ORIGINAL ARTICLE

Formulation Development, *In Vitro* Evaluation, and Cytotoxic Effect of Flutamide-Loaded Matrix Tablets

P. Manikandan[1], R. Sundara Ganapathy[2]

[1]Research scholar, Department of Pharmacy, Karpagam University, Karpagam Academy of Higher Education, Coimbatore, Tamil Nadu, India, [2]Dean, Faculty of Pharmacy, Karpagam University, Karpagam Academy of Higher Education, Coimbatore, Tamil Nadu, India

Abstract

Background: Flutamide, a substituted anilide, is a potent antiandrogenic that has been used in the treatment of prostate carcinoma having short biological half-life of 5-6 h; thus it is a good candidate for the formulation of sustained release (SR) dosage form. The present work was focused on the preparation of matrix tablets using various polymers with different ratios. **Materials and Methods:** Flutamide-loaded solid dispersion was formulated by solvent evaporation, coprecipitation, co-grinding, and fusion techniques using Gelucire 50/13/ polyvinylpyrrolidone K30. The developed solid dispersions were characterized for its percentage yield, drug content, morphology, and *in vitro* release studies. The optimized formulation was developed into an SR matrix tablet using different polymers and ratios. Furthermore, the tablets were evaluated for thickness, hardness, friability, weight variation, content uniformity, and dissolution rate, and the optimized tablet which was subjected to cytotoxic evaluation in pc3 cell lines. **Results and Discussion:** The obtained solid dispersion has rectangular flaky appearing particles. The dissolution rate profile of physical mixture and flutamide formulation of solid dispersions gets enhanced in comparison with the pure drug. Finally, flutamide-loaded in matrix tablets gives satisfactory pre- and post-characterization results. **Conclusion:** Cytotoxic evaluation of flutamide-loaded matrix tablets (at concentrations of 62.5-500 µg/ml) illustrates an inhibited growth in the human prostate cancer cell line at a dose-dependent manner.

Key words: Dissolution, flutamide, matrix tablets, polymer, solid dispersion

INTRODUCTION

Flutamide is steroidal antiandrogen drug potentially reported for the treatment of prostate cancer. Flutamide competes with testosterone along with its powerful metabolite, dihydrotestosterone for binding to androgen receptors in the prostate gland, which possess significant anticancer activities.[1] Therapeutically, flutamide is used in the treatment of prostatic carcinoma, congenital adrenal hyperplasia, hirsutism, and in malignant neoplasm.[2,3] Flutamide acts by inhibiting the uptake or binding of androgens in target tissues, which is rapidly and extensively metabolized. The major metabolite 2-hydroxyflutamide possesses antiandrogenic properties. In women's encountered with polycystic ovarian syndrome, flutamide possesses the capacity to induce the androgen levels.[4,5] Flutamide is a poorly water soluble drug with low bioavailability and poor wettability after oral administration. Flutamide undergoes rapid first-pass hepatic metabolism after oral administrations which results in a relatively short half-life of 5-6 h, thus the dose of the drug has been attempted to increase, which may end with severe toxicities. Therefore, developing novel formulation with improved solubility and dissolution profile will lead to achieve higher concentrations of flutamide in solution form at the absorption site and may overcome the first-pass effect-mediated poor bioavailability.

Recently, discovered drugs of around 40% have negligible water solubility which represents a serious challenge for the

Address for correspondence:
P. Manikandan, Research scholar, Department of Pharmacy, Karpagam University, Karpagam Academy of Higher Education, Coimbatore-21, Tamil Nadu.
Phone: 8606081008.
E-mail: psmanikandan12@gmail.com

Received: 20-05-2017
Revised: 07-07-2017
Accepted: 13-07-2017

successful development and commercialization of new drugs in the pharmaceutical industry. The major problem of poor solubility of drugs in aqueous system is the critical issue for oral bioavailability. The most convenient and preferred route for drug delivery system are the oral route due to its ease of administration, patience compliance, least sterility constraints, and flexible design of dosage form. However, oral administration of most drugs in conventional dosage forms has short-term limitations due to their inability to restrain and localize the system at gastrointestinal tract. Delivering drugs to the targeted tissue may maximize the therapeutic efficacy causing little toxicity with minimized side effects. In this regiment, the malignant tumor (prostate cancer) occurs due to alterations in zinc accumulation, alteration of metabolism, and citrate production. Affecting the androgen receptor signaling,[6-8] recently the prevalence of prostate cancer has increase. The present work has been focused for the treatment of prostate cancer.

Solid dispersions were one of the recently developed formulation approach utilized to improve the solubility and bioavailability of the encapsulated drug. Parameters, such as carrier molecular weight composition, drug crystallinity, particle porosity and wettability, when successfully controlled in solid dispersion, can produce improvements in bioavailability.[9] Mannitols containing solid dispersions have been reported to possess better solubilizing effect.[10] Solid dispersions were reported for many pharmaceutical drugs like nifedipine, felodipine, oxazepam, piroxicam, zolpidem, and glyburide.

