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DESIGN, FORMULATION AND EVALUATION OF GUAIPHENESIN SUSTAINED RELEASE TABLETS

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ABSTRACT

Guaiphenesin (GUA) is a weakly basic drug and used as an expectorant. The half -life of Guaiphenesin is 1hour and generally administered as immediate release tablet at a dose of 200-400mg every 4 to 6 hours. The main objective of research work was to develop once daily extended release tablets of Guaiphenesin by both wet granulation and direct compression techniques and to compare the in-vitro dissolution profiles with the domestic reference product. We evaluated all the physicochemical parameters like drug content, bulk density, tapped density, compressibility, weight variation, hardness, friability and dissolution method. They followed zero order and first order effect. The optimized formulation F12 showed the higher cumulative drug percent release compared to other formulations. Solubility showed that the drug is more soluble in acidic medium. The in-vitro release of Guaiphenesin extended release tablets were studied in 900ml of 0.1N HCL for 12hrs was used as dissolution medium using USP type I dissolution apparatus at 37±2^{o}C and 75rpm speed.

KEYWORDS: Drug name, sustained release, Carbopol 934P NF, HPMC polymers.

INTRODUCTION

Oral drug delivery system is the most desirable and preferred method of administering therapeutic agents for their systemic effects, when compared to other routes of administration. In general, the oral medication is considered as the first avenue investigated in the discovery and development of new pharmaceutical active ingredients and pharmaceutical formulations, mainly because of patient acceptance, convenience in administration, and cost- effective manufacturing process. Guaiphenesin is an expectorant and it acts by reducing viscosity of sputum. It is used as expectorant in cough mixtures and tablets. It has short half-life (1hr), higher water solubility and therefore frequent administration is required. The objective in designing sustained delivery system is to reduce the frequency of dosing or to increase the effectiveness of the drug by localizing at the site of action or providing uniform drug delivery. As the expense and complication involved in marketing new drug entities have increased, with

Concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on development of sustained or controlled released drug delivery systems.

MATERIALS AND METHODS

The gift sample obtained by Guaiphenesin (gift sample from granules India, Hyderabad), Hydroxy propyl methyl cellulose (of different viscosity grades) (Colrcorn, India), Micro crystalline cellulose pH 105, pH 102 (FMC, Ireland/U.S.A), Carbopol 934P NF (Kemphasol.P.B.no.2277, Bombay), Magnesium stearate (SD-Fine chemicals).

METHODS

Solubility studies

Excess of Guaiphenesin was added to 5ml of each fluid in 25ml stoppered conical flasks and the mixture was shaken for 24hrs at room temperature (23±1^{o}C) on a rotary flask shaker. After 72hrs of shaking 1ml aliquots were withdrawn and filtered immediately using a 0.45µ nylon disk filter. The filtered samples were diluted suitably and assayed for Guaiphenesin by measuring absorbance at 274nm. Shaking was continued until three consecutive estimations were same. The solubility experiments were run in triplicate.

Calibration curve

For the estimation of Guaiphenesin, the stock solution was subsequently diluted with subsequent medium to get a series of dilutions containing 10, 20, 30, 40 and 50µg/ml of solution and measured the absorbance at 274nm (UV-VIS spectrophotometer, SL-150, Elico) against same dilution as blank.

Preparation of stock solution

10mg of Guaiphenesin was dissolved in 10ml of methanol in 10ml volumetric flask and made up to volume with methanol.

Precompression Parameters

Preformulation testing is the first step in the rational development of dosage forms. It can be defined as an investigation of physical and chemical properties of a drug substance alone and combined with excipients. The objective of preformulation testing is to generate information useful to the formulator in developing stable and bioavailable dosage forms that can be mass produced.

Determination of densities

Apparent density (Bulk): Bulk densities are the ratio of given mass of powder to its bulk volume. The bulk density, as a measure used to describe packing material granules, was determined transferring the accurately weighed amount of powder sample to the graduated cylinder with the aid of a funnel. The powder was leveled carefully without compacting and the unsettled apparent volume (Vo) was noted. The bulk density in g/mL was calculated by the formula,

Bulk density = M/Vo

Where M is the weight of the sample taken

Tapped density

After noting down the volume (V_o) in bulk density testing, the graduated cylinder was tapped mechanically using a suitable tapped density tester that provides a fixed tap of 14±2mm at 300 drops per minute, for 500 times initially and the tapped volume (Va) was measured to the nearest graduated unit. The tapping was repeated for an additional 750 times and the tapped volume (Vb) was measured to the nearest graduated unit. If the difference between the two measurements is less than 2%, Vb is the final tapped volume (Vf). If the difference greater than 2%, the tapping was repeated at the increments of 1250 until the difference between the two successive measurements is less than 2%.

