Lalitha Kumari P. *et al.* / *International Journal of Pharmacy & Therapeutics*, 4(1), 2013, 34-40.

e- ISSN 0976-0342
Print ISSN 2229-7456

International Journal of Pharmacy & Therapeutics

Journal homepage: www.ijptjournal.com

IJPT

FORMULATION AND EVALUATION OF BILAYER FLOATING OF TABLETS QUINAPRIL HYDROCHLORIDE

Lalitha Kumari P[1], Vasanth PM*[1], Suresh K[2], Ramesh T[3], Ramesh Malothu[3]

[1]Department of Pharmacy, UCEV-JNTUK, Vizianagaram, Andhra Pradesh, India.
[2]Department of Pharmaceutics, Vignan Inst of Pharm Sciences, Vishakapatnam, Andhra Pradesh, India.
[3]Department of Biotechnology, UCEV-JNTUK, Vizianagaram, Andhra Pradesh, India.

ABSTRACT

The purpose of this work was to develop sustained release bilayer floating tablets of Quinapril HCl by direct compression method. The type and the concentration of the polymer are optimized to show the maximum retentive effect with good drug release profile. The tablets were prepared by polymers like HPMC k 100, carbopol, xanthangum, guargum. Sodium bicarbonate acts as gas generating agent with a view to deliver the drug at sustained manner in GIT & consequently in to systemic circulation. Formulations were prepared and evaluated for physical parameters & were found within prescribed limits. The in vitro drug release studies were performed using USP apparatus type II. The drug release was dependent on the type and concentration of the polymer. Drug release was faster from tablets prepared with Carbopol, Xanthan gum and HPMC alone. However, in combination tablets sustained drug release effectively. The rate and mechanism of release of tablets were analysed by fitting the dissolution data into kinetic models. The In-vitro drug release followed Zero order Kinetics and drug release was found to be diffusion controlled & it follows Higuchi diffusion Mechanism model. It can be concluded that the optimized batch F6 selected as best formulation, shown buoyancy lag time of 17 sec, total floating time of 12 hrs and drug release of 99.636% by adopting biphasic drug release pattern in a single dosage could improve patient compliance by increasing the gastric retention time and give better disease management.

Key Words:- Floating, Sustained release, Quinapril, Direct compression.

INTRODUCTION

Development of oral controlled release systems has been a challenge to formulation scientists because of the difficulty in localizing the system in target areas of the gastrointestinal tract. Controlled/sustained release preparations using alternating routes have also been formulated but oral route still remains preferable. When the drug is formulated with a gel forming polymers, it swells in the gastric fluid with a bulk density less than one. It then remains buoyant and floats in the gastric fluid, affecting a prolonged gastric residence time (GRT). This floating dosage form is well known as a hydrodynamically balanced system (HBS) (Sheth PR and Tossounian JL, 1984; Chien YE, 1993; Deshpande CT et al., 1996). It has been suggested for the following instances that an active material should be formulated in the form of an HBS to enhance bioavailability: (*i*) having a dissolution and/or stability problem in the small intestine fluids, (*ii*) being locally effective in the stomach, (*iii*) being absorbed only in the stomach and/or upper part of the intestine. Several approaches of non-effervescent and effervescent formulation technologies have been used and patented in order to increase gastric residence time of the GRDF.

Corresponding Author

Vasanth PM
Email:- vasanthpharma@gmail.com

The term Bi-layered tablets refers sustained release and immediate release of tablet containing subunits that may be either the same or different. Bi-layered tablets allow for designing and modulating the dissolution and release characteristics and they are prepared with one layer of drug for immediate release. While second layer designed to release drug latter, either as second dose or in a controlled/ sustained release manner (Podczeck F et al., 2008). The goal in designing sustained or controlled drug delivery system is, to reduce the frequency of the dosing or to increase effectiveness of drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So controlled release dosage form is a dosage form that release one or more drugs continuously in a predetermined pattern for a fixed period time, either systemically or to a specified target organ.

Controlled release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effects, increased efficacy, and constant delivery. The two aspects are most important to the drug delivery namely, spatial placement and temporal delivery of drug, spatial placements relates to targeting a drug to specific organ or tissues, while temporal delivery refers to controlling and extending the rate of drug delivery to the target tissue. Sustained release/controlled dosage forms, extends the life of the drug so that people shift from three times a day dosing to the new extended release tablets, taking them just once or twice a day (Brahmankar DM and Jaiswal BS, 2004).

