American-Eurasian Journal of Scientific Research 7 (4): 150-159, 2012
ISSN 1818-6785

DOI: 10.5829/idosi.aejsr.2012.7.4.6631

Formulation and Evaluation of Controlled Release Hydrophilic Matrices of Ambroxol Hydrochloride by Melt Granulation Technique

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Abstract: The aim of the present investigation was to develop oral controlled release matrix tablets of Ambroxol hydrochloride by melt granulation technique using hydrophilic meltable binders such as PEG 6000 and Gelucire 50/13(Stearoyl polyoxyl glycerides). The FT-IR and DSC analysis indicated the stability and compatibility of drug with excipients.The *in-vitro* dissolution studies of the matrix tablets prepared using only meltable binders released almost 90 % of the drug in the first 2 hours, which lead to the incorporation of HPMC K_4M into the formulations as a release retardant to control the drug release for a prolonged period of time. The formulations F3 and F6 (both containing 30% meltable binder and 20% HPMC K_4M) controlled the drug release over a prolonged period of time i.e. 12 hrs and exhibited drug release patterns ideal with the theoretical release profiles of Ambroxol hydrochloride. The dissolution data obtained for various formulations were fitted into zero-order, first order, Higuchi's and Peppas kinetic models and results showed that the drug release followed first order kinetics, the profiles were linear with Higuchi's plot and "n" value obtained from peppas were within 0.45 to 0.89 indicated (anomalous diffusion) the mechanism of drug release was diffusion coupled with erosion. The optimized formulations F3 and F6 showed no change in their *in vitro* dissolution profiles after storage at 25°C/60%RH and 40°C/75%RH for a period of three months indicating their stability.

Key words: Ambroxol Hydrochloride · PEG 6000 · Gelucire 50/13 · Melt Granulation

INTRODUCTION

Ambroxol is a metabolite of bromohexine with similar actions and uses. It is chemically described as Trans-4-[(2-Amino-3, 5-dibromobenzyl) amino]-cyclohexanol. It is an expectoration improver and a mucolytic agent used in the treatment of acute and chronic disorders characterized by the production of excess of thick mucus. It has been successfully used for decades in the form of its hydrochloride as a secretion-releasing expectorant in a variety of respiratory disorders. Its short biological half life (3-4 hrs) that calls for frequent daily dosing (2 to 3 times) and the therapeutic use in chronic respiratory disease necessitates its formulation into controlled release dosage form [1]. The development of oral controlled release dosage forms has attracted much attention in the recent years and hydrophilic matrix tablets are among the most widely used of the numerous controlled release dosage forms currently available. The most important variable in hydrophilic matrix systems is the rate at which the drug substance is released. The release of drug is controlled by the formation of a hydrogel layer around the matrix following exposure to aqueous fluid [2, 3].

Controlled-release (CR) formulations have been introduced into drug therapy with two main purposes: to reduce the number of single doses per day improving patient compliance of treatments and to decrease the fluctuations of plasma levels, in order to obtain better therapeutic efficacy and lower toxicity. There are many controlled-release pharmaceutical systems currently known, ranging from monolithic matrices, membrane reservoirs, erodible polymers, to the more technologically complex and sophisticated pH independent formulations, ion exchange resins, osmotically and geometrically modified systems. Many of these systems are not produced in a form that is amenable to large-scale manufacturing processes and the cost of formulation development, raw materials and manufacturing technology are among the principal factors in CR delivery systems formulation for oral dosing [4]. An interesting

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approach to develop CR matrix formulations is based on melt granulation, which is a very short and easy one-step technique converting fine powders into granules. The powder agglomeration is promoted by the addition of a low melting point binder, which is solid at room temperature and melts at relatively low temperatures (50-80°C). The interest in melt granulation has increased due to the advantages of this technique over other CR delivery technologies. Since it is a solvent-free process, the drying phase is eliminated and thus it becomes less consuming in terms of time and energy [5, 6].

Moreover, melt granulation is one of the most widely applied processing technique in the array of pharmaceutical manufacturing operations due to its simplicity and easy scale up [7,9]. In recent years, melt granulation has also been successfully employed to improve the dissolution rate of poorly soluble compounds increasing the bioavailability of these kinds of drugs, [10,12] and in the development of CR formulations [13,15] and masking the bitter taste of an active drug [16,17].

Hence, the purpose of the present investigation was to develop oral controlled-release matrix tablets of Ambroxol hydrochloride using polyethylene glycol (PEG 6000) and Gelucire 50/13 as meltable binders, Hydroxypropyl methyl cellulose (HPMC K4M) and di-calcium phosphate were used as matrix forming agent and filler respectively, which would release the drug for prolonged period of time in view to maximize therapeutic effect of the drug.