Polyvinylpyrrolidone (PVPs) is a polymer which holds molecular weights ranging from 2500 to 3,000,000 kDa. PVPs holds the properties of enhanced water solubility and can improve the wettability of the dispersed compound.[11] The chain length of the PVPs has the significant effect on improved dissolution rate. Moreover, the viscosity and molecular weight of PVPs have the significant effect over the dissolution rate of encapsulated drug using PVPs. Gelucire Official in European Pharmacopeia is a composition of glyceryl and polyethylene glycol 1500 esters of long-chain fatty acids.[12] Gelucire-based formulation has been reported to improve the bioavailability of drugs.

Recently, novel drug delivery system using solid dispersions with the added attributes of being biodegradable and biocompatible properties for specific treatment was paving interest over the delivery of poorly soluble drugs[13], especially for anticancer drug delivery. The aim of this present work is to formulate and evaluate flutamide-loaded solid dispersion and tablet using Gelucire/PVP as a polymer to improve the solubility of flutamide. The formulated solid dispersion/tablets were characterized for its morphologic behavior and the drug release properties of the solid dispersion/tablets were evaluated by *in vitro* drug dissolution studies along with *in vitro* cytotoxic potential.

MATERIALS AND METHODS

Materials

Flutamide was obtained as a gift sample from Panchsheel Organics Pvt. Ltd. Gelucire 50/13 and PVP K30 were obtained as a gift sample from Dr. Reddy's Laboratories. Hydroxylpropyl methylcellulose, ethyl cellulose (EC), guar gum, and xanthan gum were obtained from Cipla Pharmaceutical Pvt. Ltd, Bengaluru. All other chemicals and solvents used were of analytical grade.

Fourier transform infrared (IR) spectroscopic analysis

Flutamide (2.0 mg) along with admixtures of suitable proportion of polymers polymer physical mixtures were weighed and triturated with potassium bromide (297 mg) to get a uniform mixture.[14] A small quantity of triturated powder was compressed into a thin semi-transparent pellet by application of pressure. The IR spectrum of the prepared pellet was recorded at 4000 cm^{-1} to 400 cm^{-1}.

Phase solubility study

Solubility measurements were performed in triplicate using the method reported by Higuchi and Connors. An accurately weighed amount of flutamide was added to the aqueous solutions with increasing concentrations of Gelucire 50/13 (1%, 2%, 5%, and 10% w/v). Then, the flasks were maintained at room temperature for 7 days with continuous stirring using magnetic stirrer. The saturated solution was sonicated for 20 min and then centrifuged, the supernant were filtered through a Whatman filter paper No. 1. The filtrate was suitably diluted and analyzed spectrophotometrically at 306 nm using ultraviolet (UV) spectrophotometer.

Formulation of flutamide-loaded solid dispersions

Flutamide-loaded solid dispersion were prepared by fusion technique. Accurately weighed amount of flutamide was incorporated into the melted carrier(s) temperature maintained at 60°C with stirring to ensure homogeneity. The mixture was heated until a clear homogeneous melt was obtained. The melted mixtures were left to congeal and then passed through 60-mesh screen.[14]

Morphology

The morphology of flutamide-loaded solid dispersion was evaluated by scanning electron microscope (SEM). The solid dispersion was mounted directly onto the SEM sample stub using a tape and coated with gold film and then analyzed.[15]

In vitro release studies

USP Type II (paddle) apparatus was used (DS8000 laboratory India) for dissolution study. The amount of samples equivalent to 50 mg of drug were taken in muslin cloth and tied with paddle, vessel containing 900 ml of phosphate buffer pH 7.2. The dissolution media was maintained at 37°C±1°C and stirred at 100 rpm. Samples were collected periodically (every 1 h time intervals) and replaced with fresh dissolution medium. After filtration through microfilter (0.45 µm), the concentration of flutamide was determined spectrophotometrically at 306 nm. All experiments were carried out in triplicate.

Formulation of flutamide tablets

Flutamide tablets were prepared by direct compression method (wet granulation technique) using polymers, Avicel pH 102 and magnesium stearate. All other polymers with different ratios were sieved through 60-mesh before compression and mixed in geometrical order [Tables 1 and 2]. Tablets were prepared using 12 mm standard concave round punch using single punch tablet machine (Cadmach, India).

Encapsulation efficiency/assay

The flutamide-loaded solid dispersion/tablets was checked for its content using UV spectrophotometer by crushing an accurately weighed amount in a glass mortar suspended in 10 ml of pH 7.2 phosphate buffer. The resultant solution was filtered through 0.45 µ filter and checked at 306 nm.

Evaluation of powders

The powder blend was evaluated for its angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio using reported standard optimized protocols.

Evaluation of flutamide tablets

The formulated flutamide tablets were evaluated for its weight variations, friability, thickness, and hardness using reported standard optimized protocols.

