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Original Research Article

ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF BCS CLASS II DRUG DANAZOL

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ABSTRACT

This study aimed to develop and characterize fast dissolving oral films (FDOFs) of the antiemetic drug Aprepitant to enhance its solubility and dissolution rate, thereby improving its bioavailability and therapeutic efficacy. Aprepitant, a BCS Class II drug, was formulated into FDOFs using different polymer ratios. The films were evaluated for general appearance, thickness, weight, mechanical properties, disintegration time, drug content, and *in-vitro* drug release. The optimized formulation (F7) exhibited excellent transparency, optimal thickness (51±5 µm), and appropriate weight (115±3 mg). It demonstrated the highest folding endurance (245±4 times), shortest disintegration time (36±4 seconds), and rapid drug release (99.65% cumulative release at 10 minutes). The drug release kinetics followed a first-order model (r^2 = 0.999), indicating a concentration-dependent release mechanism. The results confirm that FDOFs of Aprepitant can significantly enhance its solubility and dissolution rate, offering a promising alternative to conventional oral dosage forms for improved patient compliance and efficacy in managing nausea and vomiting.

Key Words: Aprepitant, Fast Dissolving Oral Films (FDOFs), Solubility enhancement Dissolution rate**,** Antiemetic drug

INTRODUCTION

The enhancement of solubility and dissolution rate of poorly water-soluble drugs is a significant challenge in pharmaceutical development. Among the Biopharmaceutical Classification System (BCS) Class II drugs, danazol stands out due to its extremely low aqueous solubility, which leads to poor bioavailability. Danazol, a synthetic androgen and antigonadotropin, is used primarily in the treatment of endometriosis, fibrocystic breast disease, and hereditary angioedema. Despite its therapeutic potential, the clinical efficacy of danazol is often limited by its poor solubility and consequent low oral bioavailability (Akbari *et al.,* 2011).

Danazol is practically insoluble in water (less than 0.001 mg/mL) but exhibits good permeability across biological membranes, which categorizes it as a BCS Class II drug. The primary hurdle in developing an effective oral dosage form of danazol is enhancing its solubility and dissolution rate, which are critical for improving its bioavailability and therapeutic efficacy (Dixit & Amiji, 2012).

Various techniques have been explored to enhance the solubility and dissolution rate of poorly soluble drugs like danazol. These techniques include the use of solubilizing excipients, particle size reduction, solid dispersions, complexation with cyclodextrins, and the use of lipid-based formulations. Among these, solid dispersion has emerged as

a promising approach due to its ability to enhance the dissolution rate significantly by improving the wettability and dispersibility of the drug (Patel *et al.,* 2010).

Solid dispersion involves dispersing the drug in a carrier matrix, which can be either hydrophilic or hydrophobic. The choice of carrier plays a crucial role in the solubility enhancement of the drug. Hydrophilic carriers such as polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), and hydroxypropyl methylcellulose (HPMC) have been extensively used due to their ability to enhance the dissolution rate of poorly soluble drugs by improving wettability and reducing crystallinity (Vemula & Lagishetty, 2010).

Recent studies have demonstrated the effectiveness of various solid dispersion techniques in enhancing the solubility and dissolution rate of danazol. For instance, one study reported a significant increase in the dissolution rate of danazol when formulated with PEG 6000 as the carrier using the solvent evaporation method (Akiladevi & Basak, 2010). Another approach involved the use of PVP K30 as a carrier, which also showed a marked improvement in the solubility and dissolution rate of danazol (Chokshi *et al.,* 2007).

This study aims to evaluate different solid dispersion methods to enhance the solubility and dissolution rate of danazol, thereby improving its bioavailability. By comparing the effectiveness of various carriers and techniques, this research seeks to identify the most efficient method for developing a more effective oral dosage form of danazol. Enhanced solubility and dissolution rate of danazol not only improve its therapeutic efficacy but also pave the way for its successful application in clinical settings (Shah *et al.,* 2007; Vasconcelos *et al.,* 2007; Serajuddin, 1999).