MATERIALS AND METHODS

Materials: Ambroxol hydrochloride was obtained from Darwin Laboratories, Vijayawada, India. PEG 6000 was obtained from Clariant Chemicals India Ltd., India. Gelucire 50/13 was obtained from Gattefosse, France. HPMC K4M was obtained from Colorcon Asia pvt. Ltd. Goa. Di-Calcium phosphate (dihydrate), Magnesium stearate and Talc were obtained from S.D. Fine Chem. Ltd., Mumbai, India. All other ingredients used throughout the study were of analytical grade.

Methods: Calculation of theoretical controlled release rate of ambroxol hydrochloride matrix tablets [18]:

The total dose of ambroxol hydrochloride controlled release formulation was calculated by Robinson Eriksen equation using available pharmacokinetic data. The drug release rate constant was calculated by the following equation:

$$D_t = Dose(1+(0.693\times t)/t_{1/2})$$

Where,
D_t = Total dose of the drug,
Dose = Dose of the IR part,
t = time (hrs) during which the CR is desired (12 hrs),
$t_{1/2}$ = half life of the drug (3 hrs).
Dt = 19.8 (1= (0.693*12) / 3) = 75mg.

Hence, the formulation should release 19.8 mg in the first hour like conventional tablets and 5.19 mg per hour up to 12 hours thereafter.

Estimation of Ambroxol Hydrochloride: Ambroxol hydrochloride in pure form and in developed formulations was estimated spectrophotometrically using Elico SL150 UV-Visible Spectrophotometer at 248 nm in 1.2 pH and pH 7.4 phosphate buffer [19].

Fourier Transform Infrared Spectroscopy (FTIR) Study: The compatibility between drug and excipients was detected by IR spectra obtained on Parkin Elimer FT-IR. The pellets were prepared on KBr-press and the spectra were recorded over the wave number range of 4000 to 500 cm.

Differential Scanning Calorimetry (DSC) Study: Thermo grams were obtained by using a differential scanning calorimeter (Thermal analysis centre, IICT, Hyd: METTLER) at a heating rate 10° C/min over a temperature range of 35-300°C. The sample was hermetically sealed in an aluminium crucible. Nitrogen gas was purged at the rate of 10 ml/min for maintaining inert atmospheres.

Preparation of Ambroxol Hydrochloride Controlled Release Matrix Tablets by Melt Granulation Technique: Ambroxol hydrochloride oral controlled release matrix tablets were prepared by melt granulation method, as per the formulae given in Table 1. Accurately weighed meltable binder was melted in a porcelain dish on a heating metal and then accurate quantity of ambroxol hydrochloride, HPMC K4M and di-calcium phosphate were taken, mixed thoroughly and were added to the melted mass of binder and stirred well to mix. Then mass was removed from the hot plate and subjected to scrapping until it attained room temperature. The coherent mass was passed through sieve # 22 and the resulting granules were resifted over sieve # 40 to separate granules and fines.

Table 1: Composition of Controlled Release Formulations of Ambroxol Hcl Matrix Tablets

		Formulations					
S.N0.	Ingredients (mg/tab)	F1	F2	F3	F4	F5	F6
1	AmbroxolHcL	75	75	75	75	75	75
2	PEG 6000	75	60	60	--	--	--
3	Gelucire 50/13	--	--	--	75	60	60
4	HPMC K4M	--	60	40	--	60	40
5	Di-calcium phosphate	45	--	20	45	--	20
6	Talc	2.5	2.5	2.5	2.5	2.5	2.5
7	Mg stearate	2.5	2.5	2.5	2.5	2.5	2.5
Total Weight		200	200	200	200	200	200

The granules were collected and mixed with talc and magnesium stearate. The lubricated blend was compressed using 8mm round flat punch on a single punch tablet machine (Cad mach, Ahmadabad). Compression was adjusted to obtain tablets with hardness in the range of 5-6 kg/cm^2 [20].

Micromeritic Evaluation of Granules: Micromeritic properties of the prepared granules of all the formulations were studied by determining the bulk density, tapped density, Compressibility Index, Hausner's ratio and angle of repose [21].

Evaluation of Compressed Tablets: The prepared tablets were evaluated for hardness, friability, weight variation, thickness and drug content uniformity. Hardness of the tablets was tested using Monsanto hardness tester (Campbell electronics, Mumbai). Friability of the tablets was determined in a Roche friabilator (Campbell Electronics, Mumbai). The thickness of tablets was measured using Vernier callipers. Weight variation test was performed according to official method specified in IP [22]. Drug content for ambroxol hydrochloride was carried out by measuring the absorbance of samples at 248 nm using Elico SL150 UV-Visible Spectrophotometer (Elico Ltd., Hyderabad).

