Formulation and Evaluation of Oro dispersible Tablets of Fosinopril Sodium

T. Mamatha, Md. Zubair, N. Sarah Nasreen and Md. Ahmeduddin

Department of Pharmaceutics, Sultan-ul-Uloom College of Pharmacy, Hills, Hyderabad- 500034, India

Received: June 04, 2014; Accepted: November 25, 2014; Published (web): February 09, 2015

ABSTRACT: The purpose of present research was to formulate and evaluate oro dispersible tablets (ODTs) of fosinopril sodium (FS). It has been developed at 20 mg dose and was prepared using different types of superdisintegrants such as (sodium starch glycolate, Ac-Di-Sol, crospovidone (CP), different types of subliming agents such as ammonium bicarbonate (AB) and camphor at different concentrations by direct compression method. The formulations were evaluated for uniformity of weight, content, hardness, friability, wetting time, *in vitro* dispersion time and dissolution rate. All formulations showed satisfactory mechanical strength, uniform weight, uniform drug content, and lesser wetting time and dispersion time. All the formulations showed more than 90% of drug release within 15 minutes. Among 10 formulations, formulation A5 (consisting of 2 % CP) and F4 (consisting of 15 % AB) were found to yield best results in terms of wetting time, *in vitro* dispersion time and dissolution rate.

Key words: Direct compression, fosinopril, mouth dissolving tablets, super disintegrants

INTRODUCTION

ODTs are oral solid dosage forms that disintegrate in the oral cavity in easy swallow residue.[1] They are also known as mouth dissolving tablets, orally disintegrating tablets, melt- in-mouth fast dissolving drug delivery, rapimelts tablets, porous tablets, quick dissolving tablets etc.[2]

US FDA defined ODTs tablets as a solid dosage form containing medicinal substances which disintegrates rapidly usually within a matter of seconds, when placed upon the tongue. They are made of either very porous or soft moulded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, which are difficult to handle, often requiring specialized peel-off blister packaging.[3,4] The newest generation of ODTs can produce more robust, versatile tablets that overcome some of the limitations of earlier ODTs. Advantages of fast dissolving drug delivery system includes: improved compliance/added convenience, easy administration for mentally ill, disabled & uncooperative patients, no water needed, can be designed to leave minimal or no residue in mouth after administration and also to provide a pleasant mouth feel, chewing is not needed, better taste obtained by taste masking, improved stability, low sensitivity to environmental condition, suitable for controlled/sustained release actives, allows high drug loading, cost effective etc.

Various technologies are used in the manufacture of fast dissolving tablets which include freeze drying or lyophilisation[5,6], molding[5-7], spray drying[8,9], sublimation, direct compression and mass extrusion. Literature survey was performed on different ODTs like baclofen[10,11], propranolol hydrochloride[12], carvedilol[13], ornidazole[14], pheniramine maleate[15], enalpril maleate[16], promethazine theoclate[17], lornoxicam[18], levocetrizine orodispersible tablet[19], diazepam [20] etc.

MONOPRIL (fosinopril sodium tablets) is the sodium salt of fosinopril, the ester prodrug of an angiotensin-converting enzyme (ACE) inhibitor. Fosinopril sodium is a white to off-white crystalline powder. It is soluble in water (100 mg/ml), methanol

Correspondence to: T. Mamatha
E-mail: tmamatha12@gmail.com

and ethanol and slightly soluble in hexane. Its structural formula is shown in figure 1.

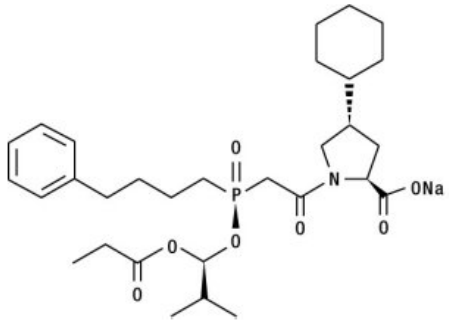

Figure 1. Structural formula of fosinopril sodium.

Its empirical formula is $C_{30}H_{45}NNaO_7P$ and molecular weight is 585.65.

