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FORMULATION AND INVITRO EVALUATION OF AMBROXOL HYDROCHLORIDE SUSTAINED RELEASE PELLETS

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ABSTRACT

Ambroxol Hydrochloride is an active N-desmethyl metabolite of the mucolytic bromhexine and it is referred as "Surface activator" as it stimulates the synthesis and secretion of pulmonary tract surfactant. It acts as mucolytic agent by increasing the quantity and decreasing the viscosity of tracheobronchial secretions. It may also acts as an expectorant, increasing mucociliary transport by stimulation of ciliary motility. The present research was focused mainly to formulate sustain release pellet formulations of Ambroxol Hydrochloride using ethyl cellulose 7 cps and 15cps followed by evaluating the formulations for physical parameter, *in-vitro* drug release studies. The drug excipient compatability studies were determined by FTIR studies. Among all the formulations F5 showed good Physical characteristics and better *in-vitro* release rates when compared to other formulations and it showed bioequivalence with the innovator product. The stability studies were also performed for these formulations and the release mechanisms of these formulations was explained with Higuchi and Hixon crowl equations which indicate that pellets followed diffusion followed erosion mechanisms for drug release.

KEY WORDS: Ambroxol Hydrochloride, Ethyl cellulose, Pellets, *In-vitro*, Sustained Release.

1. INTRODUCTION

The goal of sustained release formulations is to maintain therapeutic blood or tissue levels of drug for an extended period of time. This can be achieved by attempting "zero order" release from the dosage form. The term "Controlled- release drug product" has been used to describe various types of oral extended release rate dosage forms, including sustained release (sustained action), prolonged release (long action) and retarded release. A modified-release dosage form is defined as one for which the drug release characteristics of time course and location are chosen to accomplish therapeutic convenience. SR/CR can be achieved by incorporating suitable polymer in the formulation. The selection of the polymer for SR/CR release dosage forms depends upon the physico-chemical and biological properties of the polymer. Depending upon the release pattern of the drug from polymer, the sustained or controlled release systems are divided as diffusion controlled systems, dissolution controlled systems, diffusion and dissolution controlled systems, ion exchange systems and osmotically controlled systems(Manish,2009) (Nagasamy,2008) (Ishtiaq, 2008). The selection of a drug as sustained or controlled release formulation depends upon factors like physico-chemical properties and biological properties of the drug. The present research is to develop and evaluate a better sustained release multiple unit pellet formulations for Ambroxol hydrochloride. It includes the preformulation studies and stability studies of different pellet formulations of the drug. Ambroxol is an active N-desmethyl metabolite of the mucolytic bromhexine. Although its mechanism of action has not been fully defined, it may increase the quantity and decrease the viscosity of trachea-bronchial secretions. It may also act as an expectorant, increasing mucociliary transport via stimulation of cilliary motility(Phani,2008; Tomasz,2006; Basak,2006). Ambroxol may stimulate the synthesis and secretion of pulmonary surfactant; the drug has been referred to as "surfactant activator". The effects of Ambroxol in preventing bronchial hyper-reactivity were investigated. No adverse interaction with other drugs is known. The combination of Ambroxol with other drug is possible, particularly with corticosteroids, bronchodilators and antibiotics. In the present work, the Ambroxol hydrochloride is formulated as pellets (Joao,2007; Schutz,2002; Zhang,2002). Pellets can be defined as small, free-flowing, spherical or semi-spherical solid units, typically from about 0.5mm to 1.5mm, which are usually intended for oral administration, manufactured by the agglomerates of fine powders or granules of bulk drugs and Excipients using appropriate processing equipment. Pellets can be prepared by many methods, the compaction and drug-layering being the most widely used today. The other methods include Pelletization by extrusion and Spheronization, Globulation or droplet formation, Cryopelletization, Compression, and Balling (Chitano,1989; Germouty,1987).