Quinapril is an angiotensin-converting enzyme (ACE) inhibitor similar to benazepril, fosinopril, and ramipril. An inactive prodrug, Quinapril is converted to Quinaprilat in the liver and It is an antihypertensive agent, has been widely used for the treatment of hypertension and congestive heart failure, to reduce proteinuria and renal disease in patients with nephropathies (Anonymous 1; Mary Anne Hochadel, 2006). Quinapril is having a short biological half life of 1-2 hrs It has been reported, however, that the duration of antihypertensive action after a single oral dose of quinapril is only 6–8 h, so clinical use requires a daily dose of three times (Dollery C, 1999). In contest of the above statements, a strong need was recognized for the development of gastroretentive dosage form of Quinapril to achieve controlled release of Quinapril.

MATERIALS AND METHODS

Materials

Quinapril Hydrochloride, Hydroxypropyl methyl cellulose (HPMC K 100), Carbopol 934, Xanthan Gum, Guar Gum, Cross povidone, Sodium bicarbonate ($NaHCO_3$), Lactose, Polyethylene Glycol(PEG), Magnesium stearate, ethyl cellulose were obtained from Loba Chemicals, Mumbai, SD Fine Chemicals Limited industries and all other chemicals/reagents used were of analytical grade.

Preparation of quinapril HCl tablets

Tablets were prepared by direct compression technology using cadmach single punch machine. Bilayer floating tablets were prepared in two stages. First stage was formulation of floating layer tablets. The drug, polymer, sodium bicarbonate, PEG and lactose are weighed accurately and passed through mesh and blended for 10mins. Then sieved materials were mixed with lubricant for 5mins & mixed geometrically and compressed to produce floating layer tablets. Second stage was formulation of bilayer floating tablets. The drug, PEG, Cross povidone and lactose are weighed accurately and passed through sieve no.40 to avoid the large particles. The sieved materials were then blended for about 10 minutes and then this powder was subsequently lubricated by mixing with the lubricant (magnesium stearate) for 5mins mixed geometrically and compressed to produce immediate release layer tablets. Floating layer was placed in punching die. Then place 1mg of ethyl cellulose eventually & placed contents of immediate release layer over the floating layer tablet and compressed to produce bilayer floating tablets(150mg). The compositions details of Bilayer floating tablets are given in Table-1

Before tablet preparation the mixture blend of all formulations are subjected to preformulation studies like bulk density, tapped density, compressibility index (%), hausner ratio, angle of repose.

Evaluation of Tablets

The prepared tablets can be evaluated for various official and non-official specifications (Chinam NP et al., 2007; Narendiran C et al., 2006; Jain NK, 2007).

Thickness

The thickness of the tablet is measured by Vernier calipers scale. Thickness of the tablet related to the tablet hardness and can be used an initial control parameter. It is expressed in mm

Weight Variation

Twenty tablets were selected at a random and average weight was calculated. Then individual tablets were weighed and the individual weight was compared with an average weight. The % weight variation was calculated with the following formula.

%Weight variation= Average weight-individual weight/individual weight *100

Hardness

Hardness or tablet crushing strength (the force required to break a tablet in a diametric compression) was measured using Monsanto tablet hardness tester. It is expressed in Newtons.

% Friability

Ten tablets were carefully dedusted prior to testing and weighed accurately (Wo). The tablets were placed in the drum of Roche friabiltor. The drum was rotated for 100 times at a speed of 25rpm. The tablets were collected, re-dedusted and accurately weighed (W1). It is calculated form the following formula;

% Friability= $1 - \frac{W1}{W0} * 100.$

***In vitro* Buoyancy Studies**

The *in vitro* buoyancy was determined by floating lag time. The tablets were placed in a beaker containing 100mL 0.1N HCl and the time required for the tablet to rise to the surface and float was determined as floating lag time (FDA Guidance for Industry, 1997).

