately weighed and were sifted through sieve no. 40 (425 microns) (Table 1). The mixture was granulated with minimum quantity of water. The wet mass was dried in a rapid drier until the loss on drying (LOD) reached less than 2% w/w. Dried granules were passed through sieve no. 20 (850 microns) and were mixed with presifted crospovidone through sieve no. 40. The above granules were lubricated with presifted magnesium stearate through sieve no. 60 (250 microns) and mixed for 3 min. Lubricated granules were evaluated for flow characteristics and were compressed into tablets by using 8-station Rimek compression machine. Compressed tablets were allowed to equilibrate in a dessicator for 24 h before evaluation.

Evaluation of granules

Packing property of the granules

The packing properties were determined by measuring the difference between bulk density (BD) and the tapped density (TD) using standard procedure. In the procedure, a 20 g quantity of granule sample was placed into 250 ml clean, dry measuring cylinder and the volume V_0 occupied by the sample without tapping was determined. An automated tap density tester (model C-TDA2, Campbell Electronics, Mumbai, India) was used for tapping the granules according to US Pharmacopeia (USP, 2006). After 100 taps, the occupied volume, V_{100} was also noted. The bulk and tap densities were calculated from these volumes (V_0 and V_{100}) using the formula: Density = Weight/Volume occupied by sample. The Hausner ratio was determined by dividing TD by BD, and Carr's compressibility index (CI) (Carr, 1965) was determined using Equation 1:

$$CI = \left\{ \left(\frac{TD - BD}{TD} \right) \times 100 \% \right\} \quad (1)$$

Evaluation of tablets

The formulated tablets were evaluated for all the physical parameters. The parameters evaluated include hardness, friability,

Table 1. Formulation of bicalutamide tablets.

Ingredients	F1	F2	F3	F4	F5	F6	F7
Bicalutamide	50	50	50	50	50	50	50
Magnesium aluminum silicate	50	100	150	-	-	-	150
Povidone K 30	-	-	-	50	100	150	50
Avicel PH 200	41	38	35	41	38	35	32
Crospovidone	7.5	10	12.5	7.5	10	12.5	15
Magnesium stearate	1.5	2	2.5	1.5	2	2.5	3
Total Weight (mg)	150	200	250	150	200	250	300

disintegration time and drug content.

Determination of tablet tensile strength (T)

The hardness of ten tablets were determined individually with the Monsanto hardness tester (Brook and Marshall, 1968). The mean values of the fracture loads were recorded.

Disintegration test

The method described in the British Pharmacopoeia (2002) was followed using water maintained at 37°C as the disintegration fluid. Six tablets were used in each determination, which was carried out in triplicate and the mean results reported.

Friability test

The friability test is to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. Ten (10) tablets were weighed initially (w_1), placed in friabilator (Roche) and were allowed to rotate at the speed of 25 rpm for 4 min. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight (w_2) compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The friability (%) was calculated by using Equation 2:

$$\text{Friability (\%)} = (w_1 - w_2) \times 100 / w_1 \quad (2)$$

Drug content

From each batch, 10 tablets were randomly collected and powdered in a glass mortar. Accurately weighed drug equivalent of 50 mg of the powder was transferred into a 100 ml volumetric flask and dissolved in 20 ml of acetonitrile. The drug-acetonitrile solution was extracted with 1% sodium lauryl sulphate (SLS) solution with vigorous shaking on a mechanical shaker for 1 h and filtered into another 100 ml volumetric flask through 0.45 mm millipore nylon filter disc and the filtrate was made up to the mark with 1% SLS solution to obtain 500 µg/ml. 0.5 ml of the above solution was further transferred into 50 ml volumetric flask and was diluted up to the mark with 1% SLS solution to get 5 µg/ml. Absorbance of the obtained solution was measured at 272 nm against blank (1% SLS solution) using a Ultraviolet and visible (UV/Vis) spectrophotometer (Elico SL 210) and the drug content was measured by using pre-

calibrated curve equation ($Y = 0.0527X - 0.0438$). All the above physico-chemical properties were conducted on the existed marketed product 'Tabi' for comparison.

In vitro studies

In vitro studies were performed separately in 900 ml of 1% SLS maintained at $37 \pm 0.5^\circ\text{C}$ using USP XXII type II dissolution rate test apparatus at a stirring speed of 50 rpm which is official in Food and Drug Administration (FDA) dissolution methods. 5 ml aliquots were withdrawn at different time intervals up to one hour and replaced with same volume of drug free fresh dissolution medium so as to maintain sink conditions. The samples were filtered and estimated for the amount of bicalutamide dissolved by measuring the absorbance at 272 nm in ultra violet (UV) spectrophotometer (Elico SL 210). The dissolution experiments were done in triplicate. Dissolution studies were carried out on existed marketed product 'Tabi' in the similar way for comparison of drug release behavior.