The tapped density, in g/mL was calculated by the formula.

Tapped density=M/Vf,

Where M is sample taken for bulk density testing.

Carr's index (compressibility)

The compressibility and Hausner's ratio are the measures of the propensity of a powder to be compressed. As such, these are the measures of relative importance of interparticulate interaction. In a free flowing powder, such interactions are less significant and the bulk and tapped densities will be closer in value. For poor flowing materials, the bulk and tapped densities will be observed. These differences are reflected in the compressibility index and the Hausner's ratio.

Based on the apparent bulk density and the tapped density, the percentage compressibility of the bulk drug was determined by using the following formula.

$$\%\text{compressibility} = \frac{\text{tapped density} - \text{bulkdensity}}{\text{Tapped density}} * 100$$

Hausner's ratio

The ratio of Tapped density to the bulk density of the powders is called the Hausner's ratio.

Hausner's ratio = $\frac{tapped\ density}{bulk\ density}$

Table 1: The following table shows the acceptance criteria for flow properties of the compound according to USP.

Compressibility index(%)	Flow properties	Hausner's ratio
<10	Excellent	1.00-1.11
11-15	Good	1.12-1.18
16-20	Fair	1.19-1.25
21-25	Passable	1.26-1.34
26-31	Poor	1.35-1.45
32-37	Very poor	1.46-1.59
>38	Very, very poor	>1.60

Ftir Studies

The FTIR studies were done to characterise the drug. The peak is observed at 3212.619cm^{-1} is characteristic of the O-H stretching seen in alcohols. The peak produced at 1453.85cm^{-1} is characteristic of the C=C stretching of the benzene ring in the molecule. The peak observed at 1589.97cm^{-1} is typical of the C-H bend. No interaction between polymers and drugs were observed from the spectrum.

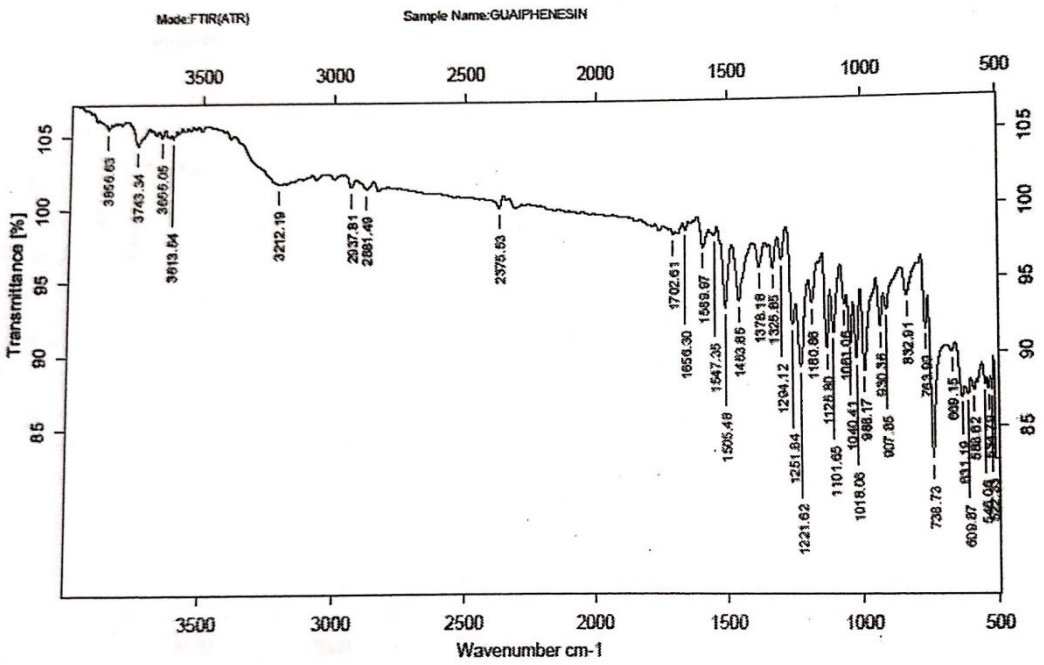

Fig. 1: FTIR Spectrum for Guaiphenesin pure drug.