2. EXPERIMNTAL

2.1Materials: Ambroxol HCl was obtained as a gift sample from Swift Pharma Pvt Ltd, Starch, PVP-K30, Sugar spheres, Isopropyl Alcohol, Ethyl cellulose, Methyl dichloride, Talc were obtained from fine Chem ltd, Ahmadabad, India. All other ingredients, reagents and solvent used were of analytical grade.

2.2 Methodology: Ambroxol hydrochloride sustained release pellets are prepared by wurster coating method using different excipients and polymers to release the drug slowly through an extend period of time. The method of preparation of Ambroxol HCl SR pellets involves in two steps, namely drug coating and polymer coating. In the drug coating process drug is coated as a suspension form to dummy pellets and dried and sieved. Drug coated pellets are coated with SR polymer to form SR pellets (Singh,2009; Asterios,1989). These SR pellets are dried, sieved and send to quality control. in the present study 6 formulations of Ambroxol HCl SR pellets were prepared and the formulations composition was mentioned in the Table 3.

2.3 Formulation of Ambroxol Hydrochloride Sustained Release Pellets: Weigh the raw materials according to the manufacturing work order into double lined poly bags and affix dispensing labels with all details. Pulverize the Ambroxol HCL powder thoroughly and collect in double lined Polybags. Sieve through #30 mesh by using sifter. Load the sifted material along with the starch in double cone blender and mix for 30 minutes. PVP K90 is dissolved in isopropyl alcohol under stirring. Load the non-pariel seeds into coating pan and wet it by spraying the Solution and dust the blend powder till material stick to wet pellets, to form round spheres and repeat the operation till blend powder completes. Unload the drug pellets from the coating pan and load into tray drier for drying. Initially dry the pellets under the current of air for 30min switch on the heaters and maintain temperature from 28º C-32ºc. Dry the pellets till the moisture content of pellets reduce to 1.5% (Rahman,2005; Mustafa,2007). Shift the pellets through 18mesh, collected the sample and pass through 25mesh, Labelled as 18/25 fraction pellets. Take isopropyl alcohol and methylene dichloride in a stainless steel container to this add TEC under stirring continuously. To the above solution add ethyl cellulose by stirring. Filter the solution through nylon mesh to get a uniform solution. Load the drug pellets into Fluidized bed coater and spray the SR coating Solution by using Fluidized bed coater Maintain the required conditions in coater. Initially dry the pellets under the current of air for 30min by using heaters and maintain temperature from 28-32ºc. Dry the pellets till the moisture content of pellets reduce to 1.5%. Sift the SR coated pellets through sieve #12mesh, collect #12 mesh passing. Sifting the #12 mesh passing through #16 mesh retained pellets and labeled as 12/16 fraction pellets. Totally six Formulation trails were done using the same procedure(Da-Peng,1999; Masazumi,2002). During all the stages of the manufacturing process, temperature and humidity was maintained at 25±5^{0}C and 50±10% RH. To optimize the formulation, the capsules were assay by U.V Spectroscopic method and drug release study. The optimized batch F5 selected for further evaluation studies. Filling of the pellets into capsules by manually, coated pellets were transferred into capsules by spreading it into equal quantities equivalent to 75 mg Ambroxol HCL. As per the above procedure, drug loading was carried out for 6 trails.

Table 1: In-Process Parameters

In-Process Parameters for SR coating		**In-process parameters for drug coating**	
Process parameters	**Range**	**Process parameters**	**Range**
Inlet temperature	38-42^{0}C	Inlet temperature	38-42ºc
Product temperature	32-36^{0}C	Rpm of coating pan	10-15
CFC	800-2500	Spray rate (mg/min)	9-15 mg/min
Atomization	1-3	Atomization air	1-3
Spray pressure(Barr)	3-4	-	-
Peristaltic pump speed	12-18rpm	-	-
Spray rate(mg/min)	8-12	-	-
Wurster height(mm)	20-60	-	-

2.4 Evaluation Parameters: Physical Evaluation of Sustained Release Coated Pellets such as Angle of Repose, Bulk Density, Tapped Density, Moisture Content (Or) Water by Kf. Chemical Evaluation of SR coated pellets such as Assay and Dissolution and Evaluation of Capsules for their Uniformity of weight, Lock length, particle size by Scanning Electron Microscope (SEM analysis).