In vitro release studies

In vitro release studies of prepared matrix tablets were conducted for 12 h. Using an eight station USP XXII Type 2 apparatus at 37°C ± 1°C, speed of basket was set at 75 ± 1 rpm. In each flask, 900 ml of phosphate buffer to a pH 7.2 was used as dissolution media. A volume of 5 ml samples were withdrawn at every 1 h interval and replaced with fresh medium to maintain sink condition. Sample was filtered and diluted appropriately, analyzed at 306 nm by double beam UV/visible spectrophotometer using dissolution medium as blank. Experiments were performed in triplicate. The amount of drug present in the samples was calculated using calibration curve constructed from reference standard. Dissolution data of the matrix tablets were plotted and *in vitro* drug release data were subjected to goodness of fit test by linear regression analysis according to zero order, first order, kinetic equations such as Higuchi and Peppas models to determine the mechanism of drug release.

Kinetic data evaluation

The dissolution data were fitted to zero order, $W = W_0 - k_0 t$; first order, Lnw = In $W_0 - k_1 t$; Hixson-Crowell's cube root of time, $W^{1/3} = W_0^{1/3} - k_x t$; and Higuchi square-root of time, $W = W_0 - k_H t^{1/2}$ kinetic models. To estimate the drug release mechanism, dissolution data were also analyzed by Korsmeyer-Peppas model, $M_t/M_\infty = kt^n$, where M_t/M_∞ is the amount of drug released at time t, k is a constant incorporating structural characteristic of the dosage form, and n is the release exponent. When $n < 0.5$, the drug diffuses through the polymeric matrix by Fickian (Case I) diffusion mechanism. For $0.5 < n < 1$, an anomalous (non-Fickian) mechanism occurs. $n = 1$ indicates a zero order (Case II) and $n > 1$ indicates non-Fickian super Case II release mechanism.

Swelling index

Swelling nature of tablet was measured by equilibrium weight gain method in triplicates using dissolution apparatus without applying stirring. Pre-weighed tablets (W_0) were placed in the basket containing 900 ml of phosphate buffer pH (7.4), dissolution medium maintained at 37°C ± 0.5°C, and observed for its swelling behavior. The swollen tablets were taken out from the dissolution basket at predetermined time intervals of 1, 2, 4, 6, 8, and 12 h, respectively.[16,17] At each time point (t), tablets were taken out from the basket; excess water adhered to the swollen surface was wiped using tissue paper immediately and accurately weighed using analytical balance (W_t).

$$\% \text{ Swelling index} = \frac{\left(\begin{array}{l}(W_t)\ \text{Weight of tablet at time intervals} \\ -\ (W_0)\ \text{Initial weight of tablet}\end{array}\right)}{(W_0)\ \text{initial weight of tablet}} \times 100$$

Cytotoxicity evaluation

To check the cytototoxic effect of developed formulations, prostate cancer cells (1.0×10^5 cells/ml) was seeded onto 96-well plate in Dulbecco's Modified Eagle's medium supplemented with fetal calf serum (10%), penicillin and

streptomycin (50 µg/mL) at 37°C and incubated with respective concentration of formulations (62.5-500 µg/ml) and then further incubated up to 72 h at 37°C. After 72 h, the sample solutions in the wells were discarded and 20 µl of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (2 mg/ml) was added.[18] The plates were gently shaken and incubated for 3 h at 37°C in 5% CO_2 atmosphere. The supernatant was removed and 50 µl of isopropanol was added and the plates were gently shaken to solubilize the formed formation. The absorbance was measured using a microplate reader at a wavelength of 540 nm, and then the cytotoxic effect was evaluated.

RESULTS AND DISCUSSION

IR spectral studies

The IR spectra of all the pure samples and the flutamide physical admixtures of suitable proportion of polymers were subjected to the study and the results are shown in Figure 1. By comparing, the IR spectral data of pure drug flutamide and physical admixture indicates that functional groups such as N-H, C=O, C-F3, N=O, C-N and it has been observed that the N-H stretching, C=O stretching, N=O stretching, C-F3 stretching, and C-N stretching of pure drug flutamide