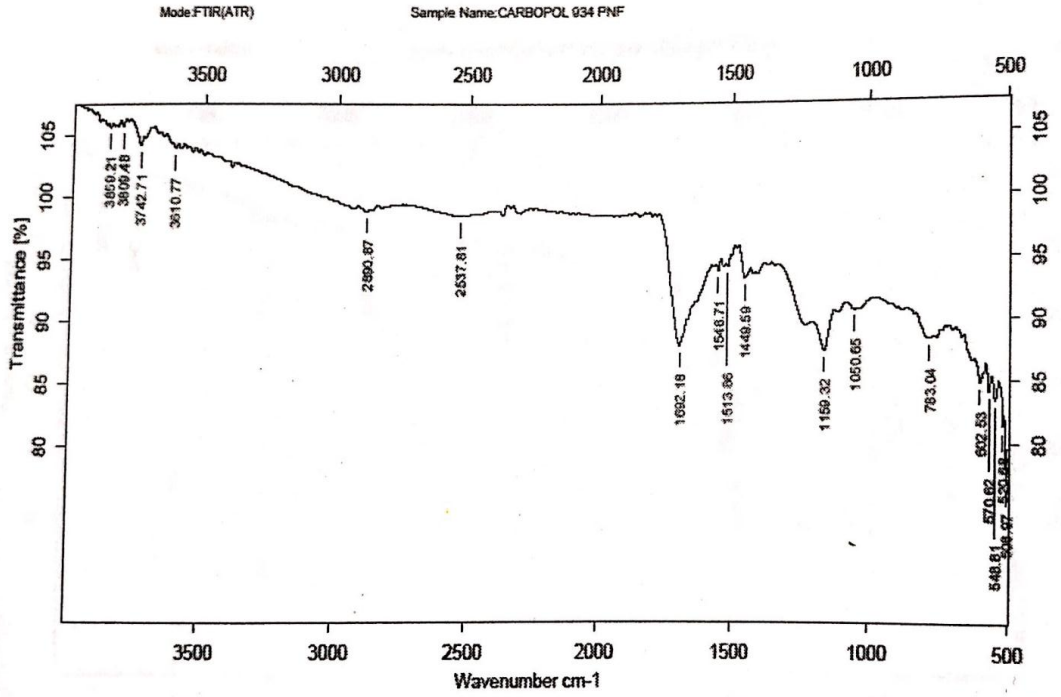

Fig. 2: FTIR Spectrum for Carbopol 934P NF.

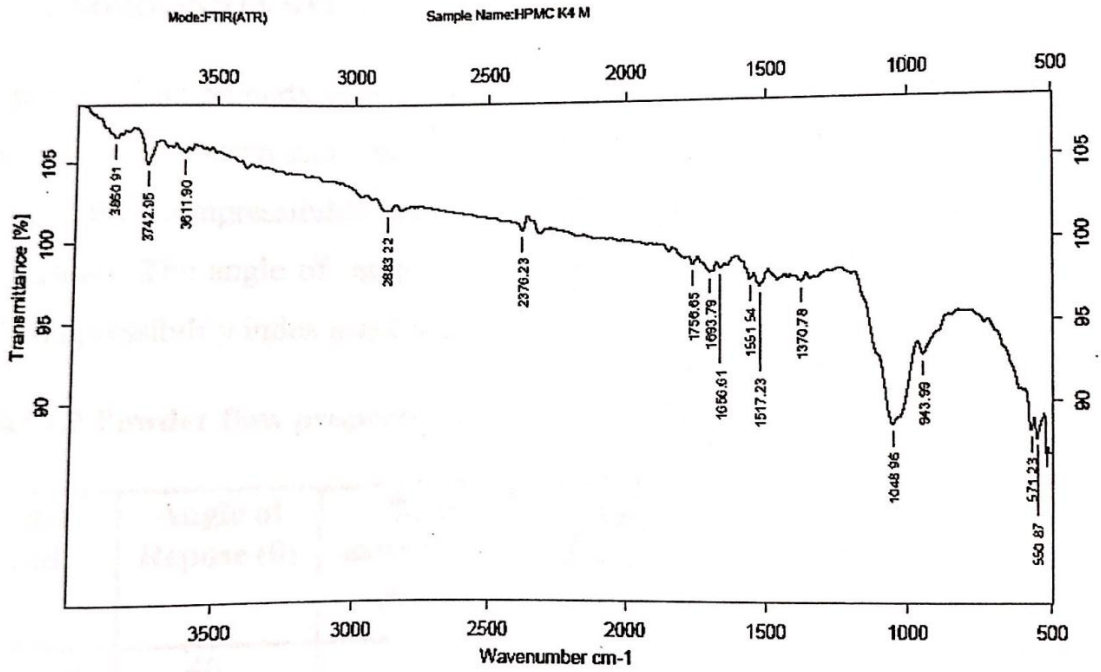

Fig. 3: FTIR Spectrum for HPMC K4M.