2.5 Drug Excipient Compatibility Studies: Compatibility studies were carried out to study the possible interactions between AMBROXOL HCL and other inactive ingredients in the formulation. The compatibility studies were carried out at 40°C/75% RH for 0,2 and 4 weeks and control samples were to be kept at 2-8°C. With respect to physical and chemical aspects, they were tested. The results were given in Table no.2

3. RESULTS

The pre-formulation studies were performed in order to identify the physical and chemical properties of the drug substance. The results were as shown in the following table 2.

Table 2 Pre-formulation Study of Active Pharmaceutical Ingredient

Characteristics	Results
Physical appearance	A white (or) almost white powder, odourless.
Solubility	Sparingly soluble in water,soluble in Methanol, practically soluble in Methylene chloride
Bulk density	0.75gm/ml
Tapped density	0.89gm/ml
Compressibility index	15.73%
Melting point	235-240^{0}C
Molecular weight	414.6.

Table No.3 Drug Excipient Compatibility Studies: (NCC-No color change)

Composition Details	Observations Storage Condition / Duration						
	Initial	40°C/ 75%RH			60°C		2-8°C
		1M	2M	3M	15D	30D	3M
Ambroxol HCL	A White colour powder	NCC	NCC	NCC	NCC	NCC	NCC
Ambroxol HCL and Sugar spheres (30-35mesh)	A White colour Powder	NCC	NCC	NCC	NCC	NCC	NCC
Ambroxol HCL and starch	A White colour Powder	NCC	NCC	NCC	NCC	NCC	NCC
Ambroxol HCL and PVP-K-90	A White colour Powder	NCC	NCC	NCC	NCC	NCC	NCC
Ambroxol HCL and ethyl cellulose	A White colour Powder	NCC	NCC	NCC	NCC	NCC	NCC

Table 4 Formulations of Ambroxol HCl SR Pellets

Ingredient	F1	F2	F3	F4	F5	F6
Ambroxol HCl	20	20	20	20	20	20
Starch	10	10	10	10	10	10
Sugar Pellets	18	18	18	18	18	18
PVP K90	1.2	1.2	1.2	1.2	1.2	1.2
IPA (ml)	30	30	30	30	30	30
SR COATING						
EC 7cps	0.22**(0.5 %)**	0.44**(1%)**	0.66**(1.5%)**	-	-	-
EC 50cps	-	-	-	0.98**(2%)**	1.7**(3.5%)**	2.46**(5%)**
IPA (ml)	0.17	0.17	0.17	0.17	0.17	0.17
MDC (ml)	50	50	50	50	50	50
TEC (ml)	17	17	17	17	17	17

Table No.5 Pre-formulation Characteristics

Code	Angle of Repose (º)	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Compressibility Index (%)	Moisture Content(%)
F1	25.7	0.74	0.86	13.95	2.2
F2	26.4	0.72	0.82	12.19	2.1
F3	28.9	0.69	0.87	20.68	2.2
F4	24.3	0.64	0.85	24.70	2.5
F5	25.4	0.75	0.89	15.73	2.5
F6	28.2	0.78	0.89	12.35	2.6

Table 6 Chemical Evaluation

Physical parameter	F1	F2	F3	F4	F5	F6
Drug content (%)	97.62	97.97	97.81	98.24	98.62	98.45

Table 7 *In-vitro* Dissolution Studies

Dissolution Time(hr)	Percentage Drug Release (%)						
	F1	F2	F3	F4	F5	F6	Innovator
1	26.8	23.6	21.4	18.6	18.2	11.3	18.6
2	38.3	29.5	36.4	22.6	23.7	17.2	22.0
4	51.7	45.4	46.7	44.8	47.7	45.8	48.1
8	58.9	61.7	60.9	59.3	61.8	53.4	62.0
12	61.4	63.9	76.6	85.8	86.3	71.9	86.4
24	72.3	72.3	88.4	90.3	98.2	80.4	98.7