***In vitro* dissolution Studies**

The in vitro drug release studies of tablets were carried out as per USP guidelines. The dissolution method and equipment were validated before the study. The dissolution of all batches of tablets was carried out using LABINDIA DISSO 8000, a USP Apparatus-II Paddle type apparatus with 0.1N HCl (1.2pH phosphate buffer) as dissolution media with volume of 900ml. The dissolution medium was subjected to degassing by placing the dissolution vessel with medium in a water bath at 37 ± 2^0C. The paddle speed was set at 75 Rpm and the temperature was maintained at 37 ± 0.5^0C. A sample (5 mL) of the solution was withdrawn from the dissolution apparatus at specified time intervals and the samples were replaced with 5ml of fresh dissolution medium. The samples were filtered through a membrane filter. Absorbance of these solutions was measured at 214 nm using a Shimadzu UV-1601 UV-spectrophotometer. Cumulative percentage drug release was calculated using an equation obtained from a standard curve. From the obtained values the graphs were plotted between the cumulative % drug release and the time (Subharamanyam CVS, 2006).

RESULTS AND DISCUSSION

In the present study Quinapril Hydrochloride Bilayered tablet were prepared by dry compression process by using ingredients shown in (table-1). A total number of ten formulations were prepared. The values of preformulation parameters evaluated were within prescribed limit and indicated good fine flow property (*United States Pharmacopoeia, 1993*) (table-3).

Evaluation of tablets

The prepared tablets were evaluated for weight variation, thickness, hardness, friability and Floating lag time. The formulated batches showed thickness between 3.96 and 4.39 mm (Average thickness 4.17 mm), hardness between 5.62 and 5.97 kg/cm2 (Average hardness 5.7 kg/cm^2), friability between 0.23 and 0.45 % (Average friability 0.34 %) The results of these parameters are given in (Table 4).

***In vitro* floating behavior**

The floating behavior study explained that the formulated bilayer tablets has minimum floating lag time maximum total floating time (≤ 12 hrs) which is essential requirement for a gastroretentive drug delivery. This suggest that the floating tablets required less time to rise on the surface and has the capability to remain in a floating state for longer time to release the drug in surrounding gastric liquid. The floating behavior studies of formulated batches showed the floating lag time between 15 and 102 seconds as well as shown total floating time ≤ 12 hrs.

***In vitro* dissolution study**

The Bilayer floating formulations F1 to F10 were subjected for the dissolution studies using USP dissolution apparatus 2 (paddle) in 900 mL of 0.1N HCl medium. In case of bilayer floating tablets the IR disintegrates with in 1hr and then the SR comes in contact with medium starts swelling and builds gel layer around the tablet. Sodium bicarbonate reacts with the Hcl and generates CO_2, which is entrapped in the gel reducing the density of SR. The polymer HPMC K100 is one of the carriers most commonly used for the preparation of oral controlled drug delivery systems because of its ability to swell upon gellification once in contact with water. The gel becomes a viscous layer, acting as a protective barrier to both the influx of water and the efflux of the drug in solution. The percentage drug release shows formulations (F1-F10) in the range of 98.561% to 99.636%. The formulations F1-F5, F7, F10 using alone HPMC, Guargum, Xanthan gum, Carbopol fails to sustain the drug for a period of 12Hrs but the formulations of F8, F9 using combinations of HPMC, Carbopol, Xanthan gum retards the drug upto 11hrs with % of drug release 98.977% & 99.146% whereas the combination of Xanthan Gum &

Guar gum of formulation (F6) sustained the release of drug upto 12hrs with the % of drug release 99.636%. To analyze the quinapril Hcl release mechanism as well as to select the BFT formulation for the *in vitro* release data were fitted into various release equations and kinetic models [first order, zero order, Higuchi and Korsmeyer and Peppas. The F6 was chosen as the optimized formulation because it showed more linearity between the cumulative percentage drug released *versus* time, as indicated by the highest value of the correlation coefficient *R* or *R*2 in all the selected models, among all formulations, and best fitted both zero order (*R*2= 0.984), Higuchi(R^2 =0.975) model. As indicated by the value of R^2, the Higuchi model was found to be efficient in describing the kinetics of drug release from the BFT formulation, with drug release being proportional to the square root of release time. In the optimized formulation (F6) was found to be: polymers(xanthangum+guargum) 28%, quinqpril Hcl 10%, sodium bicarbonate 4%, PEG 20%, lactose 33.33%, crosspovidone 2% and magnesium stearate 2.6% The formulation F6 showed a constant rate of release in a sustained manner similar to zero order kinetics with good buoyancy property (Suvakanta Das et al., 2010). The data of invitro drug release was tabulated. (Table no: 5). The figure no: 1 indicates the floating of the tablet during dissolution, figure no : 2 is the graph of invitro drug release data.