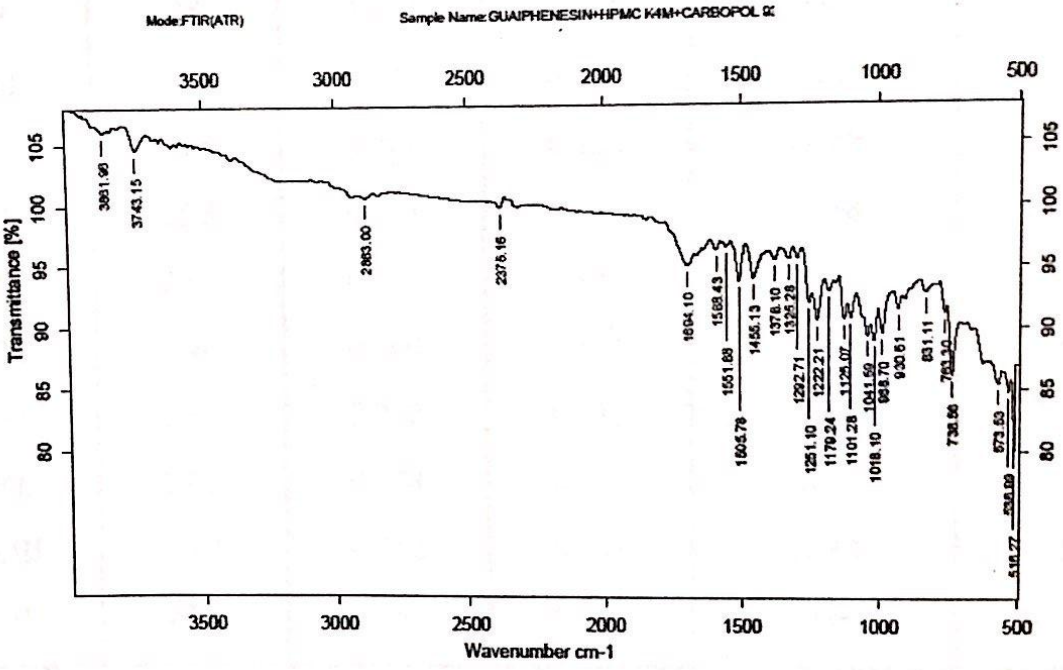

Fig. 4: FTIR Spectrum for Guaiphenesin with Carbopol 934P NF and HPMC K4M.

Table 2: Formulae for the tablets of Guaiphenesin with different polymers by direct compression method.

Formulation Ingredients (850mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14
Guaiphenesin	600	600	600	600	600	600	600	600	600	600	600	600	600	600
Carbopol 934P NF	42.5	63.5	85	127.5	42.5	170	170	85	42.5	42.5	42.5	42.5	42.5	42.5
HPMC E5	85	63.5	42.5	-	-	-	-	-	-	-	-	-	-	-
HPMC K4M	-	-	-	-	127.7	-	-	85	127.5	85	42.5	63.75	63.75	63.75
MCC 105	114.5	114.5	114.5	114.5	71.5	71.5	63	71.5	54.5	114	157	135.25	-	135.25
MCC 101	-	-	-	-	-	-	-	-	-	-	-	-	135.25	-
Magnesium Sterate	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5
Acacia	-	-	-	-	-	-	8.5	-	17	-	-	-	-	-

Post Compression Parameters

Drug content

Five tablets were weighed and powdered in a mortar. Accurately weighed tablet powder samples equivalent to 20mg of Guaiphenesin was transferred to a 100ml volumetric flask, and the Guaiphenesin was extracted into 75ml methanol. This solution is filtered and collected in to a 100ml volumetric flask and made up to the volume with methanol. The solution was suitably diluted with 0.1N HCL and the absorbance was measured at 274nm.

Hardness

Six tablets from each batch were selected and hardness was measured using Monsanto hardness tester (M/s Campbell Electronics, MODEL EIC-66, India).