MATERIALS AND METHODS

Preparation of solid dispersions

Optimization of Drug: Polymer Ratio

In order to optimize the drug is to polymer ratio, we have prepared the matrices by both i.e. physical mixture method and solid dispersion method (Aggarwal *et al.,* 2010).

Physical mixture method: All the ingredients were weighed accurately and passed through sieve no. 85 in order to obtain powder of fine particle size with narrow size distribution. The physical mixture of drug with carrier PEG 4000 was prepared in different concentration by slightly grinding the drug and carrier in mortar for 2 min. The drug: PEG 4000 ratio which was taken as 1:0.5, 1:1, and 1:1.5 respectively. Then the resultant powder was passed through sieve no 60 and was stored in desiccator for 2-6 hrs to carry out further analysis. The prepared physical mixture was subjected to dissolution study.

Preparation of solid dispersion of Danazol

For the preparation of Danazol-PEG 4000 solid dispersion by conventional method, PVP K-90 was weighed and melted at 58°C (±1°C) and a measured amount of Danazol was added and stirred. After solidification at room temperature, sample was pulverized with use of a pestle and mortar and sieved through a 400-mm mesh. 6mg of Danazol-PEG 4000 powder (containing 200mg of

Danazol and 300mg of PEG 4000) was used for further investigations.

Preparation of physical mixture

For the preparation of Danazol-PEG 4000 physical mixture were weighed and mixed for 5 min with use of a pestle and mortar and sieved through a 400mm mesh. Danazol-PEG 4000 powder mixture was used for further tablet preparation.

Evaluation of dispersion granules

Percentage drug content

For the determination of Danazol content, dispersion granules equivalent to 5mg of Danazol, were weighed and extracted with 10 ml of methanol by mechanical mixing. The solution was filtered through 0.45µ membrane filter, and the filtered solutions were suitably diluted and analyzed for Danazol at 285nm using a validated UV spectrophotometric method (Seth, 2011).

Formulation of fast dissolving tablets

Preparation of tablets of Danazol

Fast dissolving tablets of Danazol (200mg) were prepared by direct compression method after incorporating different superdisintegrants such as, sodium starch glycolate and croscarmellose sodium (Ac-Di-Sol) 10, 15, and 20 mg for optimization of best formulation. The ingredients given below were weighed and mixed in geometric progression in a dry and clean mortar. Then the ingredients were passed through mesh 60. Magnesium stearate (6mg) as lubricant and talc (5 mg) as glidant and Microcrystalline cellulose as bulking agent (79, 74 and 69 mg) were added in a final step and mixed, this blend was subjected to analysis of pre-compression parameters which included angle of repose, bulk density, tap density, carr's index and hausner's ratio. The Blend was compressed on 8 mm (diameter) fat punches on a 'Rimek mini press 16 station rotary compression machine. Six formulations of Danazol granules were prepared and each formulation contained one of the three disintegrant in different concentration. Each tablet weighing 600 mg was obtained. Composition of tablets is mentioned in Table no 1.

Evaluation of Precompression Parameter

Angle of repose (θ): The frictional forces in a loose powder or granules can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane (Fu *et al.,* 2004).

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

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

The granules were allowed to flow through the funnel fixed to a stand at definit height. The angle of repose was then calculated by measuring the height and radius of the heap of granules formed

Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. Accurately weighed amount of granules taken in a 50 ml capacity measuring cylinder was tapped for 100 times on a plane hard wooden surface and estimated the LBD and TBD, calculated by using following formulas.

$$LBD\ (Loose\ Bulk\ Density) = \frac{Mass\ of\ Powder}{Volume\ of\ Packing}$$

$$TBD\ (Tapped\ Bulk\ Density) = \frac{Mass\ of\ Powder}{Tapped\ volume\ of\ Packing}$$

Compressibility index: Percent compressibility of powder mix was determined by Carr's compressibility index, calculated by using following formula:-

$$\textbf{Compressibility index} = \frac{TBD - LBD}{TBD}$$

Hausners ratio: It is determined by comparing tapped density to the bulk density by using following equation:-

Housner's ratio = Tapped bulk density/loose Bulk density

Hausner's ratio value <1.25 shows better flow properties

Evaluation of post compression Parameter

Shape and colour of tablets

Uncoated tablets were examined under a lens for the shape of the tablet and colour was observed by keeping the tablets in light.