Table No.8 Comparison of Dissolution Profiles by Similarity Factors

Formulation	Difference Factor (f_1)	Similarity Factor (f_2)
F1	24	43
F2	13	57
F3	11	56
F4	3	83
F5	1	92
F6	16	52

Table No.9 Stability Studies of Ambroxol Hcl at the end of first Month

Conditions	Initial	25°C/60% RH	30°C/65% RH	40°C/75% RH
Physical Appearance	White to off White Spherical Pellets	Colour is initial but shape is not uniform	Colour is initial but shape is not uniform	Colour is initial but shape is not uniform
Drugcontent(%)	98.62	97.64	97.51	97.83
Dissolution				
1st hr	18.2	17.8	18.6	18.1
2nd hr	23.7	23.4	25.78	23.5
4th hr	47.7	47.1	45.8	46.9
8th hr	61.8	63.4	67.4	64.5
12th hr	86.3	85.9	89.4	86.8
24th hr	98.2	96.3	97.3	96.5

Table No.10 Stability Studies of Ambroxol Hcl at the end of second Month

Conditions	Initial	25°C/60% RH	30°C/65% RH	40°C/75% RH
Physical Appearance	White to off White Spherical Pellets	Colour is initial but shape is not uniform	Colour is initial but shape is not uniform	Colour is initial but shape is not uniform
Drugcontent (%)	98.62	97.43	98.58	96.49
Dissolution				
1st hr	18.2	17.9	18.8	17.8
2nd hr	23.7	23.4	22.4	21.7
4th hr	47.7	46.9	47.3	45.9
8th hr	61.8	63.8	65.4	64.4
12th hr	86.3	84.3	86.9	85.3
24th hr	98.2	95.7	96.2	97.4

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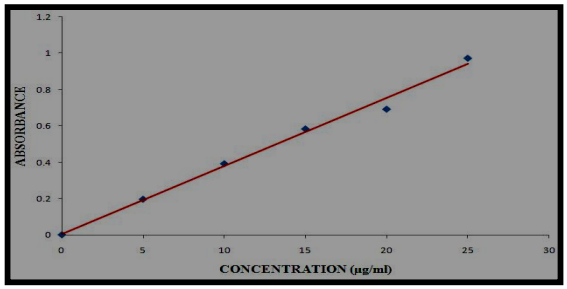
Table No.11 Stability Studies of Ambroxol Hcl at the end of third Month

Conditions	Initial	25°C/60% RH	30°C/65% RH	40°C/75% RH
Physical Appearance	White to off White Spherical Pellets	Colour is initial but shape is not uniform	Pellets became brown colour	Pellets became brown colour
Drugcontent (%)	98.62	97.38	98.17	96.34
Dissolution				
1st hr	18.2	17.4	18.1	17.9
2nd hr	23.7	23.1	22.6	22.3
4th hr	47.7	46.8	45.3	44.8
8th hr	61.8	62.4	60.8	61.5
12th hr	86.3	84.5	83.4	85.7
24th hr	98.2	97.4	97.7	96.3



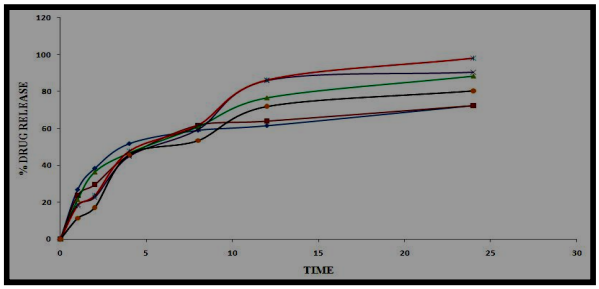
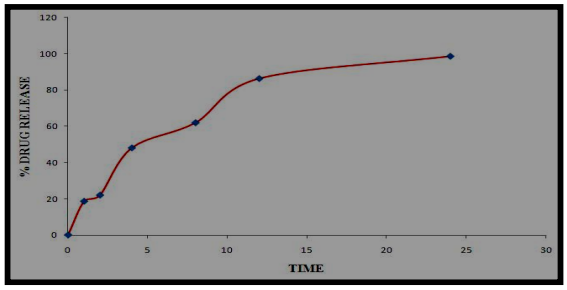