***In vitro* Drug Release Study:** The prepared matrix tablets were subjected to *in-vitro* dissolution study using USP type II dissolution apparatus (Labindia, Disso 2000). The dissolution studies were carried out in 1.2 pH for 2 hrs and in pH 7.4 Phosphate buffer for remaining period of 10 hrs at 37± 0.5°C at 50 rpm. At regular time intervals, 5 ml of sample was withdrawn from the dissolution medium and replaced with equal volume of fresh medium to maintain sink conditions. After filtration and appropriate dilution, the samples were analyzed at 248 nm for ambroxol hydrochloride against blank using UV-Visible spectrophotometer. The amount of drug present in the samples was calculated using standard curve [19].

Drug Release Kinetics: The rate and mechanism of release of ambroxol hydrochloride from the prepared matrix tablets were analyzed by fitting the dissolution data into the following equations.

Zero-Order Equation:

$$Q_t = Q_0 + K_0 t$$

Where, Q_t is the initial amount of drug dissolved at time t, Q_o is the initial amount of drug in the solution, most of the times it is equal to zero, K_o is the zero order release rate constant [23].

First Order Equation:

$$lnQ_t = lnQ_0 \times K_1 t$$

Where,
Q_t is the initial amount of drug dissolved at time t, Q_o is the initial amount of drug in the solution, K_1 is the first order release rate constant [24].

Higuchi's Equation:

$$Q = K_H t^{1/2}$$

Where,
Q is the amount of drug released at time t per unit area,
k_H is the Higuchi diffusion rate constant [25].

Korsmeyer-Peppas Equation:

$$M_t/M_\infty = Kt^n$$

Where, M_t and M_8 are the amounts of drug released at time t and infinite time, k is a constant incorporating structural and geometric characteristics of the device, 'n' is the drug release exponent, indicative of the mechanism of drug release [26].

Swelling Study: The extent of swelling was measured in terms of percent weight gain by the tablets. The swelling behaviour of all tablets was studied. One tablet from each formulation was placed in a petridish containing phosphate buffer solution (pH 7.4). At regular time intervals, the tablet was withdrawn, blotted with a tissue paper and weighed. The process was continued for 12 hours and the percent weight gain by the tablets was calculated by using formula [27].

$$Swelling\ index\ (S.I) = \left\{\frac{M_t - M_0}{M_0}\right\} x100$$

Where,

M_t = weight of tablet at time 't'

M_o = weight of tablet at time t = 0.

Similarity Factor: The similarity factor (f_2) was used to compare the dissolution profile of each formulation with that of the marketed formulation. In this approach, recommended by the FDA guidance for the industry, when the value is between 50 and 100, the two profiles are nearly identical [28, 29].

The value is determined by the following equation

$$f_2 = 50+log\{[1+(1/n)\ \Sigma_t = 1\times n(R_t-T_t)^2]^{-0.5}\times 100\}$$

Where, n is the number of dissolution time points, R_t and T_t are the reference and test dissolution values at time t.

Stability Studies: An accelerated stability study was conducted by storing tablets in amber coloured bottles at 25°C/60%RH and 40°C/75%RH. The tablets were evaluated for the *in vitro* drug release from the matrix tablets monthly for three months [30].

RESULTS AND DISCUSSION

Fourier Transform Infrared Spectroscopy (FTIR) Study: Figure 1 shows the IR spectra of pure drug Ambroxol hydrochloride, formulations F3 and F6. The IR spectrum of ambroxol hydrochloride shows peak at 3397 due to-OH stretching. The groups of peaks at between 3196, 3281-NH_2 stretching asymmetric and symmetric. The peak at 3060 may be due to aromatic C-H stretching. The peaks at 2911, 2999 may be due to C-H stretching of CH_2 groups. The peak at 1634 NH bending of-NH_2 groups. The peaks at 1618, 1417, 1450 may be due to C=C ring stretching. The peaks at 1440, 1350 maybe due to C-H bending of CH_2 groups. The peak at 1240 is due to-OH bending. The peak at 890 is due to Substituted benzene ring. The peak at 634 may be due to C-Br. From the results, it was clear that as there were no appreciable shifts in the positions of the bands for drug comparison to the spectra of its formulation, clearly suggesting that there was no interaction of the drug with different excipients used in the present study.

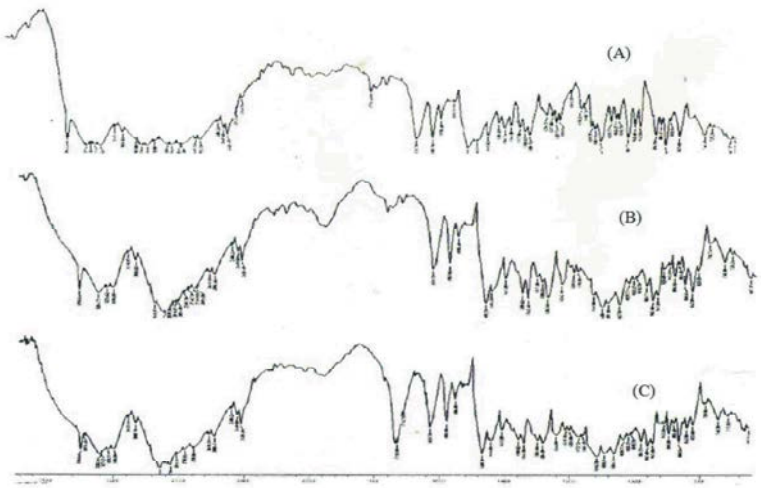


Fig. 1: FTIR Spectra of (A) Pure drug-ambroxol Hydrochloride, (B) Formulation F3 and (C) Formulation F6