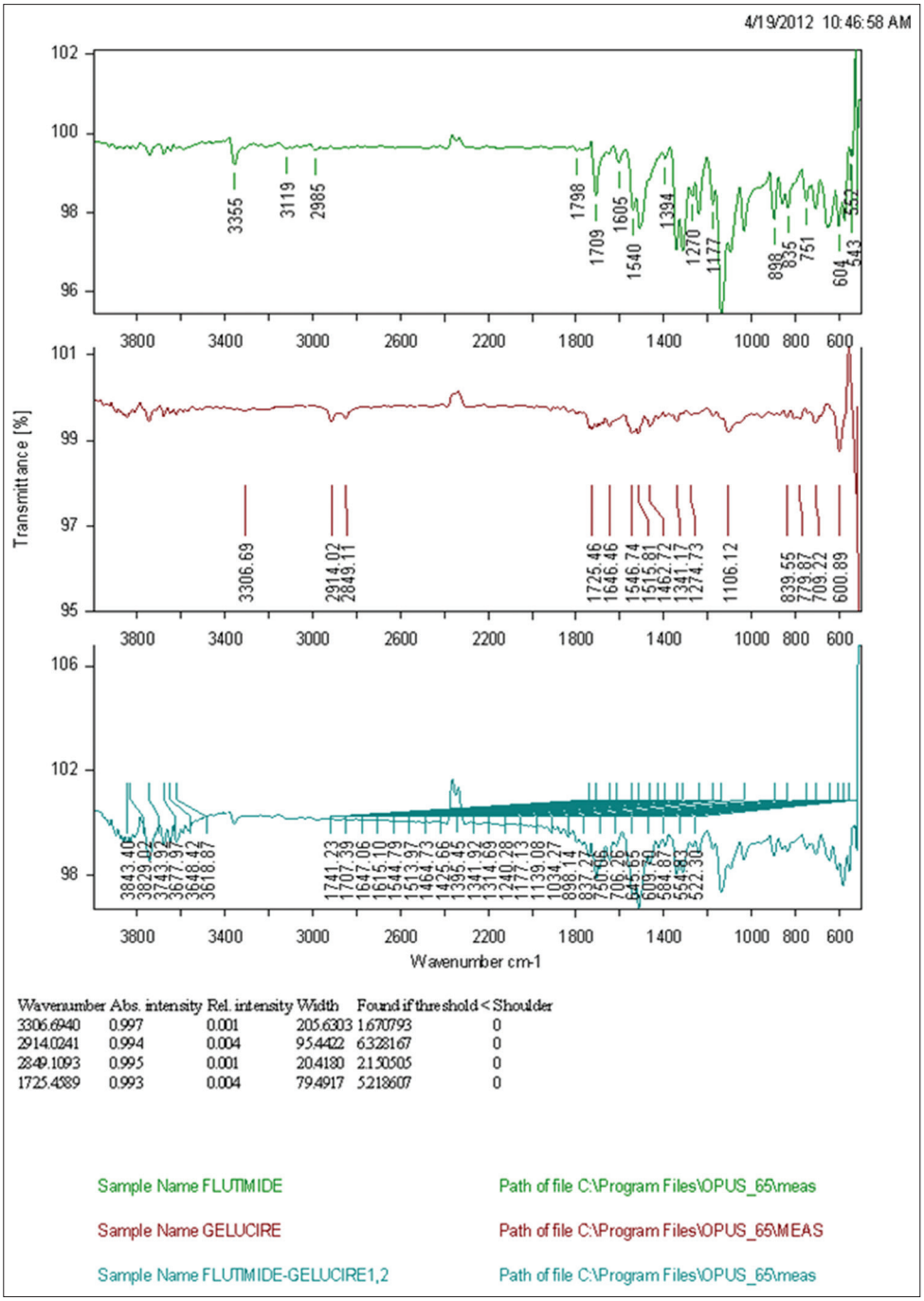

Figure 1: A typical infrared spectra of Gelucire 50/13 and physical mixtures of flutamide and Gelucire 50/13 in ratio 1:2

remains unchanged in the spectra of flutamide physical mixture. All the six spectrums show following absorption of flutamide. Due to similar peaks, it clearly indicates that there is no interaction between drug and the polymers.

Phase solubility

Phase solubility studies indicate that Gelucire 50/13 have a significant solubilizing effect on flutamide. The phase solubility curve of flutamide in the presence of Gelucire 50/13 was shown in Figure 2. The solubility of flutamide in water at room temperature was found to be 128.11 µg/ml.

Morphology

SEM analysis was carried out to check the surface morphology of all the formulations for its shape and size of microspheres [Figure 3]. The result shows that native flutamide powder has rectangular flaky appearing particles. The incorporation of Gelucire 50/13 in the solution gave rise to spongy scaly appearing particles with relatively blunt margins; these give a waxy appearing particle with the disappearance of the flutamide particle shape showing spongier appearance and higher void spaces. The SEM micrograph of solid dispersion formulation suggests that particle size of the drug might have been reduced than the pure drug which accelerates solubility and dissolution.