The present study was planned with the objectives to prepare the orodispersible tablets of Fosinopril sodium using various superdisintegrating and subliming agents to improve bioavailability of the drug. It gives quick onset of action, to allow high drug loading and to give more patient compliance.

MATERIALS AND METHODS

Sodium starch glycolate (SSG), ammonium bicarbonate, camphor, mannitol, microcrystalline cellulose, magnesium stearate, talc, saccharine sodium and buffer salts were procured from S.D. fine chemicals Ltd. Croscarmellose sodium, crospovidone were gift samples from Aurobindo Pharmaceuticals Ltd., Hyderabad.

Preparation of phosphate buffer pH 6.8. 6.805 g of monobasic potassium phosphate was dissolved in water and to that solution, 22.4 ml of 0.2 M sodium hydroxide solution was added and the volume was made 1000 ml with water.

Standard graph of fosinopril sodium in phosphate buffer pH 6.8.

Stock solution. Fosinopril sodium, 10 mg was accurately weighed and it was dissolved in 10 ml of phosphate buffer at pH 6.8. Then the volume was made up to 100 ml with phosphate buffer pH 6.8. The above solution is served as stock solution.

Dilutions. From the stock solution 1 ml was taken and it was diluted with phosphate buffer of pH 6.8 to 10 ml to get 10 µg/ml. Similarly 2 ml, 3 ml, 4 ml, 5 ml and 6 ml was taken from stock solution and diluted with phosphate buffer of 10 ml of pH 6.8 to get 20, 30, 40, 50, 60 µg/ml respectively. The absorbance of the resulting solutions is determined at 252 nm using UV-Visible spectrophotometer (Shimadzu, Japan).

Tablet punching by direct compression method. Manufacturing steps for direct compression involves comparatively few steps like milling of drug and excipients, mixing of drug and excipients and tablet compression.

The orodispersible tablets of batch size 50 of A-series and F- series were prepared by direct compression process and the compositions are shown in tables 1 and 2. All the materials i.e., drug, mannitol, microcrystalline cellulose (MCC), subliming agents, superdisintegrating agents talc and saccharine were sifted through mesh no. 40 and were collected in mortar and mixed well to get a uniform mixture. Magnesium stearate was sifted through mesh no. 60 sieve, collected into the mortar containing other ingredients and mixed. The lubricated directly compressible blend was compressed by using direct compression machine (Cadmach, India) to get hardness above 2.5 kg/ cm^2. The tablets were sublimed at 40-50 °C in a vacuum oven for 24 hours to sublime subliming agent. End point of process is indicated by complete removal of subliming agent by sublimation.

Evaluation of tablets

Uniformity of weight. The test was carried out according to the Indian pharmacopoeia. Twenty tablets from each formulation were individually weighed and the mean of tablet weight was calculated. The percentage weight variation was calculated individually comparing to mean tablet weight.

Hardness. The fracture strength, which is defined as the force required to break a tablet by radial compression, was measured with a tablet hardness tester (Monsanto hardness tester) (n=3).

Friability. The friability of twenty tablets was measured using Roche Friabilator. Pre-weighed tablets were rotated at 25 rpm for 4 minutes. The tablets were then reweighed after removal of fines using 60 mesh screen and the percentage of weight loss was calculated.

% Friability = (Loss in weight / Initial weight) × 100

Wetting time. Effect of super disintegrant type: A piece of tissue paper folded twice was placed in a small petri dish containing 6 ml of phosphate buffer of pH 6.8. A tablet was put on the paper and the time required for complete wetting was measured (n=3) as shown in figure 2.

Effect of subliming agent type: The effect of subliming agent type was studied by preparing F-series formulations containing and camphor and ammonium bicarbonate respectively, as subliming agents.