Figure 1 Standard Graph of Ambroxol HCl Fiigure 2 Dissolution profile of the formulations



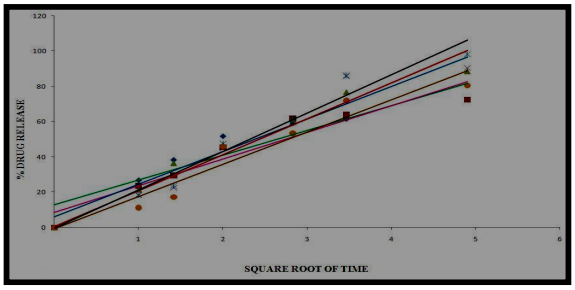
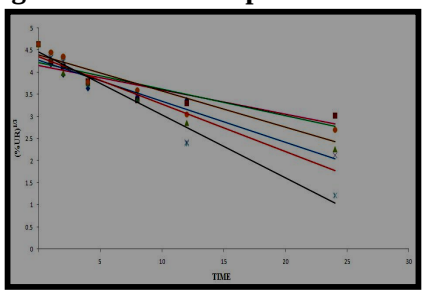


Figure 3 Dissolution profile of the innovator Fig No.4 Curve fitting of Dissolution study-Higuchi model



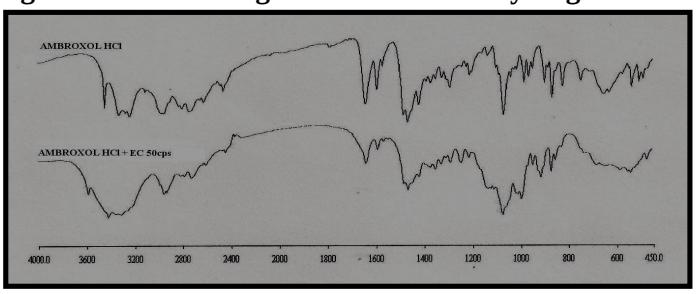


Fig No.5 Curve fitting of dissolution study- Hixon Crowl model Figure No.6 Drug polymer interaction study (FTIR studies)