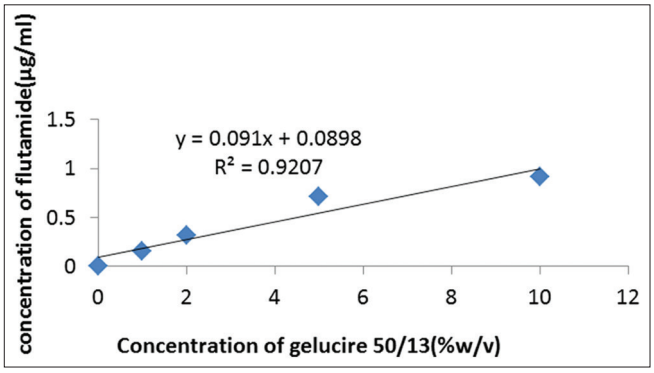

Figure 2: Phase solubility graph of flutamide in Gelucire 50/13

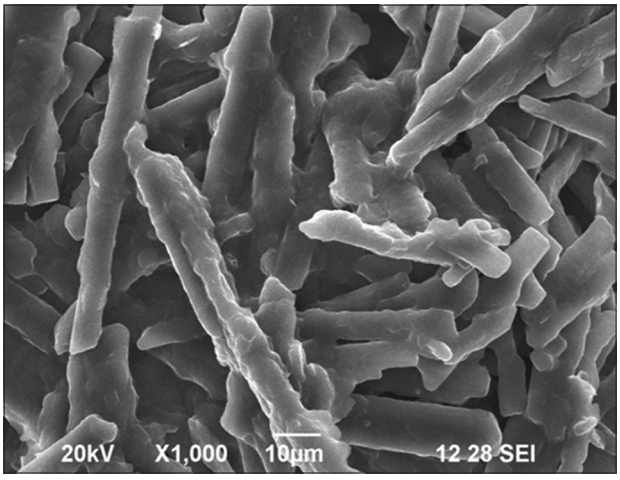

Figure 3: Standard error of mean image of solid dispersion of flutamide with drug to polymer ratio 1:2 using fusion method

In vitro release

The *in vitro* dissolution profile of solid dispersions of flutamide was compared to that of pure drug and it was found that percentage drug release of solid dispersion was increased than pure drug. Studies being carried out for 6 h using pH 7.2 phosphate buffer [Figures 4 and 5]. The dissolution rate of pure flutamide was very slow compared to that of physical mixture and flutamide-loaded solid dispersions. The results of dissolution studies indicate the more pronounced dissolution effect with increase in polymer concentration. As compared to PVP, flutamide release from Gelucire 50/13 has more pronounced cumulative flutamide release. The percentage flutamide release from the solid dispersion (fusion method) of Gelucire 50/13 (1:2) was found to be maximum (91.06%) at the end of 6 h.

Formulation and evaluation of flutamide tablets

Formulations were prepared by direct compression method; 125 mg of flutamide equivalent solid dispersed products were taken along with polymers in different ratios, and sieved through 60-mesh before compression and mixed in

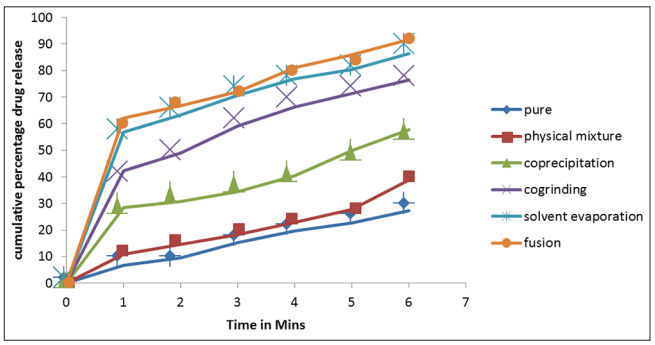

Figure 4: Comparative *in vitro* drug release plot of flutamide Gelucire 50/13 solid dispersions with ratio of 1:2

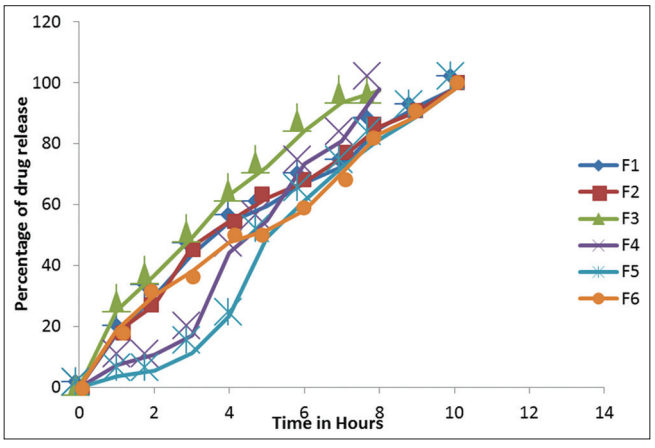

Figure 5: *In vitro* release studies of flutamide matrix tablets (F1-F6)

geometrical order. Excipients such as Avicel pH 102 and magnesium stearate were also added. Mixing was continued until all the excipients mixed thoroughly. Then, blended powders were evaluated for their physical properties such as angle of repose, bulk density, tapped density, and compressibility. Tablets were prepared using 12 mm standard concave round punch using single-punch tablet machine (Tablet Punching Machine, Cadmach, India). Tablets were evaluated for its thickness, hardness, friability, weight variation, content uniformity, and dissolution rate.