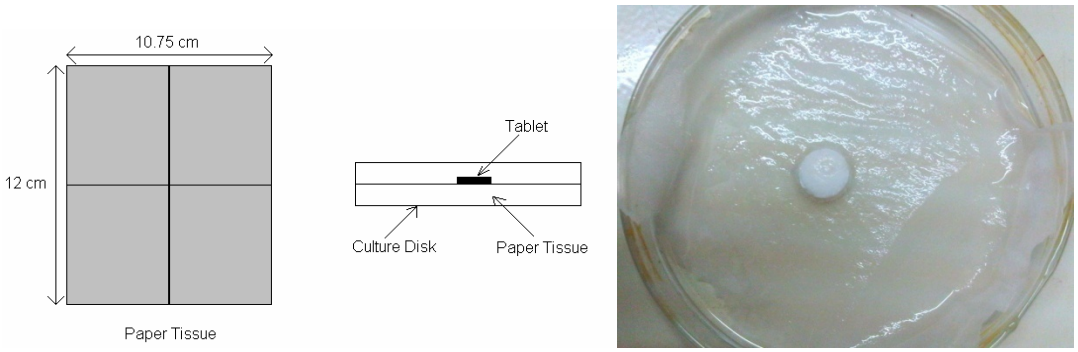

Figure 2. Wetting time of orodispersible tablet of fosinopril sodium.

Drug content uniformity. Ten tablets from each formulation were powdered and the blend equivalent to 20 mg of fosinopril sodium was weighed and dissolved in phosphate buffer of pH 6.8. The solution was filtered and diluted with phosphate buffer pH 6.8. Drug content was analyzed spectrophotometrically at 252 nm. Each sample was analyzed in triplicate.

***In vitro* dispersion time.** *In vitro* dispersion time was measured by using 10ml of phosphate buffer of pH 6.8 in 25 ml beaker at 37 ± 0.5 °C temperature. Time required for dispersion of the tablets was noted. In each formulation three tablets were tested (n=3).

***In vitro* dissolution study.** ODTs were evaluated for dissolution behavior. Dissolution test was carried out using USP apparatus 2, paddle type (Electrolab – TDP 06P). Dissolution was carried out with the rotation speed of 50 rpm using 900 ml of phosphate buffer of pH 6.8 as the dissolution medium maintained at a temperature of 37 ± 0.5 °C. Samples were withdrawn at predetermined time interval, diluted suitably and analyzed at 252 nm for cumulative drug release using UV-Visible spectrophotometer (UV 1700 PharmaSpec, Shimadzu).

RESULTS AND DISCUSSION

Determination of maximum wavelength of fosinopril sodium. The absorbance of 2 µg/ml solution of fosinoprilwas measured at 200 nm to 400 nm. The maximum wavelength of fosinopril sodium was found to be 252 nm.

Standard graph of fosinopril sodium phosphate buffer pH 6.8. The absorbance of different concentrations of fosinopril was measured using UV-VIS spectrophotometer at 252 nm. The results are shown in figure 3.

Uniformity of weight. The weight variation (percent weight within the pharmacopoeial limits of ± 7.5% of the average weight) of the prepared fosinopril sodium orodispersible tablets complied with IP specifications.

Hardness. Hardness test was carried out for prepared fosinopril sodium oro dispersible tablets

using Monsanto hardness tester. The results for hardness test were found to be within acceptable limits for both the series of preparations.

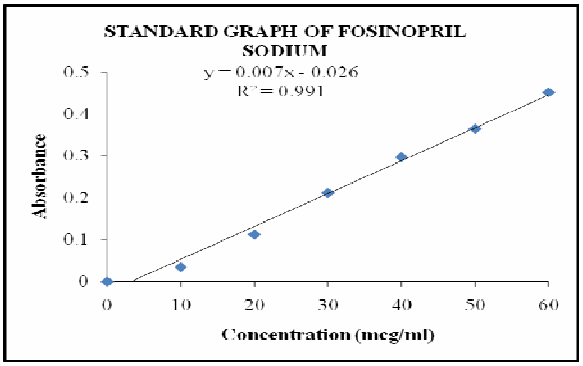

Figure 3. Standard graph of fosinopril sodium.

Evaluation of tablets

Friability. Pre-weighed 20 tablets were rotated at 25 rpm for 4 minutes in Roche Friabilator. Then they were reweighed after removal of fines using 60 mesh screens and the percentage of weight loss was calculated. The result of friability test for A1 to A6 and F1 to F4 was found to be within acceptable limits.