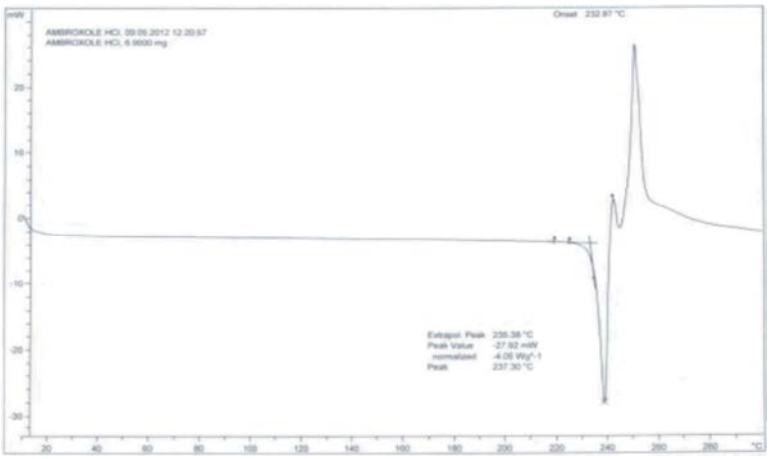


Fig. 2: DSC Thermogram of pure drug ambroxol Hydrochloride

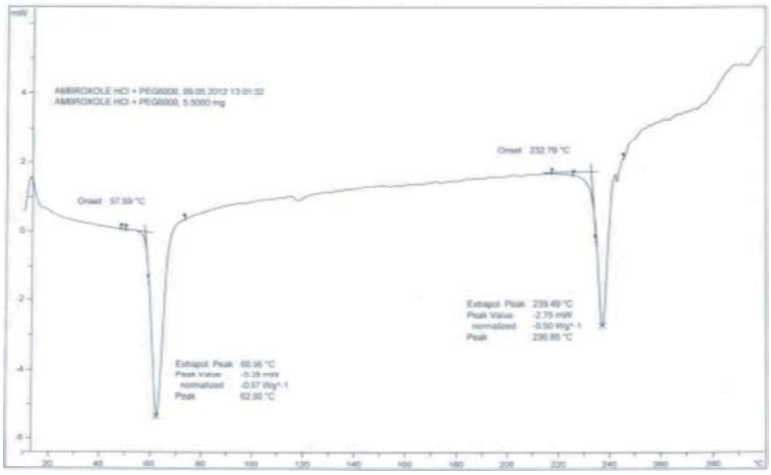


Fig. 3: DSC Thermogram of formulation F3

Differential Scanning Calorimetry (DSC) Study: The DSC thermograms of pure drug Ambroxol hydrochloride and formulation F3 were shown in Figure 2. Thermograms of pure drug and formulation F3 showed an endothermic peak having the sharp melting point 237.30°C and 236.85°C. The above observation indicated that there was no significant change in the thermal properties of the drug in its normal pure form and in the formulation with other excipients. This clearly indicates that, there was no interaction of the drug with other excipients used in the present study.

Evaluation of Granules: The micromeritic properties of the granules such as bulk density, tapped density, Hausner's ratio and angle of repose for the physical mixtures of the formulations were evaluated and the results were within the limits (Table 2).

Bulk density and tapped density for the formulations were within the range of 0.532±0.03-0.689±0.09gm/mL and 0.612±0.01-0.776±0.09gm/mL. Compressibility index and Hausner's ratio were in the range of 15.50±0.13%-17.63±0.19% and 1.14±0.02-1.21±0.07. The angle of repose of the formulations was found to be in the range of 21°±0.42-25°±0.76. Thus, the results obtained confirm that all the formulations exhibited good flow properties and good packing characteristics.

Evaluation of Compressed Tablets: The tablets with weight of 200mg, were obtained and subjected for evaluation of the post compressional parameters such as hardness, friability, weight variation, thickness and drug content uniformity and the results complied with the pharmacopoieal limits of the tablets. The values were depicted in the Table 3.