Thickness test

Three tablets were picked from each formulation randomly and thickness was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using dial-caliper (Mitutoyo, Japan) (Bi *et al.,* 1999).

Weight variation test

Twenty tablets were selected randomly from each formulation and average weight was determined. The tablets were weighed individually and compared with average weight. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The following percentage deviation in weight variation is allowed (Table No.7.5) (Ahmed *et al.,* 2006).

Hardness test

The hardness of tablet was measured by Pfizer hardness tester and results were expressed in Kg/cm^2 (Cirri *et al.,* 2005).

Friability test

For this, 20 tablets were taken from each formulation and the friability was determined using Roche friabilator. The equipment was run for 4min at 25 revolutions per minute. The tablets were taken out, dedusted and reweighted and % friability was calculated. The friability was determined as the mass loss in percent according to Equation:-

$$\%Friability = (Loss\ in\ weight/Initial\ weight) \times 100$$

The test complies if tablets not loss more than 1% of their weight

Uniformity of drug content:

The test is mandatory for tablets with 10 mg or less weight of active ingredient. Ten randomly selected tablets from each formulation (F1 to F6) were finely powdered and Drug equivalent to 10 mg of drug dissolved in 10 ml phosphate buffer pH 6.8) sonicate it for 20 minutes, till the entire drug leached out from complex, then the solution was filtered through whatman filter paper No. 41. From this Solution take 1 ml and Diluted up to 100 ml with Phosphate buffer pH 6.8 and the drug content was determined spectrophotometrically at 285.0 nm.

Dissolution rate studies

The prepared tablets were evaluated for *in vitro* drug release. The drug release studies were carried out using USP XXII paddle type Dissolution test apparatus. The dissolution study was carried out in 900 ml dissolution medium which was stirred at 75 rpm maintained at 37±0.2°C. The scheme of using the simulated fluids at different timing was as follows:

A tablet placed in dissolution media (900 ml) at 37±0.2°C. Samples were withdrawn at different time interval and compensated with same amount of fresh dissolution medium. Volume of sample withdrawn was made up to 10ml Phosphate buffer pH 6.8. The samples withdrawn were assayed spectrophotometrically at 285 nm using UV visible spectrophotometer. The release of drug was calculated with the help of standard curve of Danazol (Ostrander, 2003).

RESULTS AND DISCUSSION

The present study focused on enhancing the solubility and dissolution rate of the poorly water-soluble drug danazol using solid dispersion techniques with PEG 4000 as the carrier. The effectiveness of different drug-to-carrier ratios was evaluated through various parameters, including percentage cumulative drug release, drug content, pre-compression, and post-compression characteristics.

Table 2 illustrates the percentage cumulative drug release of the physical mixture of danazol with PEG 4000 at different ratios (1:1, 1:2, 1:3) over various time intervals. The results indicate a significant improvement in the drug release profile when danazol was combined with PEG 4000. The physical mixtures demonstrated enhanced dissolution rates compared to the pure drug. Specifically, the 1:3 ratio exhibited the highest percentage cumulative drug release at each time interval, reaching 39.98% after 240 minutes, compared to only 8.12% for the pure drug. This enhancement is attributed to the increased wettability and reduced crystallinity of danazol when dispersed in PEG 4000.

The results of drug content analysis in dispersion granules are presented in Table 3. The label claim for danazol was 200 mg, and the amount found was 197.45 mg, corresponding to a label claim percentage of 98.72%. The standard deviation (S.D.) and the percentage relative standard deviation (% RSD) were 0.015 and 0.023, respectively, indicating high precision and accuracy in the drug content measurement.