Wetting time. Wetting time of the ODTs is an important parameter which needs to be assessed to give an insight into the disintegration properties of the tablets. A lower wetting time implies a quicker disintegration of the tablet. Moreover, a good correlation between the concentration of the subliming agent and friability is observed, because when a higher percentage of subliming agent is used, more porous and consequently more mechanically weak tablets are produced.

The superdisintegrants alleviate most of the problems associated with long tablet disintegration time. Morever, the use of the superdisintegrants in ODTs is possible as the tablet shows optimum physical properties. Formulas A1- A6 were prepared to study the effect of type of superdisintegrants, SSG, Croscarmellose sodium (Ac-Di-Sol) and crospovidone, on the *in vitro* dispersion time of the prepared fosinopril sodium ODTs.

Table 1. Composition of different formulations of ODTs of fosinopril sodium.

Formulation ingredients (%)	A1	A2	A3	A4	A5	A6
Fosinopril sodium	10	10	10	10	10	10
Sodium starch glycolate	2	5	-	-	-	-
Croscarmellose sodium	-	-	2	5	-	-
Crospovidone	-	-	-	-	2	5
Mannitol	47.96	44.96	47.96	44.96	47.96	44.96
Microcrystalline cellulose	40	40	40	40	40	40
Talc	0.02	0.02	0.02	0.02	0.02	0.02
Magnesium stearate	0.01	0.01	0.01	0.01	0.01	0.01
Saccharain sodium	0.01	0.01	0.01	0.01	0.01	0.01

Table 2. Composition of different formulations of ODTs of fosinopril sodium.

Formulation ingredients (%)	F1	F2	F3	F4
Fosinopril sodium	10	10	10	10
Camphor	10	15	-	-
Ammonium bicarbonate	-	-	10	15
Mannitol	54.96	49.96	54.96	49.96
Microcrystalline cellulose	25	25	25	25
Talc	0.02	0.02	0.02	0.02
Magnesium stearate	0.01	0.01	0.01	0.01
Saccharine sodium	0.01	0.01	0.01	0.01

Table 3. Evaluation of prepared orodispersible tablets of fosinopril sodium (Mean ± SD, n=3).

Properties	A1	A2	A3	A4	A5	A6
Hardness (kg)	2.1 ± 0.09	2.1 ± 0.15	2.5 ± 0.28	2.3 ± 0.36	2.3 ± 0.38	2.5 ± 0.49
Friability (%)	0.38	0.34	0.49	0.63	0.78	0.35
Wetting time (sec)	81 ± 2.8	44.18 ± 4.09	30 ± 4.76	64 ± 3.92	28 ± 2.65	38 ± 1.35
In vitro dispersion time (sec)	18 ± 1.23	25 ± 0.56	15 ± 2.98	16 ± 2.65	10 ± 0.55	16 ± 3.39
Drug content (%)	98.08 ± 2.85	97.29 ± 4.67	97.35 ± 4.87	99.26 ± 3.32	96.56 ± 2.77	98.26 ± 3.56

Table 4. Evaluation of prepared orodispersible tablets of fosinopril sodium (Mean ± SD, n=3).

Properties	F1	F2	F3	F4
Hardness (kg)	3.2 ± 0.46	2.8 ± 0.36	3.1 ± 0.53	2.9 ± 0.21
Friability (%)	1.49	1.52	1.34	1.87
Wetting time (sec)	122 ± 5.6	59 ± 4.95	55.07 ± 7.16	51.2 ± 2.02
In vitro dispersion time (sec)	28 ± 2.85	18 ± 3.54	29 ± 3.06	14 ± 4.53
Drug content (%)	97.86 ± 3.78.	96.29 ± 2.34	98.29 ± 4.84	98.33 ± 4.55

The results shown in table 3 indicate that crospovidone is the strongest among other superdisintegrants, which results in the fastest *in vitro* dispersion time followed by Ac-Di-Sol then SSG (which may be attributed to the strong wicking action of this superdisintegrant).