RESULTS AND DISCUSSION

Packing and flow properties of the granules

The results (Table 2) showed the packing properties of the granules obtained by wet granulation technique. The results showed that the granules were compressible by tapping. The CI values were between 18 to 24% while the Hausner ratio was between 1.2 to 1.4, indicating that the granules exhibited good flow properties (Rakhi et al., 2008).

Evaluation of the physical parameters of the tablets

The tableting parameters of the formulated tablets are presented in Table 3. All formulated tablets had hardness and friability values in-between 72 to 75 N and 0.2 to 0.5%, respectively. The formulated tablets also disintegrated within 5 min as against the stipulated official time of 15 min in the British Pharmacopoeia (2002). The drug contents for all formulations were > 97%. All the experimental formulations exhibited similar behavior compared

Table 2. Evaluation of the granules.

Formulations	Bulk density (g/ml)	Tapped density (g/ml)	CI	Hausner ratio
F1	0.612	0.695	12	1.14
F2	0.643	0.735	12.5	1.14
F3	0.664	0.772	14	1.16
F4	0.648	0.761	14.8	1.17
F5	0.656	0.756	13.2	1.15
F6	0.697	0.792	12	1.14
F7	0.71	0.816	13	1.15

CI = Compressibility index

Table 3. Tableting parameters.

Formulation	Thickness (mm)	Hardness (N)	% Friability	% Drug content	Disintegration (min)
F1	3.7±0.45	75±0.14	0.24	99.2±0.5	3.2±0.21
F2	3.9±0.32	74±0.22	0.33	98.4±0.2	2.4±0.07
F3	4.1±0.67	72±0.09	0.45	99.1±0.7	3.5±0.03
F4	3.6±0.27	77±0.34	0.19	98.2±0.6	4.5±0.43
F5	3.8±0.54	75±0.59	0.28	101.4±0.8	4.7±0.22
F6	4.0±0.63	73±0.75	0.36	100.3±0.2	4.2±0.39
F7	4.4±0.16	74±0.44	0.31	100.2±0.1	3.9±0.11
Tabi	5.2±0.29	69±0.58	0.49	100.04±0.4	4.9±0.44

with marketed formulation.

Dissolution profiles

The dissolution profiles of bicalutamide from different formulations are shown in Figures 2 to 4. The results showed that the dissolution rate of the drug was greatly influenced by the amount of adsorbate concentration present. Dissolution rate of bicalutamide tablets increased with the presence of magnesium aluminum silicate concentration as shown in Figure 2. It was observed that as the ratio of magnesium aluminum silicate in the formulation increased, the dissolution rate increased correspondingly. From the dissolution data, it was also observed that pure drug released its active content less than 60% at the end of one hour, whereas the physical mixture with higher concentration (1:3) of drug: carrier released about 70% of the drug at the end of one hour. The bicalutamide-magnesium aluminum silicate adsorbates at 1:1, 1:2 and 1:3 (F1, F2 and F3) ratios exhibit 1.5, 1.8 and 2.2 fold increase in sequence after 10 min, 1.4, 1.7 and 1.8 fold increase in sequence after 30 min and 1.5, 1.7 and 1.9 fold increase in sequence after 60 min in the

dissolution rate of the formulations compared with pure drug. Thus, presence of the adsorbate greatly influenced the dissolution rate.

The results of the dissolution data with povidone K 30 (F4, F5 and F6) as the drug to carrier in ratios of 1:1, 1:2 and 1:3 are shown in Figure 3. It was observed that dissolution rate was slightly enhanced by the increased concentration of povidone K 30. According to the results, pure drug released its active content less than 60% at the end of one hour, whereas physical mixture with higher concentration (1:3) of carrier released about 65% its drug content at the end of one hour. However, in case of tablet formulations the dissolution rate was enhanced by increased concentrations of carrier. As shown from the results, the drug released was 76% for F4, 82% for F5 and 85% for F6 at the end of one hour. When compared with adsorbate dissolution results, povidone made formulation had no much influence on the dissolution rate. So further trials were focused based on the formulation F3.

In the present formulation studies, the main target was to improve the dissolution rate to a maximum extent within a short period of time. Even though the drug release was fast and complete in formulation F3, there is

Figure 2. Dissolution profiles of bicalutamide formulations: (□) bicalutamide, (Δ) physical mixture, F1, F2 and F3.

Figure 3. Dissolution profiles of bicalutamide formulations: (◇) bicalutamide, (□) physical mixture, F4, F5 and F6.

a need to further improve the drug release at initial time points (10 to 20 min) to bring about immediate relieve of symptoms. So povidone as third component was incorporated into the existing formulation F3 and treated as F7.

The dissolution data of formulation F7 is presented in Figure 4. It was observed that the dissolution rate was greatly increased by 3 fold by the use of povidone in the formulation F7 causing a burst release at this point. The improvement of the dissolution rate on addition of povidone to the magnesium aluminum silicate may be attributed to its wetting and solubilising effect (Saleh et al., 1998). Dissolution rate as compared to pure drug at 10 min interval has been enhanced a lot and reached 98% within 20 min. Hence, this was considered as the optimized formulation. Marketed formulation 'Tabi' released

65% of the drug by the end of 10 min. From the dissolution profile it was observed that the optimized formulation (F7) enhanced the dissolution rate of bicalutamide greatly compared with marketed formulation Tabi.