Formulations of flutamide tablets with controlled release pattern were prepared using hydroxypropyl methyl cellulose, EC, guar gum, and xanthan gum as a rate retarding polymers. The polymers were used at various concentrations. Most of the formulation exhibited good flow properties and compressibility index. The bulk density, tapped density, angle of repose, Hausner's ratio, and Carr's index of the blend were in the ratio of 0.45-0.5 g/cc, 0.51-0.59 g/cc, 30.6-34.6%, 1.11-1.17%, and 10.5-16.2%, respectively [Table 3].

The weight variations of the tablets were within acceptable limits of <4%. The tablets possessed satisfactory friability of <1.5%; hardness was found to be within the range of 4.5-5.2 kg/cm^2. The thicknesses of tablets were within 4.7-5.0 mm. All the formulations rendered good physical characteristics of within acceptable limits. The drug content percentage of flutamide in the tablet ranges between 97.23 ± 2.7% w/w and 102.58 ± 1.1% w/w.

Swelling index

Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) K100 with guar gum (F9) as shown in Figure 6 showed good swelling behavior, due to its better imbibition capacity in water or simulated gastric fluid. Swelling

Table 1: Composition of different formulations of flutamide matrix tablets

Ingredients (mg)	Formulation code											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Solid dispersed products equivalent to flutamide (mg)*	125	125	125	125	125	125	125	125	125	125	125	125
HPMC K100M (mg)	100	70	30	-	-	-	-		70	30	-	-
EC (mg)	-	30	70	100	-	-	-	-	-	-	70	30
Guar gum (mg)	-	-	-	-	100	70	30	-	30	70	-	-
Xanthan gum (mg)	-	-	-	-	-	30	70	100	-	-	30	70
Avicel pH 102 (mg)	10	10	10	10	10	10	10	10	10	10	10	10
Magnesium stearate (mg)	5	5	5	5	5	5	5	5	5	5	5	5
Total weight (mg)*	516	516	516	516	516	516	516	516	516	516	516	516

*396.35 mg of solid dispersion products equivalent to 125 mg of flutamide. HPMC: Hydroxypropyl methylcellulose, EC: Ethyl cellulose

Table 2: Results of the post-compressional evaluation of all formulation of flutamide matrix tablets (mean±SD, *n*=3)

Formulation code	Thickness of tablets (mm) (±SD) *n*=3	Hardness (kg/cm^2) (±SD) *n*=5	Friability (%) (±SD) *n*=10	Weight variations (mg) (±SD) *n*=20	% of drug content (±SD) *n*=3
F1	5.03±0.115	4.724±0.34	0.30±0.14	517.50±0.82	98.69±2.73
F2	4.96±0.115	4.72±0.52	0.34±0.24	518.73±0.9	98.56±0.791
F3	4.9±0.264	5.162±0.36	0.46±0.04	515.57±2.1	97.23±2.72
F4	4.76±0.152	5.048±0.26	0.53±0.33	516.09±2.3	97.64±0.42
F5	4.93±0.152	4.546±0.40	0.60±0.78	514.36±1.7	100.39±1.01
F6	4.9±0.264	5.026±0.27	0.46±0.60	515.16±0.79	100.96±1.66
F7	5±0.1	4.566±0.49	0.25±0.37	513.49±2.3	97.57±0.92
F8	4.86±0.208	5.292±0.41	0.47±0.02	518.47±0.69	97.54±0.86
F9	4.83±0.152	5.106±0.56	0.31±0.12	517.68±1.1	102.58±1.11
F10	4.85±0.152	5.034±0.45	0.60±0.10	514.87±2.0	98.26±1.40
F11	4.93±0.152	4.512±0.25	0.43±0.49	512.59±1.3	97.49±0.82
F12	4.86±0.305	4.78±0.38	0.33±0.57	515.01±1.3	99.76±2.29

SD: Standard deviation

Table 3: Physical characteristic of the solid dispersion products (mean±standard deviation, *n*=3)

Formulation code	Bulk density (g/cc)	Tapped density (g/cc)	Angle of repose (θ)	Hausner's ratio	Carr's index (%)
F1	0.476±0.007	0.548±0.008	31.26±0.98	1.151	13.14
F2	0.461±0.005	0.534±0.005	33.98±0.57	1.158	13.67
F3	0.490±0.011	0.563±0.005	31.68±0.96	1.148	12.67
F4	0.512±0.002	0.596±0.017	33.95±1.15	1.164	14.09
F5	0.489±0.015	0.553±0.013	31.78±0.50	1.130	11.57
F6	0.506±0.007	0.573±0.009	34.11±1.64	1.132	11.69
F7	0.464±0.017	0.545±0.012	31.65±0.93	1.174	14.86
F8	0.474±0.006	0.546±0.012	34.41±1.04	1.151	13.18
F9	0.460±0.003	0.514±0.007	30.61±0.56	1.117	10.50
F10	0.433±0.003	0.517±0.009	31.41±0.97	1.193	16.24
F11	0.454±0.005	0.535±0.011	32.29±1.12	1.178	15.14
F12	0.464±0.002	0.536±0.009	32.81±1.94	1.155	13.13