The presence of a highly porous structure in the tablet matrix is the key factor for rapid disintegration of ODTs. Even though the conventional tablets contain highly water-soluble ingredients, they often fail to disintegrate rapidly because of low porosity. To improve the porosity, volatile substances such as camphor can be used in tableting process, which sublimates from the formed tablet. The effect of subliming agent type was studied by preparing F-series formulations containing and camphor and ammonium bicarbonate as subliming agents. Results shown in table 4 indicate ammonium bicarbonate is superior to camphor.

The results in table 4 indicate that the wetting time decreases with the increase in AB and camphor concentration, which may be attributed to the increase in water uptake rate by the porous structure formed after sublimation.

Drug content uniformity. Content uniformity tests (96.26 to 99.29) of the prepared fosinopril sodium orodispersible tablets complied with IP specifications.

***In vitro* dispersion time.** The dispersion time for tablets in each formulation was measured and the result was found to be within acceptable limits.

***In vitro* dissolution study.** The results of percentage drug release are shown in figures 4 and 5. For all oral solid dosage forms, dissolution study serves as a control test. The results of dissolution studies of all formulations have shown more than 90% release within 15 min.

In A-series formulations more than 95 % of release was observed with formulation A5 (Figure 4). In F- series formulations the dissolution rate is increased in the order (F4 >F2> F3> F1) as represented in figure 5.

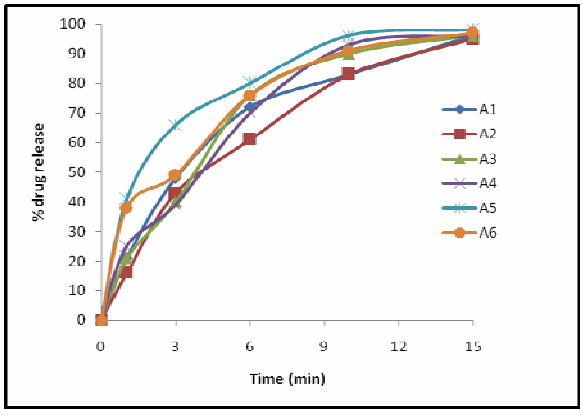

Figure 4. Percentage of drug release of prepared orodispersible tablets of fosinopril sodium, A-series.

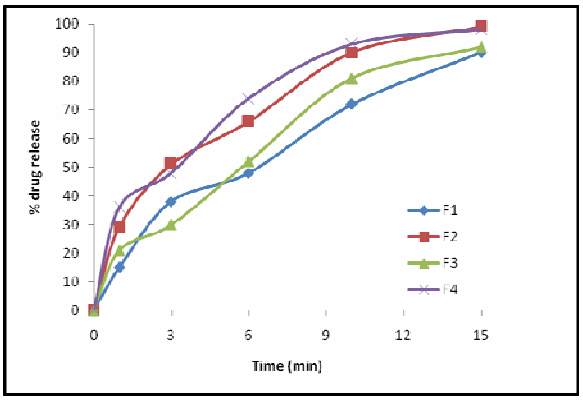

Figure 5. Percentage of drug release of prepared orodispersible tablets of fosinopril sodium, F-series.

CONCLUSION

From the results of wetting time, *in vitro* dispersion time and dissolution rate, it was concluded that all the formulations are suitable for development of ODTs of fosinopril sodium.

Compared to all formulations of A-series, A5 was found to yield best results in terms of wetting time, *in vitro* dispersion time and dissolution rate. In F-series formulations, F4 was found more porous tablet than other formulations. It can also be concluded that all the formulations were having required mechanical strength, content uniformity, weight uniformity indicating the method applied was suitable.

ACKNOWLEDGEMENT

The authors are thankful to the management of Sultan-ul-Uloom College of Pharmacy for providing necessary facilities to carry out this work.