Friability

Six tablets from each batch were selected randomly and weighed. These pre weighed tablets were subjected to friability testing using Roche Friabilator (M/s Campbell Electronics, India) for 100 revolutions. The tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25rpm and dropping a tablet at a height of 6 inches in each revolution. Tablets were removed, de-dusted and weighed again. Following formula was used to calculate the friability.

%F=1-(loss in weight/initial weight)*100

Weight variation

Weight variation was calculated as per method described in USP. 20 tablets were weighed individually and the average weight is calculated. The requirements are met if the weights of not more than 2 tablets of tablets differ by more than the percentage and no tablets differ in weight by more than double that percentage.

In-vitro dissolution studies

The tablet samples were subjected In-vitro dissolution studies using USP type I dissolution apparatus at 37±2^{o}C and 75 rpm speed. As per the official recommendation of USFDA, 900ml of 0.1 N HCL (12hrs) was used as dissolution medium. Aliquot equal to 5ml was withdrawn at specific time intervals and replaced with fresh buffer. The aliquots were diluted and drug release was determined spectrophotometrically at a wavelength of 274nm by comparing with the standard calibration curve.

RESULTS AND DESCISSION

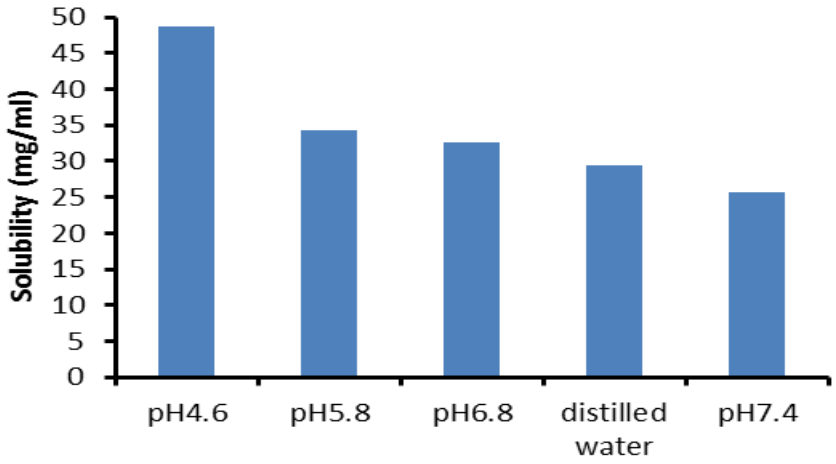

Fig. 5: Solubility determination in different buffers.

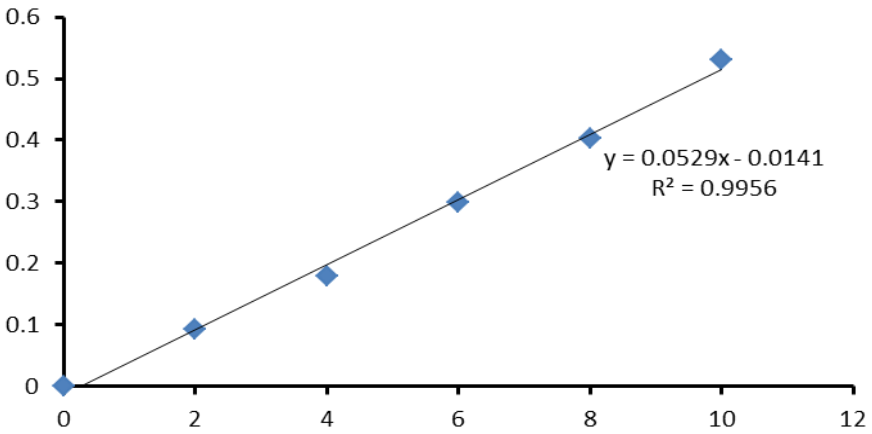

Fig. 6: Calibration curve for Guaiphenesin in 0.1N HCL.

Table 3: Precompression parameters.

Powder blend	Angle of repose (ɵ)	Bulk density(ρ_b)	Tapped density(ρ_t)	Compressibility index(%)	Hausner's ratio
Pure drug	40.2	0.816	1.11	26.4	1.36
F1	24.5	0.781	0.819	4.6	1.05
F2	23.8	0.841	0.862	2.44	1.02
F3	24	0.667	0.735	9.25	1.10
F4	23.2	0.689	0.769	10.4	1.11
F5	25	0.698	0.811	13.9	1.16
F6	24.8	0.574	0.654	12.2	1.14
F7	23.6	0.722	0.821	12.05	1.14
F8	25.5	0.748	0.884	15.38	1.18
F9	26.4	0.691	0.832	16.9	1.20
F10	26	0.760	0.851	10.69	1.12
F11	25.5	0.712	0.832	14.4	1.17
F12	27.2	0.678	0.795	14.7	1.17
F13	25.3	0.752	0.851	11.63	1.13
F14	25.6	0.669	0.769	13.00	1.15

Table 4: Evaluation of Postparameters for all formulations.