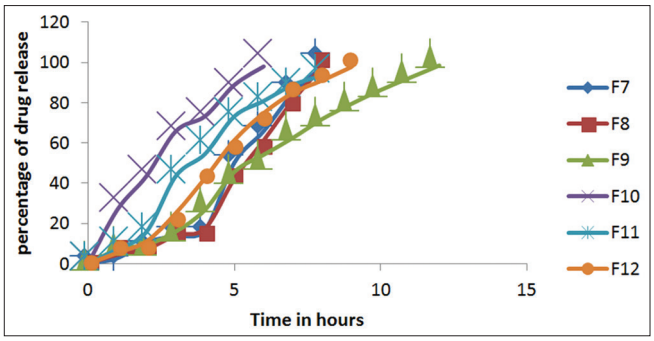

Figure 6: *In vitro* release studies of flutamide matrix tablets (F7-F12)

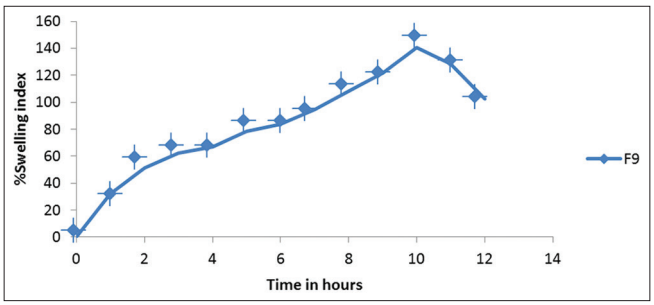

Figure 7: A typical swelling index property of flutamide-loaded matrix tablet formulation F9

behavior gets increased on time and weight gain by the prepared tablets for up to 10 h. Further, it gets gradually decreased due to its dissolution of the outermost tablet gel layer into the dissolution medium. This indicates that the swelling property was directly proportional to the polymer concentration. In general matrix tablet, on contact with an aqueous medium, undergoes wettability from its surface, followed by the progression through microscopic pores into the inner core of the tablet. Nature of the polymer, therefore, plays an important role in this swelling process. When significant swelling occurs, the diffusional path length gets increased, and the drug release is retarded or sustained. These data suggest that the use of HPMC, EC, guar gum, and xanthan gum in the polymeric granules not only supports for the sustained release (SR) but also provides complete release from the SR tablets.

In vitro cytotoxic evaluation

Flutamide matrix tablet (62.5-500 µg/ml) inhibited the growth of human prostate cancer cell line in a dose-dependent manner [Figure 7]. The inhibition concentration 50% (IC_{50}) values for matrix tablet of flutamide was calculated and utilized for the study. Human prostate cancer (PC-3) cells were much more sensitive to the treatment with F9 formulation of matrix tablet of flutamide. The results indicated that IC_{50} value of flutamide matrix tablet (F9 formulation) increased by 2-fold in the human prostate cancer (PC-3) cell line as compared with other formulations [Figure 8]. The induction of resistance of the human prostate cancer (PC-3) cell line by F9 formulation could be increasing the solubility of flutamide in matrix tablet form.

The developed flutamide-loaded solid dispersions were successfully prepared having a scaly nature with a waxy appearance with high void spaces which could possibly accelerate solubility and dissolution by improving its surface area. In the present study, 16 formulations of solid dispersions were prepared using various techniques such as solvent evaporation method, fusion method, co-grinding, and coprecipitation methods. Among the prepared solid dispersion technique, the percentage drug loading and the dissolution rate were found to be better in fusion technique using Gelucire 50/13 in the ratio of 1:2. The developed flutamide matrix tablets also hold better dissolution profile reaching around 100% at the studied time intervals.

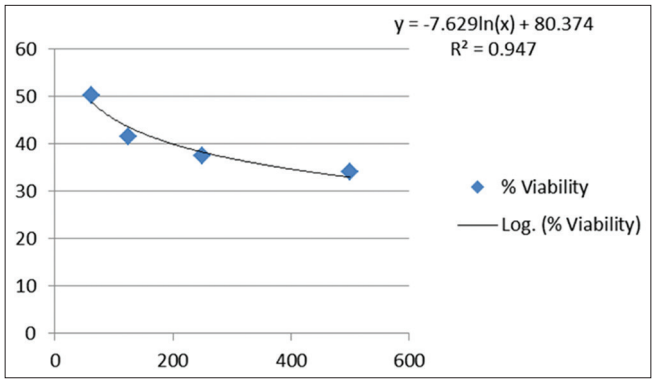

Figure 8: *In vitro* cytotoxicity evaluation of flutamide matrix tablet (F9) to PC-3 cells after 72 h exposure, determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay

CONCLUSION

To attain an efficient treatment for prostate cancer treatment, the present study has been focused with greater potential for the delivery of flutamide in the form of flutamide matrix tablets by its improvement in solubility using Gelucire 50/13. The results from encapsulation efficiency studies indicate that the tablets hold good encapsulation. The tablet evaluation parameter results were found to be with in the standard limiting criteria for weight variations, friability, thickness, and hardness analysis. The results of F9 formulation of *in vitro* dissolution profile indicate a release of above 97% for 12 h with an SR pattern. The enhanced swelling property on increase in polymer concentration supports the matrix tablets for its *in vitro* release. The cytotoxic evaluation using MTT assay indicates that the developed formulation possess its anticancer effect against human prostate cancer (PC-3) cells at a dose-dependent manner. However, it would be necessary to undertake higher studies, including bioavailability in cancer-induced animal models with a view of determining the biodistribution in different sites including diseased site.

ACKNOWLEDGMENT

The authors are thankful to Sigma-Aldrich, Bengaluru, for providing free gift samples of flutamide. We thank the Management and Principal of Devaki Amma Memorial College of Pharmacy, for providing the facilities to carry out the work.

REFERENCES

1. Jyothi BJ, Sreelakshmi K. Design and evaluation of self-nanoemulsifying drug delivery system of flutamide. J Young Pharm 2011;3:1-11.
2. Thamizhvanan K, Umakrithika S, Vijayashanthi K, Shaheen S, Nandini K, Aisha TS, *et al.* Evaluation of solubility of flutamide by using supramolecular technique. Int J Pharm Pract Drug Res 2013;3:6-19.
3. Emami J, Tajeddin M, Ahmadi F. Preparation and *in vitro* evaluation of sustained-release matrix tablets of flutamide using synthetic and naturally occurring polymers. Iran J Pharm Res 2008;7:247-57.
4. Elgindy N, Elkhodairy K, Molokhia A, Elzoghby A. Lyophilization monophase solution technique for improvement of the physicochemical properties of an anticancer drug, flutamide. Eur J Pharm Biopharm 2010;74:397-405.
5. Nesalin JA, Gowthamarajan K, Somashekhara CN. Formulation and evaluation of nanoparticles containing flutamid. Int J ChemTech Res 2009;1:1331-4.
6. Slosarek K, Bystrzycka J, Fijałkowski M. Real time brachytherapy for prostate cancer - A new challenge for medical physicists. Rep Pract Oncol Radiother 2005;10:255-9.
7. Choi IY, Park S, Park B, Chung BH, Kim CS, Lee HM, *et al.* Development of prostate cancer research database with the clinical data warehouse technology for direct linkage with electronic medical record system. Prostate Int 2013;1:59-64.
8. Valdagni R, Albers P, Bangma C, Drudge Coates L, Magnani T, Moynihan C, *et al.* The requirements of a specialist Prostate Cancer Unit: A discussion paper from the European School of Oncology. Eur J Cancer 2011;47:1-7.
9. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov Today 2007;12:1068-75.
10. Punitha S, Hari BN, Karthikeyan D. Enhancement of celecoxib solubility by solid dispersion using mannitol. Int J Pharm Pharm Sci 2010;2:109-11.
11. Tantishaiyakul V, Kaewnopparat N, Ingkatawornwong S. Properties of solid dispersions of piroxicam in polyvinylpyrrolidone. Int J Pharm 1999;181:143-51.
12. Manohar SD, Shridhar DA, Mallikarjuna SC. Solubility and dissolution enhancement of carvedilol by solid dispersion technique using gelucire 50/13. Int J Pharm Sci Rev Res 2014;29:161-5.
13. Saffoon N, Uddin R, Huda NH, Sutradhar KB. Enhancement of oral bioavailability and solid dispersion: A review. J Appl Pharm Sci 2011;1:13-20.
14. Joshi HN, Tejwani RW, Davidovich M, Sahasrabudhe VP, Jemal M, Bathala MS, *et al.* Bioavailability enhancement of a poorly water-soluble drug by solid dispersion in polyethylene glycol-polysorbate 80 mixture. Int J Pharm 2004;269:251-8.
15. Lekshmi UM, Poovi G, Reddy PN. *In vitro* observation of repaglinide engineered polymeric nanoparticles, dig. J Nanomater Biostruct 2012;7:1-12.
16. Abrahamsson B, Alpsten M, Bake B, Larsson A, Sjögren J. *In vitro* and *in vivo* erosion of two different hydrophilic gel matrix tablets. Eur J Pharm Biopharm 1998;46:69-75.

17. Gupta R, Kamalinder Singh K. Stability studies on a cough syrup in plastic containers. Indian J Pharm Sci 2007;69:408.
18. Denizot F, Lang R. Rapid colorimetric assay for cell growth and survival: Modifications to the tetrazolium dye procedure giving improved sensitivity and reliability. J Immunol Methods 1986;89:271-7.

Source of Support: Nil. **Conflict of Interest:** None declared.