Table 2: Micromeritic properties of the prepared granules (n=3)

Formulation	Bulk density± S.D(gm/mL)	Tapped density± S.D(gm/mL)	Carr's index± S.D (%)	Hausner's ratio± S.D	Angle of repose± S.D (θ)
F1	0.576 ±0.08	0.654 ±0.05	16.07 ±0.14	1.18 ±0.01	21.5 ±0.27
F2	0.532 ±0.03	0.612 ±0.01	15.90 ±0.11	1.17 ±0.12	25 ±0.76
F3	0.569 ±0.01	0.636 ±0.01	15.50 ±0.13	1.19 ±0.05	21 ±0.42
F4	0.592 ±0.07	0.664 ±0.06	16.67 ± 0.09	1.21 ±0.07	22 ±0.95
F5	0.657 ±0.05	0.743 ±0.05	16.07 ±0.13	1.16 ±0.03	23 ±0.63
F6	0.689 ±0.09	0.776 ±0.09	17.63 ±0.19	1.14 ±0.02	24 ±0.44

Table 3: Post Compressional Parameters of ambroxol Hcl Matrix Tablets (n=3)

Formulations	Hardness± S.D(Kg/cm^2)	Friability± S.D(% wt loss)	Weight variation± S.D(mg)	Thickness± S.D(mm)	Drug content± S.D (%)
F1	5.5±0.95	0.62±0.04	198.02±2.4	2.56±0.04	96.15±0.02
F2	5.6±0.63	0.66±0.02	196.01±1.2	2.54±0.06	97.23±0.06
F3	5.4±0.51	0.64±0.01	198.04±2.1	2.49±0.03	97.14±0.04
F4	5.5±0.45	0.59±0.03	195.06±1.8	2.56±0.05	96.54±0.05
F5	5.7±0.46	0.59±0.04	198.08±2.6	2.53±0.03	97.26±0.02
F6	5.4±0.51	0.62±0.02	197.01±1.6	2.55±0.02	98.20±0.06

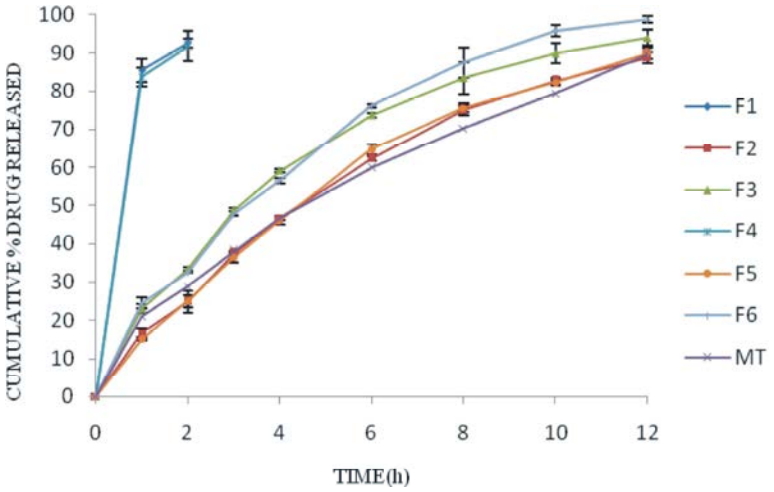


Fig. 4: Cumulative percent drug release profiles of formulations F1-F6 and Marketed formulation

The contents of the formulations were found to be uniform, since the amount of the active ingredients in each of the 10 units tested was within the range of 96.15±0.02%-98.20±0.06% indicating uniform mixing of the drug, binders and other excipients. The mean values for the hardness were found to be in the range of 5.4±0.51-5.7±0.46 kg/cm^{2}and all the formulations exhibited friability less than 0.8% during the friability determination.

***In vitro* Drug Release Studies:** The formulations F1 and F4 which contained drug and binder in the ratio of 1:1 released almost 90% of the drug in the first 2 hrs and hence could not provide controlled release of the drug, which indicated that a sufficient polymer concentration in the hydrophilic matrix systems is required to form a uniform gel barrier around the tablet upon hydration. This barrier is expected to prevent the drug from immediate release into the dissolution medium, thus it was necessary to incorporate a release retarding polymer, HPMC K_4M into the formulations to control the release of the drug.

The cumulative percent drug release for formulations F2, F3, F5 and F6 was 88.83±1.39, 93.99±2.0, 90.96±1.42 and 98.75±0.94 at the end of 12hrs. The release of ambroxol hydrochloride from the matrix tablets was found to be slow and extended up to a period of 12 hrs. It was observed that as the proportion of polymer (HPMC K_4M) increased, the release rate of ambroxol hydrochloride decreased. The cumulative percent drug release profiles of the prepared formulations were shown in Figure 4.