Fig 1. Floating of tablets

Fig 2. Graph of in vitro drug release

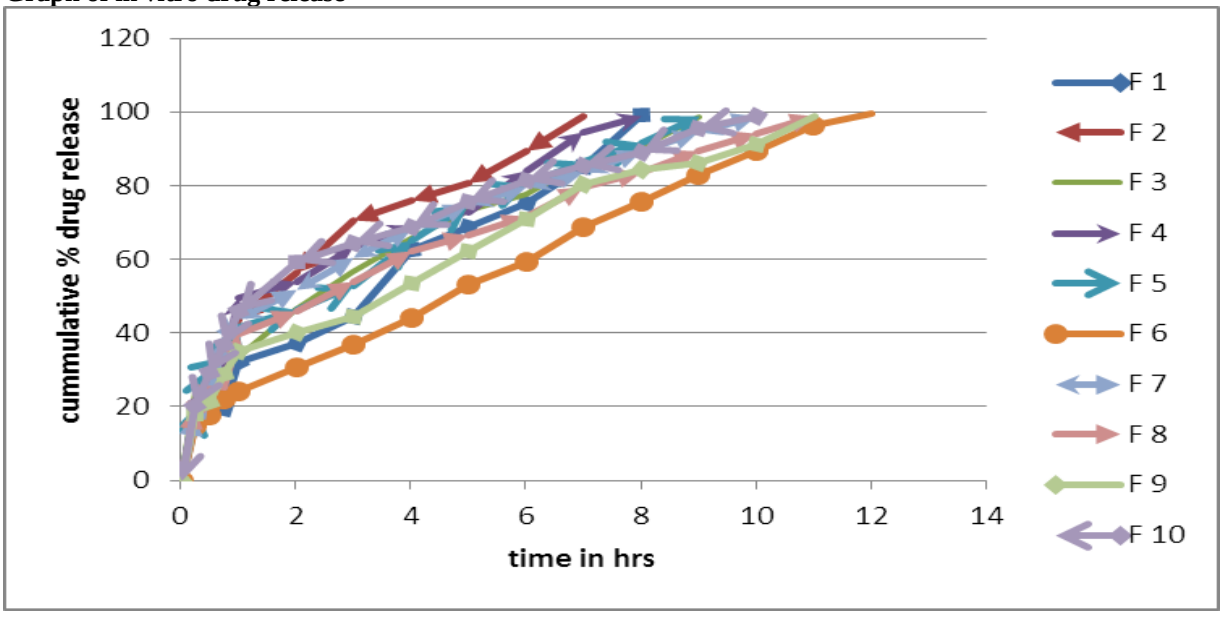

Table 1. Composition of Quinapril Hcl tablets subjected to optimization studies

Sl. No.	Ingredients	Quantity Per Tablet in mg																			
		BFT1		BFT 2		BFT 3		BFT 4		BFT 5		BFT 6		BFT 7		BFT 8		BFT 9		BFT 10	
		IR	SR	IR	SR	IR	SR	IR	SR	IR	SR	IR	SR	IR	SR	IR	SR	IR	SR	IR	SR
1	Quinapril HCl(mg)	5	10	5	10	5	10	5	10	5	10	5	10	5	10	5	10	5	10	5	10
2	Lactose (mg)	30	20	30	20	30	20	30	20	30	20	30	20	30	20	30	20	30	20	30	20
3	Peg(mg)	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20	10	20
4	Cross Povidone (mg)	3	-	3	-	3	-	3	-	3	-	3	-	3	-	3	-	3	-	3	-
5	Mg.str (mg)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
6	NaHCO3 (mg)	-	6	-	6	-	6	-	6	-	6	-	6	-	6	-	6	-	6	-	6
7	Carbopol (mg)	-	-	-	42	-	-	-	-	-	21	-	-	-	-	-	-	-	21	-	21
8	Xanthum (mg)	-	-	-	-	-	-	-	42	-	-	-	21	-	-	-	21	-	-	-	21
9	Guargum (mg)	-	-	-	-	-	42	-	-	-	21	-	21	-	21	-	-	-	-	-	-
10	HPMC (mg)	-	42	-	-	-	-	-	-	-	-	-	-	-	21	-	21	-	21	-	-
		50	100	50	100	50	100	50	100	50	100	50	100	50	100	50	100	50	100	50	100
	Total tablet wt	150		150		150		150		150		150		150		150		150		150	