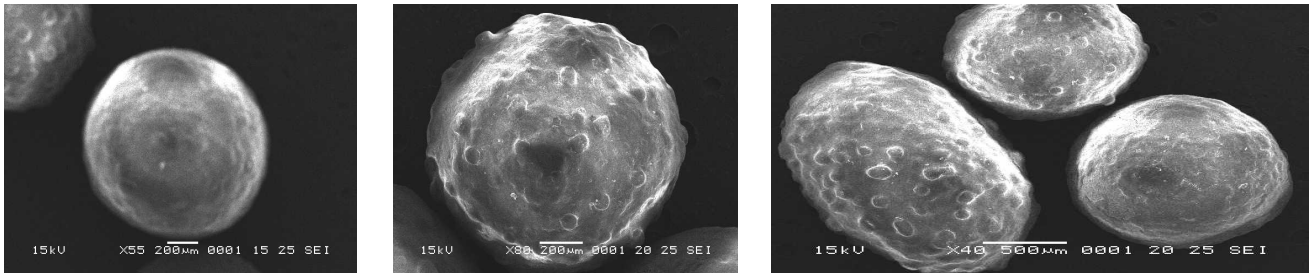


Figure no7: Scanning electron microscopy of the optimized batch F5

4. CONCLUSION

Ambroxol HCl acts as a mucolytic agent, which is stipulated by stimulation of serous cells of tonsils of bronchial tubes. The aim of the present study was to formulate and evaluate the SR pellets of Ambroxol HCl. When preformulation studies were carried out, the colour of the drug loaded pellets was found almost white and round shape. FTIR studies comes under preformulation studies which was carried out between the drug and SR polymer mixture showed no unaccountable extra peaks, which confirms the absence of chemical interaction between the drug and polymer (Figure No.6). Pellets were prepared by wurster process so little amount of moisture was expected. The moisture content of pellets was determined and loss on drying of pellets was found to be 2.5%w/w, which indicates that the layering processes as well as the raw materials were suitable to manufacture. Flow properties of pellets were estimated by angle of repose. All the formulations, except F4 showed angle of repose within the range of $25\text{-}30^0$, indicates that they had good flow property. Tapped density of pellets was found around 0.8gm/ml. This value will be suitable to fill the pellets in empty hard gelatin capsule shell. The release rate of the drug was based on the particle size and the size of pellets was found to be in micrometers range (Figure 7).Thus the physical characteristics of the pellets prepared by wurster process was satisfactory and further studies were carried out with the sample. The percentage drug content of drug was determined by UV-Visible double beam spectrophotometer at 245nm.All the formulations showed the percentage drug content100±5%.SEM analysis was carried out and the photographs of pellets showed a uniform coating of SR polymer, the surface structure was appeared to be smooth(Figure No.7). Dissolution studies were carried out to know the drug release of formulations up to 24hrs and results were 72.3%,72.3%,88.4%,90.3%,98.2% and 80.4% for formulations containing EC7cps 0.5%,1%,1.5% and EC50cps 2%,3.5% and 5% respectively. The dissolution profile was shown in figure 2 and 3. The formulations prepared by EC 7cps (F1,F2 and F3) were not showed the SR effect, because EC 7cps did not had the capability to show SR effect. So in the further formulations (F4, F5 and F6) we changed grade (EC 7cps to 50cps) and concentration of EC. The formulation F4 (2% w/w EC 50cps) showed SR drug release but drug release results was less than innovator. The formulation F5 (3.5%w/w EC 50cps) showed SR drug results, which were same when compare with innovator, further increased in concentration of EC 50 cps i.e. in the formulation F6 (5%w/w EC 50cps) ,the drug was not released for long time due to high concentration of EC 50 cps. So we confirmed that F5 was best formulation. The drug delivery system of F5 showed better linearity for Higuchi Linear kinetics ($r^2 = 0.97$) and Hixon crowl indicates that the drug release mechanism followed both diffusion and erosion mechanisms shown in figure 4 and 5.

Among the formulations, the formulation F5 (3.5%w/w EC 50cps) was found to be as the best, which released the drug 98.2% in 24 hrs and maintained its SR activity when compared with the innovator product. All the critical parameters like angle of repose, bulk density, tapped density and percentage drug content of F5 were good when compared with other formulations. The f2 = 92 ensures the equivalence of F5 (3.5%w/w EC 50cps) with innovator (Table no.7). From the above results, it can be concluded that F5 formulation showed the desired results and was found to be suitable for large scale production. The release mechanism was explored and explained with higuchi and hixoncrowel model, which indicates that pellets followed diffusion and erosion mechanisms for drug release.

Accordingly, it can be concluded that the F5 (3.5%w/w EC 50cps) is robust one and the performance is less likely to be affected by the various factors studied. The formulations were kept at stability studies according to ICH guidelines for 3 months, which showed that all the formulations were stable.

REFERENCES

Asterios Kyroudis, Sophia L, The effect of food on the movement of pellets in the GIT, Pharmacy World and Science, 11, 1989, 44-49.

Basak SC, Jaya Kumar Reddy BM, Lucas Mani KP, Formulation and evaluation of ambroxol Hcl matrix tablets as SR tablets, Ind.J.Pharm.Sci., 68, 2006, 594-598.

Branka IVIC, Svetlana IVRIC, Evaluation of Dicloenac sodium release from matrix pellets compressed into MUP's tablets, The Pharmaceutical Society of Japan, 129, 2009, 1375-1384.

Chitano P, Distefano A, Effect of ambroxol on airway hyper responsiveness and bronchoalveolar neutrophilia, Drug.Dev.Ind.Pharm., 55, 1989, 74-78.