Table 4: *In-Vitro* Drug Release Kinetic Data of prepared matrix tablets

	Zero order		First order		Higuchi		Peppas	
Formulations	K(mol.L^{-1}h^{-1})	r^2	K(h^{-1})	r^2	K(mg/hr$^{1/2}$)	r^2	'n'value	r^2
F1	46.66	0.813	0.588	0.945	69.56	0.955	0.229	0.987
F2	7.413	0.950	0.079	0.997	28.27	0.975	0.638	0.970
F3	7.496	0.896	0.101	0.999	29.54	0.982	0.642	0.996
F4	45.5	0.873	0.522	0.990	66.40	0.983	0.272	0.975
F5	7.461	0.948	0.084	0.991	28.53	0.978	0.621	0.978
F6	8.051	0.924	0.149	0.948	31.27	0.983	0.647	0.980

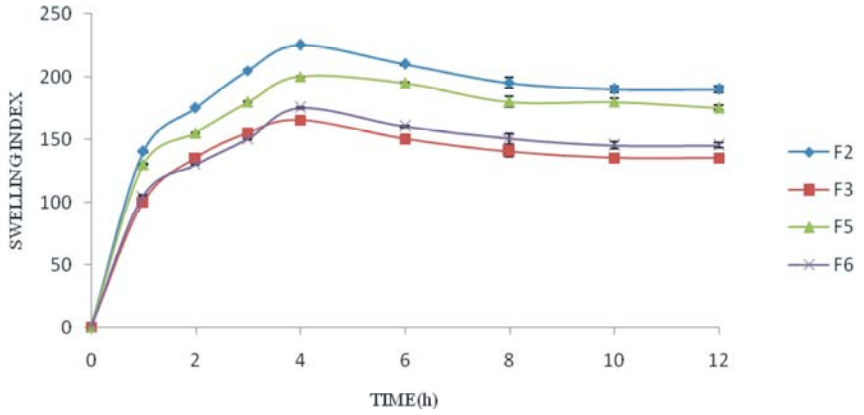
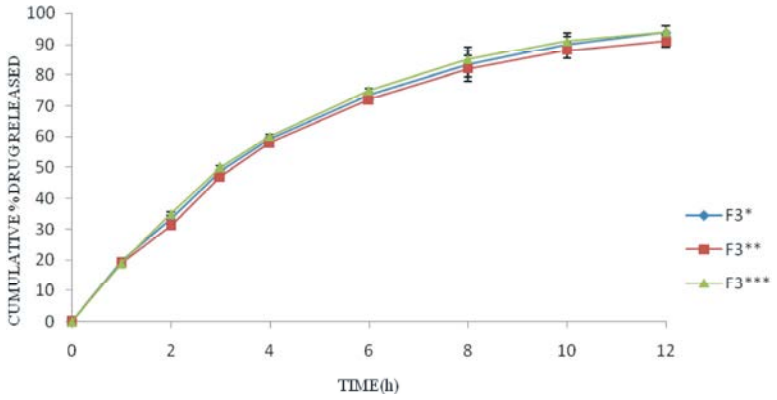


Fig 5: Swelling Behaviour of Formulations F2, F3, F5 and F6 (n=3)

In the *in vitro* dissolution studies, the prepared matrix tablets upon contact with the aqueous medium leads to hydration of the hydrophilic matrix system from the peripheral region to the centre, forming a gelatinous swollen mass, which controls the diffusion of drug molecules through the polymeric matrix system into the aqueous medium and thus releasing the drug in a controlled manner. According to theoretical sustained release profile, an oral controlled release formulation of ambroxol hydrochloride should provide a release of 25.89% in 1 h, 38.81 % in 2 h, 46.65% in 4 h, 74.40 % in 8 h and 100 % in 12 h. The formulations F3 and F6 gave release profile close to the theoretical sustained release needed for ambroxol. Initially, a small burst effect in the release of the drug was observed, which was probably sufficient for quick build up of plasma concentration. This burst effect could be due to the highly water soluble drug present in the periphery of the matrix. Subsequently, the release was more uniformly controlled by diffusion from the swelling core of the matrix.

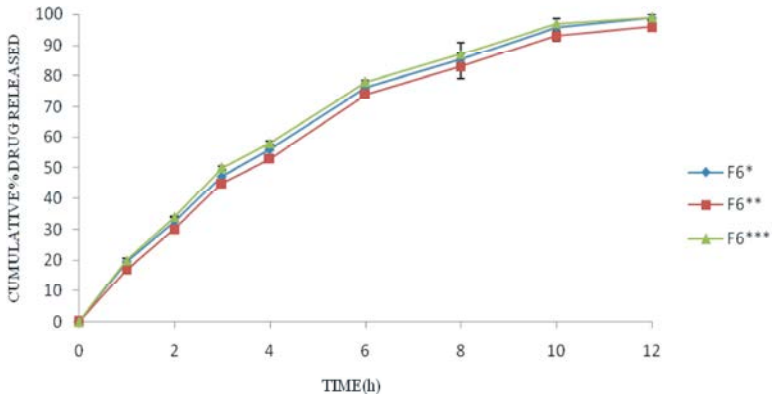
Kinetics and Mechanism of Drug Release: To ascertain the mechanism of drug release, the *in vitro* drug release data was fitted into various release kinetic models such as Zero order, First order, Higuchi and Peppas models. The first order plots obtained were linear compared with that of the zero order plots and the regression coefficients (r^2) obtained for first order kinetics were found to be higher when compared with those of zero-order kinetics, indicating that drug release from all the formulations followed first-order kinetics (Table 4). Release of the drug from a matrix tablet containing hydrophilic polymers generally involves factors of diffusion. To evaluate the drug release mechanism from the tablets, plots of percent drug released verses square root of time as per Higuchi's equation were constructed and the plots were found to be linear indicating that the drug release from the tablets was diffusion controlled. To confirm the diffusion mechanism, the data were fitted into Korsmeyer peppas equation which resulted in "n" value between 0.45 to 0.89, thus indicating the mechanism of drug release followed Non-Fickian diffusion which includes coupling of diffusion and erosion mechanisms.