Table 4 shows the pre-compressional parameters of danazol formulations, including loose bulk density, tapped bulk density, Carr's Index, and Hausner's Ratio. The values obtained indicate good flow properties for all formulations. Formulation F2 exhibited the best flow characteristics with a Carr's Index of 18.750% and a Hausner's Ratio of 1.231. These values suggest that the powders have acceptable compressibility and flow properties, which are crucial for uniform tablet production.

Table 5 provides the post-compression parameters for all formulations, such as hardness, friability, weight variation, thickness, drug content, and disintegration time. All formulations met the standard requirements for hardness and friability, indicating that the tablets possess adequate mechanical strength. The drug content ranged

from 97.89% to 99.45%, demonstrating uniform distribution of danazol within the tablets. Disintegration times varied between formulations, with F4 showing the shortest time of 60 seconds, suggesting faster disintegration and potential for improved drug release.

Regression analysis data for batch F4, shown in Table 6, reveal that the drug release kinetics followed both zero-order and first-order models with R^2 values of 0.980 and 0.983, respectively. The higher R^2 value for the first-order model indicates that the release of danazol from the solid dispersion system is concentration-dependent.

Table 1: Composition of Danazol fast dissolving tablets

Ingredients (mg)	Formulation code					
	F1	F2	F3	F4	F5	F6
Equivalent to 200 mg Danazol	500	500	500	500	500	500
Sodium Starch glycolate	10	15	20	-	-	-
Croscarmellose sodium	_	_	_	10	15	20
Microcrystalline cellulose	79	74	69	79	74	69
Talc	5	5	5	5	5	5
Magnesium stearate	6	6	6	6	6	6
Total weight	600	600	600	600	600	600

Table 2: Percentage cumulative drug release of physical mixture

F. Code	Time interval (min.)	Percentage cumulative drug release of physical mixture*			
		Drug (Danazole): PEG 4000			
		F1	F2	F3	
1	0	1:1	1:2	1:3	Pure Drug
2	30	8.98	13.32	15.56	1.12
3	60	11.25	25.65	29.98	3.32
4	120	16.65	32.12	34.45	5.65
5	240	25.56	35.69	39.98	8.12

Table 3: Results of drug content of Danazole in dispersion granules

Label claim (mg)	Amount found*	Label claim (%)	S.D.	% RSD
200	197.45	98.72	0.015	0.023

Table 4: Results of pre-compressional parameters of danazole

Formulation code	Parameters			
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio
F1	0.38	0.49	22.449	1.289
F2	0.39	0.48	18.750	1.231
F3	0.36	0.46	21.739	1.278
F4	0.35	0.48	27.083	1.371
F5	0.34	0.45	24.444	1.324
F6	0.36	0.47	23.404	1.306

Table 5: Results of post-compression parameters of all formulations

F. Code	Hardness test (kg/cm^2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)	Disintegration Time (sec.)
F1	2.46	0.689	Passes	1.12	98.85	85±5
F2	2.45	0.652	Passes	1.14	98.81	82±3
F3	2.36	0.587	Passes	1.16	99.21	80±2
F4	2.41	0.652	Passes	1.15	99.45	60±4
F5	2.42	0.654	Passes	1.13	99.10	89±2
F6	2.43	0.521	Passes	1.12	97.89	92±3

Table 6: Regression analysis data

Batch	Zero Order	First Order
	R^2	R^2
F4	0.980	0.983

CONCLUSION

The study successfully demonstrates the potential of solid dispersion techniques with PEG 4000 to enhance the solubility and dissolution rate of danazol. The improved drug release profile, confirmed through cumulative drug release studies, suggests that higher ratios of PEG 4000 significantly enhance the dissolution rate of danazol. The pre-compression and post-compression parameters indicate that the formulations possess acceptable flow properties and mechanical strength, essential for consistent tablet production. The drug content analysis confirms the uniformity and accuracy of the drug within the formulations.

In conclusion, the use of PEG 4000 as a carrier in solid dispersion significantly improves the solubility and dissolution rate of danazol, potentially leading to enhanced bioavailability and therapeutic efficacy. This approach can be further optimized and scaled up for commercial production, providing a viable solution to the challenges associated with the poor water solubility of danazol.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

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