Conclusions

Adsorbents play a significant role in the improvement of dissolution characteristics of poorly water soluble drugs. In the present study, the dissolution of bicalutamide has been enhanced by addition of adsorbents like magnesium aluminum silicate, hydrophilic carriers like povidone K 30 and combination of both. From the dissolution data it was concluded that dissolution rate was greatly enhanced in

Figure 4. Dissolution profiles of bicalutamide formulations: (◇) bicalutamide, (□) physical mixture, F6, F7 and Tabi.

the formulation F7 at the ratio 1:3:1 of drug: magnesium aluminum silicate: povidone K30, respectively compared to marketed formulation. Besides being economical, the major advantage of adsorbent based formulations is it avoids the usage of organic solvents which are major constituents in the preparation of conventional formulations. Therefore, the formulation F7 consisting of bicalutamide-magnesium aluminum silicate-povidone K 30 (1:3:1) ratio was considered as the optimum ratio for the formulation and best candidate for further scale up studies which increases the solubility and dissolution rate of the bicalutamide, suggesting a possible enhancement of its oral bioavailability.

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REFERENCES

- British Pharmacopoeia (2002). Monograph on disintegration times of uncoated tablets. Her Majesty's Stationery Office, London. p 237.
- Brook DB, Marshall K (1968). Crushing strength of compressed tablets 1: comparison of testers. *J. Pharm. Sci.* 57:481-484.
- Carr RI (1965). Evaluation of flow properties of solid. *Chem. Eng.* 72:163-168.
- Chiou WL, Riegelman S (1971). Pharmaceutical applications of solid dispersion systems. *J. Pharm. Sci.* 60:1281-1302.
- Fuzheng R, Qiufang J, Yanhui T, Yongjia S, Jialei C, Feng Gao, Cui J (2006). Characteristics of bicalutamide solid dispersions and improvement of dissolution. *Drug Dev. Ind. Pharm.* 32:967-972.
- Harish D, Madan AK (2007). Adsorption in pharmacy: A review. *Drug Dev. Tech.* 7:58-63.
- Kinoshita M, Baba K, Nagayasu A, Yamabe K, Shimooka T, Takeichi Y, Azuma M, Houchi H, Minakuchi K (2002). Improvement of solubility and oral bioavailability of a poorly water soluble drug. *J. Pharm. Sci.* 91(2):362-370.
- Leuner C, Dressman J (2005). Improving drug solubility for oral delivery using solid dispersions. *Eur. J. Pharm. Biopharm.* 50:47-60.
- Manish K, David G, Robin HB, Yin-Chao T (2001). Enhanced drug dissolution and bulk properties of solid dispersions granulated with a surface adsorbent. *Pharm. Dev. Tech.* 6(4):563-572.
- Michael D, Feng L, Charles BD, Duane D, Miller Ram (2009). Micellar Delivery of bicalutamide and embelin for treating prostate cancer. *Pharm. Res.* 26:2081-2092.
- Monkhouse DC, Lach JL (1972). Use of adsorbents in enhancement of drug dissolution I. *J. Pharm. Sci.* 61:1430-1435.
- Rakhi BS, Mobin AT, Mansoor AK (2008). Comparative Evaluation of Flow for Pharmaceutical Powders and Granules. *AAPS Pharm. Sci. Tech.* 9(1):250-258.
- Saleh MA, Abdulhakeem AA, Ahmed GE (1998). Improved dissolution rate of Indomethacin by adsorbents. *Drug Dev. Ind. Pharm.* 24(4):389-394.
- Srikanth MV, Murali Mohan Babu GV, Sreenivasa Rao N, Sunil SA, Ramana murthy KV (2010a). Dissolution rate enhancement of poorly soluble bicalutamide using β -cyclodextrin inclusion complexation. *Int. J. Pharm. Pharm. Sci.* 2(1): 191-198.
- Srikanth MV, Murali mohan babu GV, Sunil SA, Sreenivasa Rao N, Praveen kumar K, Ramana murthy KV (2010b). Studies on the effect of hydrophilic carriers in the dissolution rate enhancement of poorly soluble drug, bicalutamide. *Res. J. Pharm. Tech.* 3(2):1-4.
- Toshiro F (2006). Improvement in solubility of poorly water soluble drug by cogrinding with highly branched cyclic dextrin. *J. Incl. Phenom. Macrocycl. Chem.* 56:61-64.
- US Pharmacopeia (2006) Chapter <616> Bulk Density and Tapped Density. Rockville, MD: USP. p 2638.
- Vippagunta SR, Maul KA, Tallavajhala S, Grant DJW (2002). Solid-State characterization of solid dispersion. *Int. J. Pharm.* 236:111-123.