Swelling Studies: The swelling behaviour indicated the rate at which tablets absorb the water from dissolution media and swells. Swelling of matrix tablets increased with respect to time because the weight gain by tablets increased proportionally with rate of hydration up to 4 hrs and matrix appeared swollen almost from the beginning and a viscous gel layer was created when in contact with water, later on swelling decreased due to dissolution of outermost gelled layer of tablets (Figure 5).



[*-Initial, **-25°C/60%RH, ***-40°C/75%RH]

Fig 6*: In vitro* release profile of ambroxol hydrochloride from the matrix tablets (F3) after stability studies (n=3)



[*-Initial, **-25°C/60%RH, ***-40°C/75%RH]

Fig 7: *In vitro* release profile of Ambroxol hydrochloride from the matrix tablets (F6) after stability studies (n=3)

The formulations F1 and F4 did not swell as much and the swelling index of formulations F2, F3, F5 and F6 increased with time as increase the concentration of HPMC K_4M in each formulation. It was observed that the drug release decreases with increasing concentration of HPMC K_4M and swelling index and the reason attributed to this fact is formation of thick gel layer by matrices around tablets that delays diffusion and release of the drug.

Similarity Factor: The similarity factor (f_2) was calculated in order to compare the release profiles of F3 and F6 with that of the reference formulation. The formulation F3 and F6 had a release profile similar to that of the marketed formulation, with a similarity factor f2 =54.4 and 51.7 respectively, hence these formulations were comparable with the marketed formulation.

Stability Studies: The stability of ambroxol hydrochloride in the matrix tablets was evaluated for a period of three months at 25°C/60%RH and 40°C/75%RH for the best formulations (F3 and F6) among the prepared formulations and it was found that there was no significant difference in the dissolution profile of initial and stability study samples as shown in Figures 6 and 7.

CONCLUSION

The present study was carried out to develop oral controlled release matrix tablets of ambroxol hydrochloride using hydrophilic meltable binders like PEG 6000 and Gelucire50/13 by melt granulation technique. The formulations F3 and F6 showed an initial burst release of the drug to provide the loading dose of the drug, followed by controlled release for 12 hrs, indicating that the "one step" melt granulation technique was a viable method to prepare oral controlled release matrix tablets of ambroxol hydrochloride. The formulations were comparable with the marketed product and were stable after storage at 25°C/60%RH and 40°C/75%RH conditions for a period of three months. So the prepared formulations were stable at the above mentioned conditions.

ACKNOWLEDGEMENTS

The authors are thankful to the Darwin Research Labs, Principal and management of Siddhartha Academy of General And Technical Education, Vijayawada, for their support and cooperation in carrying out the research work.