Claudio J, Rita C, Influence of formulation and process parameters on the pellet production by powder layering technique, AAPS.Pharm.Sci.Tech., 1(2), 2000, 111-115.

Da-Peng Wang, Kun-Pin Chen, Chi-Yin Wong, Optimization and characterization of controlled release pellets of Dextromethorphan HBr, J.Med.Sci., 19 (5), 1999, 284-291.

Germouty J, Jirou-Najou JL, Clinical efficacy of ambroxol in the treatment of bronchial stasis, J.Pharm.Resch., 51, 1987, 37-41.

Guk Hyun Jo, Sung-Joo Hwang, Pharmacokinetic evaluation of Ketorolac Tromethamine SR pellets formulation after oral administration in beagle dogs, Controlled release Society 29 Annual Meeting, 2002.

Ishtiaq A, Golam kibria, Effect of plastic & acrylate polymers on the release profile of ambroxol Hcl controlled release pellets, J.Pharm.Sci., 7, 2008, 181-186.

Ishtiaq A, Golam kibria, *Invitro* release kinetic study of ambroxol Hcl pellets developed by extrusion spheronization technique followed by acrylic polymer coating, J.Pharm.Sci., 7, 2008, 75-81.

Jeevana JB, Sunitha G, Development and evaluation of gelatin microspheres of Tramadol HCl, Int.J.Pharm.Sci., 1, 2009, 24-27.

Joao LM, Santos N, Determination of ambroxol in an automated multi-pumping pulsed flow system, Eur.J.anal.Chem., 2, 2007, 423-429.

Manish R, Raju B, Formulation and evaluation of SR suspension of ambroxol Hcl using ion exchange resin, Int.J.Pharm.Tech.Resch., 4, 2009, 1322-1325.

Masazumi K, Hiroaki N, Development of controlled release matrix pellets by Annealing with micronized water insoluble or enteric polymers, Int.J.Pharm., 16, 2002, 87-91.

Mustafa SK, Suheylakas H, Formulation of controlled release Glipizide pellets using pan coating method, Heacettete University, Journal of the Faculty of Pharmacy, 27, 2007, 93-106.

Nagasamy VD, Design and *invitro* evaluation of alginate beads of ambroxol Hcl, J.Pharm.Resch., 1, 2008, 726-730.

Phani V, Shanmuganathan S, Formulation and evaluation of matrix tablets of ambroxol Hcl using natural hydrophilic polymers, Ars.Pharmaceutica, 49, 2008, 341-352.

Qiu Yi-Hong, Development and pharmacokinetic study of SR DOxicyclin HCl pellets, Acta Pharmaceutica Sinica, 16, 1986, 554-558.

Rahman N, Yuen L, *In-vitro* performance of controlled release pellets of Diltiazem HCl, Pak.J.Pharm.Sci., 18, 2005, 44-48.

Schutz Alexander, Gund Hans-jurgen et al., Local anaesthetic property of ambroxol Hcl lozenges in view of sore throat clinical proof of concept, Arzneimittel-Forschung, 52, 2002, 194-197.

Singh SK, Singh S, Seth NR, Design, development and evaluation of Domperidone pellets, Int.J.Pharm.Tec.Resch., 1, 2009, 885-891.

Tomasz D, Bartosz Misterek, Parentral ambroxol treatment causes xanthine and calcium oxalate stones in rats, AAPS.Pharm.Sci.Tech., 23, 2006, 332-337.

Wen-Tingke,Tien-Tzohsu, Physical and clinical characterization of ambroxol SR matrix tablets containing melt coated granules of ambroxol with capritol888,Eur.J.Phram.Bio Pharm., 65, 2007, 85-93.

Yue Cui, Yu Zhang, *In-vitro* and *in-vivo* evaluation of Ofloxacin SR pellets, J.Shenyang.Phar.Univ., 22, 2008, 33-36.

Zhang li-chao,Jin-hong HU, Zhen LI, Preparation and release characterstics of ambroxol Hcl coated pellets, Chin.J.Hosp.Pharm., 13, 2002, 134-139.