Table 2. Weight variation tolerances for uncoated tablets as per USP

Average weight of Tablets (mg)	Maximum percentage difference allowed
130 or less	10
130-324	7.5
More than 324	5

Table 3. Micromeretic parameters of formulations

Formulation code		Micromeretic properties				
		Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose(^{o})	Compressibility index (%)	Hausner's ratio
F1	IR	0.27	0.32	$31^0\ 83^1$	15.62	1.22
	SR	0.272	0.324	$25^0\ 48^1$	16.07	1.19
F2	IR	0.28	0.33	$28^0\ 67^1$	16.20	1.18
	SR	0.301	0.353	$27^0\ 67^1$	14.8	1.17
F3	IR	0.29	0.35	$26^0\ 83^1$	14.14	1.23
	SR	0.299	0.350	$29^0\ 31^1$	12.4	1.16
F4	IR	0.28	0.33	$27^0\ 76^1$	15.25	1.18
	SR	0.298	0.345	$26^0\ 47^1$	13.4	1.28
F5	IR	0.26	0.31	$28^0\ 84^1$	16.12	1.20
	SR	0.302	0.353	$28^0\ 39^1$	14.6	1.17
F6	IR	0.31	0.38	$29^0\ 31^1$	18.42	1.23
	SR	0.299	0.346	$28^0\ 83^1$	13.5	1.15
F7	IR	0.29	0.34	$26^0\ 67^1$	14.70	1.19
	SR	0.292	0.332	$26^0\ 67^1$	11.9	1.13
F8	IR	0.27	0.33	$27^0\ 83^1$	16.18	1.25
	SR	0.299	0.350	$27^0\ 83^1$	14.5	1.17
F9	IR	0.25	0.30	$24^0\ 48^1$	15.66	1.17
	SR	0.292	0.344	29^072^1	15.13	1.17
F10	IR	0.29	0.35	$28^0\ 36^1$	17.14	1.21
	SR	0.293	0.332	$28^0\ 67^1$	11.9	1.13

Table 4. Evaluation of floating bilayer tablets of Quinapril HCl

S. no	Formulation	Hardness (kg/cm^3)	Wt. variation (mg)	Thickness (cm)	% Friability	FLT (SEC)
1	F1	5.75±0.08	150.7±0.50	4.08±0.018	0.28±0.08	102
2	F2	5.87±0.21	149.8±0.56	3.99±0.043	0.31±0.67	21
3	F3	5.62±0.37	150.9±0.51	4.12±0.015	0.29±0.45	23
4	F4	5.51±0.22	149.5±0.43	4.23±0.024	0.35±0.06	18
5	F5	5.68±0.13	149.8±0.64	4.39±0.035	0.31±0.01	32
6	F6	5.78±0.11	151.3±0.55	4.36±0.021	0.25±0.36	17
7	F7	5.91±0.21	150.1±0.49	4.18±0.013	0.23±0.45	19
8	F8	5.87±0.38	150.3±0.81	3.96±0.012	0.31±0.02	28
9	F9	5.97±0.17	149.9±0.68	4.02±0.015	0.28±0.47	14
10	F10	5.81±0.11	150.4±0.58	4.21±0.013	0.24±0.03	22