REFERENCES

1. Sweetman, C., 2006. Martindale, The complete drug reference, The Pharmaceutical press, London, pp: 1084.
2. Balasubramaniam, J., M.T. Kumar and G. Srinivas, 2005. HPMC-based matrix tablets of atenolol and cisapride: effect of viscosity of polymer and drug solubility on *in-vitro* release. Ind. J. Pharm. Sci., 67: 414-421.
3. Robles, L.V. and A.M.E. Campos, 1997. Influence of the viscosity grade and the particle size of HPMC on metronidazole release from matrix tablets. Eur. J. Pharm. Biopharm., 43: 173-178.
4. Bayomi, M.A., S.A. Al-Suwayeh and A.R.M. El-Helw, 2001. Excipient-excipient interaction in the design of sustained release theophylline tablets: *in-vitro* and *in-vivo* evaluation. Drug Development and Industrial Pharmacy, 27: 499-506.
5. Hamdani, J., A.J. Moes and K. Amighi, 2002. Development and evaluation of prolonged release pellets obtained by the melt pelletization process. Int. J. Pharm., 245: 167-177.
6. Suryawanshi, R.J., U. Shah and K. Vishnupad, 1996. Alternative granulation technique: melt granulation. Drug Development and Industrial Pharmacy, 22: 917-924.
7. Lue, B.M., F.S. Nielsen and T. Magnussen, 2008. Using biorelevant dissolution to obtain IVIVC of solid dosage forms containing a poorly-soluble model compound. Eur J Pharm Biopharm, 69: 648-657.
8. Goole, J., P. Deleuze and F. Vanderbist, 2008. New levodopa sustained-release floating mini tablets coated within soluble acrylic polymer. Eur. J. Pharm. Biopharm., 68: 310-318.
9. Shimpi, S., B. Chauhan and K.R. Mahadik, 2004. Preparation and evaluation of diltiazem hydrochloride-Gelucire 43/01 floating granules prepared by melt granulation. AAPS Pharm. Sci. Tech., 5(3): 51-56.
10. Panda, R. Rashmi, Tiwary and K. Ashok, 2012. Hot melt granulation: a facile approach for monolithic osmotic release tablets. Drug Development and Industrial Pharmacy, 38(4): 447-461.
11. Yang, D., R. Kulkarni and R.J. Behme, 2007. Effect of the melt granulation technique on the dissolution characteristics of griseofulvin. Int. J. Pharm., 329: 72-80.
12. Passerini, N., B. Albertini and B. Perissutti, 2006. Evaluation of melt granulation and ultrasonic spray congealing as techniques to enhance the dissolution of praziquantel. Int. J. Pharm., 318: 92-102.
13. Goole, J., F. Vanderbist and K. Amighi, 2007. Development and evaluation of new multiple-unit levodopa sustained-release floating dosage forms. Int. J. Pharm., 334: 35-41.
14. Sharma, P., P. Chaudhari and H. Bhagat, 2007. Preparation and characterization of meloxicam-myrj 52 granules obtained by melt granulation. Pharmaceutical Technology, 31: 51-59.
15. Ochoa, L., M. Igartua and R.M. Hernandez, 2010. *In-vivo* evaluation of two new sustained release formulations elaborated by one-step melt granulation: level A *in-vitro-in-vivo* correlation. Eur. J. Pharm. Biopharm., 75: 232-237.
16. Chokshi, R. and H. Zia, 2004. Hot melt extrusion technique: a review. Iranian Journal of Pharmaceutical Research, 3: 3-16.
17. Schafer, T., P. Holm and H.G. Kristensen, 1990. Melt granulation in a laboratory scale high shear mixer. Drug Development and Industrial Pharmacy, 16: 1249-1277.
18. Robinson, J.R. and S.P. Eriksen, 1966. Theoretical formulation of sustained release dosage forms. Journal of Pharmaceutical Sciences, 55: 1254-1263.
19. Ganesan, V. and D.L. Jayachandran, 2008. Design and evaluation of matrix tablets of ambroxol hydrochloride using guar gum. Research J. Pharm. and Tech., 1: 507-512.
20. Shailesh Prajapati, T., N. Amit Patel and N. Chhagan Patel, 2011. Formulation and evaluation of controlled-release tablet of zolpidem tartrate by melt granulation technique. ISRN Pharmaceutics, Article ID 208394, 1-8.
21. Aulton, M.E., 2002. Pharmaceutics-The Science of Dosage form Design, 2nd edition, pp: 133-134.
22. Leon Lachman, A. Herbert Lieberman and Joseph L. Kanig, 1987. The Theory and Practice of Industrial pharmacy, 3rd Edition, Varghese publishing house, pp: 296-300.
23. Brazel, C.S. and N.A. Peppas, 2000. Modeling of drug release from swellable polymers. Eur. J. Pharm. Biopharm., 49: 47-58.
24. Lapidus, H. and N.G. Lordi, 1966. Drug release from compressed hydrophilic matrices. J. Pharm. Sci., 55: 840-843.

25. Higuchi, T., 1963. Mechanism of sustained action medication, theoretical analysis of rate of release solid drugs dispersed in solid matrices. J. Pharm. Sci., 52: 1145-1148.
26. Korsmeyer, R.W., R. Gurny and E. Doelker, 1983. Mechanism of solute release from porous hydrophilic polymers. Int. J. Pharm., 15: 25-35.
27. Bangale, G.S., B. Stephen Rathinaraj and G.V. Shinde, 2011. Formulation and evaluation of natural gum based matrix tablets for oral controlled delivery of nimodipine. Ind. J. Pharm. Edu. Res., 45: 375-383.
28. Shah, V.P., Y. Tsong and P. Sathe, 1998. *In-vitro* dissolution profile comparison-statistics and analysis of the similarity factor, f_2. Pharm. Res, 15: 889-896.
29. Moore, J.W. and H.H. Flanner, 1996. Mathematical comparison of curves with an emphasis on *in vitro* dissolutions profiles. Pharm. Technol., 20: 64-74.
30. Sunil, R., P. Pavan kumar and K. Rajanarayana, 2010. Formulation and release characterization of a bilayer matrix tablet containing glimperide immediate release component and metformin hydrochloride as sustained release component. Int. J. Pharm. Sci. and NanoTech., 3: 851-859.