REFERENCES

1. Sreenivas, S.A. 2005. Orodispersible tablets: New- fangled drug delivery system - A Review. *Indian J. Pharm. Educ. Res.* **39**, 177-181.
2. Chein, Y.W. 1992. Oral Drug Delivery and Delivery systems, 2nd ed., New York: Marcel Dekker.
3. Rakesh, R.K. 2004. Orally disintegrating tablets novel tablets novel approach to drug delivery. *Pharma. Review*. **2**, 34-36.
4. Kuchekar, B.S., Badhan, A.C. and Mahajan, H.S. 2003. Mouth dissolving tablets: a novel drug delivery system. *Pharma. Times.* **35**, 1-8.
5. Hamilton, E. and Lutz, E. 2005. Orally disintegrating tablets. *Drug Deliv. Techno* **6**, 634-640.
6. Caramella, C. 1984. *Int. J. Pharm. Tech. Prod. Mfr*. **5**, 1-5.
7. Gohel, M., Patel, M., Agarwal, R., Amin, A., Dev, R. and Bariya, N. 2004. Formulation design and optimization of mouth dissolve tablets of nimesulide using vacuum drying technique. *AAPS Pharm. Sci. Tech*. **5**, 1-6.
8. Chang, R.K., Guo, X., Burnside, B.A. and Couch, R.A. 2000. Fast dissolving tablets. *Pharma. Tech*. **24**, 52-58.
9. Bradoo, R., Shahani, S., Deewan, B. and Sudarshan, S. 2001. Orally disintegrating drug delivery system. *J. Am. Med. Assoc. India.* **4**, 27-31.
10. Tanmoy, G., Amitava, G. and Devi, P. 2011. A review on new generation orodispersible tablets and their future prospective. *Int. J. Pharm. Pharm. Sci.* **3**, 1-7.
11. Radke, R.S., Jadhav, J.K. and Chajeed, M.R. 2009. Formulation and evaluation of orodispersible tablet of baclofen. *Int. J. Chem. Tech. Res.* **1**, 517-521.
12. Deshpande, K.B. and Ganesh, N.S. 2011. Formulation and evaluation of orodispersible tablets of propranolol hydrochloride. *Int. J. Res. Pharm. and Biomed. Sci.* **2**, 529-534.
13. Venkatrajkumarjangam, Javvaji, H., Todikonda, R. and Gollapudi, R. 2011. Formulation and *in vitro* evaluation of Orodispersible tablets of carvedilol. *Pharmanest - An Int. J. Advan. Pharma. Sci.* **2**, 50-54.
14. Maushumi, S.K., Ahmed, Z., BhiseKiran, S. and Somwanshishekhar, V. 2010. Formulation and evaluation of orodispersible tablet of ornidazole. *Int. J. Pharm. Studies Res.* **1**, 39-47.
15. Swamy, P.V., Divate, S.P., Shirsand, S.B. and Rajendra, P. 2009. Preparation and evaluation of orodispersible tablets of pheniramine maleate by effervescent method. *Indian J. pharm. Sci*. **71**, 151-154.
16. Jayaprakash, S., Pillai, K.K., Halith, S.M., Doifode, G., Abirami, and Firthouse, P.U.M. 2011. Formulation and evaluation of Orodispersible tablet of Enalpril maleate. *J. Pharm. Res. Opi.* **1**, 65-70.
17. Chacko, A.J., Jose, S., Babu, N. and Michelle, M. 2010. Design and Development of Orodispersible Tablets of Promethazine Theoclate Using Coprocessed Superdisintegrants and Subliming Materials. *Int. J. Inno. Pharm. Res.* **1**, 53-56.
18. Vishal, M., Anuj, K., Naveen, P., Kumud, P. and Sangram, S. 2011. Formulation and Evaluation of Orodispersible Tablets of Lornoxicam. *Int. J. Drug Dev. Res.* **3**, 281-285.
19. Satishkumar, G., Gandhi, Dharmendra, R., Mundhada, and Bhaskaran, S. 2011. Levocetrizine Orodispersible tablet by direct compression method. *J. Appl. Pharm. Sci.* **1**, 145-150.
20. Khalid, K., Abed, Ahmed, A., Hussein, Mowafaq, M., Ghareeb, Alaa, A. and Rasool, A. 2010. Formulation and Optimization of OrodispersibleTablets of Diazepam. *AAPS Pharm. Sci. Tech*. **11**, 356-361.