Table 5. Cumulative percent drug release data

Time(hr)	Cumulative % drug release in 0.1 N HCl									
	F1 (HPMC)	F2 (C)	F3 (G)	F4 (X)	F5 (C+G)	F6 (X+G)	F7 (G+H)	F8 (X+H)	F9 (C+H)	F10 (C+X)
0	0	0	0	0	0	0	0	0	0	0
0.25	15.51	16.83	24.305	19.306	19.823	14.549	17.582	19.306	18.272	20.34
0.50	17.755	19.651	28.098	25.167	30.339	17.553	22.064	23.96	21.547	29.132
0.75	19.479	36.885	31.885	29.649	33.441	21.885	38.096	25.167	28.96	36.889
1	32.235	43.67	33.269	49.813	41.543	24.147	43.562	39.82	34.986	45.78
2	37.234	56.437	46.487	53.995	46.37	30.453	51.669	46.023	40.164	59.471
3	44.3019	70.46	56.457	63.263	52.68	36.773	60.281	53.953	44.474	64.569
4	62.57	75.89	65.82	69.124	64.897	43.825	68.319	62.005	53.782	68.607
5	68.60	80.426	73.261	72.917	74.857	52.885	74.839	66.697	62.459	75.48
6	75.15	89.46	77.49	83.949	80.438	59.231	79.396	71.742	71.193	81.56
7	84.98	98.89	86.48	94.768	86.535	68.554	83.449	79.421	80.501	85.432
8	99.34	-	90.155	99.145	91.706	75.486	89.491	83.419	84.294	89.112
9	-	-	98.561	-	98.97	82.74	92.591	89.292	86.362	95.499
10	-	-	-	-	-	89.452	98.864	94.24	91.189	99.01
11	-	-	-	-	-	96.36	-	98.974	99.146	-
12	-	-	-	-	-	99.636	-	-	-	-

CONCLUSION

The present work was to produce bilayer floating tablet of Quinapril HCl with good sustained release profile and increased bioavailability. The tablets were obtained by direct compression for all the formulations BLF1 to BLF10 and evaluated for the buoyancy lag time and floating time, hardness, weight variation. Based on the performance with respect to buoyancy lag time, floating time and the release characteristics, the formula (F6) was selected as the best formula as it showed a buoyancy time 17 s and a floatation time of 12 h, followed by the Higuchi diffusion mechanism. This formulation (F6) showed a sustained release rate throughout its release period. Thus, results of the current study clearly indicate, a promising potential of the Quinapril HCl floating system as an alternative to the conventional dosage form.

REFERENCES

Anonymous 1. www.drugbank.com/quinapril/html

Brahmankar DM and Jaiswal BS. Biopharmaceutics and pharmacokinetics A tretise. 2004; 335-347.

Chien YE. Potential developments, new approaches in oral controlled release drug delivery systems. *Drug Dev. Ind. Pharm*, 9, 1993, 486–488.

Chinam NP, Kumar AB, Pandit HK, Singh SP and Devi MV. Design and Evaluation of Sustained Release Bilayer Tablets of Propranolol Hydrochloride. *Acta Pharm*, 57, 2007, 479-489.

Deshpande CT, Rhodes NH Shah and Malick AW. Controlled release drug deliverysystems for prolonged gastric residence: an overview, *Drug Dev. Ind. Pharm*, 22**,** 1996, 531–539.

Dollery C. *Therapeutics Drugs*, Churchill Livingstone, New York 1999.

FDA Guidance for Industry. Dissolution Testing of Immediate Release Solid Oral Dosage Forms. *Dissolution Technology*, 4, 1997, 15-22.

Jain NK. Controlled and Novel Drug Delivery", CBS Publishers & Distributors, New Delhi, #rd edition, 2007, 353-380.

Mary Anne Hochadel. *The AARP guides to pills*, 2006, 870-883

Narendiran C, Srinath MS, Ganesh babu. Optimisation of Bilayer floating tablet containing Metoprolol tartrate as a model drug for gastric retention. *AAPS Pharm Scitech*, 34, 2006, E1-E7.

Podczeck F, Drake KR, Neton JM and Harian I. The strength of bi layered tablet. *European Journal of Pharmaceutical Sciences*, 2008, 1-14.

Sheth PR and Tossounian JL. The hydrodynamic balanced system (HBS): A novel drug deliverysystem for oral use. *Drug Dev. Ind. Pharm*, 10**,** 1984, 313–339.

Subharamanyam CVS. A textbook of physical pharmaceutics. Vallaba Prakashan. 2006, 210-228.

Suvakanta Das et al. Kinetic modeling on drug release from controlled drug delivery systems. *Acta Poloniae Pharmaceutica Drug Research*, 67(3), 2010, 217-223.

United States Pharmacopoeia, US Pharmacopoeial Convention, Rockville, 1993.