Parameters / Formulations	Hardness ± SD (kg/cm^2)	Friability (%)	Weight variation ±SD (mg)	Drug content ± SD(mg/tab)
F1	7.47±0.15	0.6	850±0.15	600±1.25
F2	7.40±0.10	0.8	850±0.10	599±1.98
F3	7.57±0.15	0.6	850±0.18	597±1.67
F4	7.51±0.10	0.6	850±0.12	598±1.25
F5	7.50±0.10	0.9	850±0.04	600±0.98
F6	7.32±0.12	0.7	850±0.06	600±0.65
F7	7.21±0.08	0.9	850±0.08	600±0.54
F8	7.53±0.06	1.1	850±0.04	599±0.78
F9	7.63±0.15	0.8	850±0.01	600±0.85
F10	7.71±0.12	0.8	850±0.02	600±0.97
F11	7.52±0.11	0.6	850±0.05	600±0.36
F12	7.50±0.10	0.2	850±0.05	600±0.84
F13	7.37±0.10	0.9	850±0.03	600±0.97
F14	7.77±0.15	0.7	850±0.02	598±0.68

Table 5: Formulation trials cumulative percent drug release with standard deviation.

Time (hr)	F1	F2	F3	F4	F5	F8	F9	F10	F11	F12	F13	F14
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	39.86	26.56	25.22	25.77	10.45	28.78	32.40	18.44	46.32	36.23	24.29	10.66
1	46.40	44.74	29.51	29.00	19.79	35.51	34.61	24.38	70.33	54.92	37.49	19.70
2	53.56	47.62	34.04	32.81	26.50	46.45	37.99	36.55	72.90	66.82	44.65	27.27
4	56.08	49.11	62.34	51.74	39.97	57.63	42.36	47.54	74.38	73.53	53.71	37.72
6	56.95	50.96	72.30	55.50	46.18	62.13	46.64	55.42	75.60	78.03	61.50	48.08
8	58.52	53.44	78.42	61.00	52.90	63.26	50.01	60.78	77.72	82.85	68.66	58.89
10	-	-	-	-	58.93	64.25	52.40	66.32	-	87.58	70.42	67.85
12	60.77	56.36	84.78	69.14	65.15	64.97	53.21	74.43	-	93.57	73.71	77.85

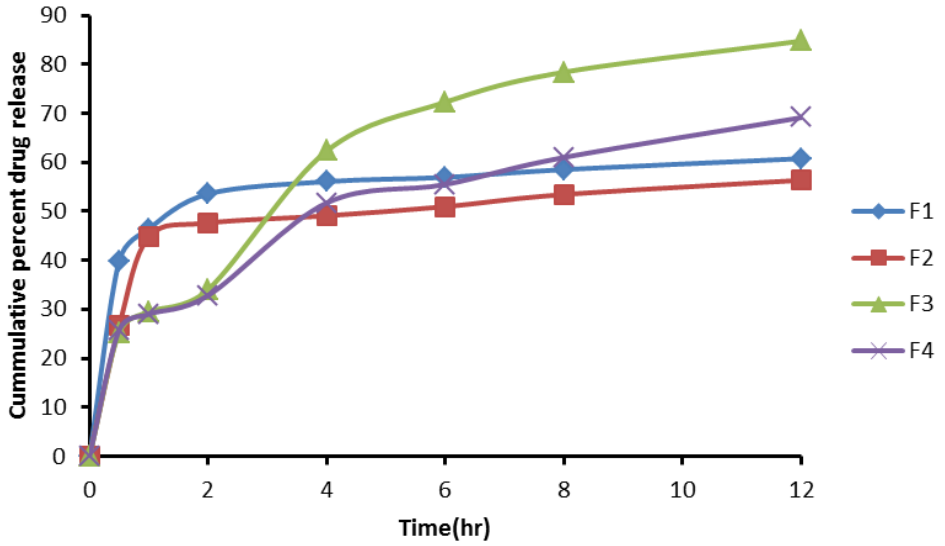

Fig. 7: Dissolution profiles for F1, F2, F3 and F4 formulations.

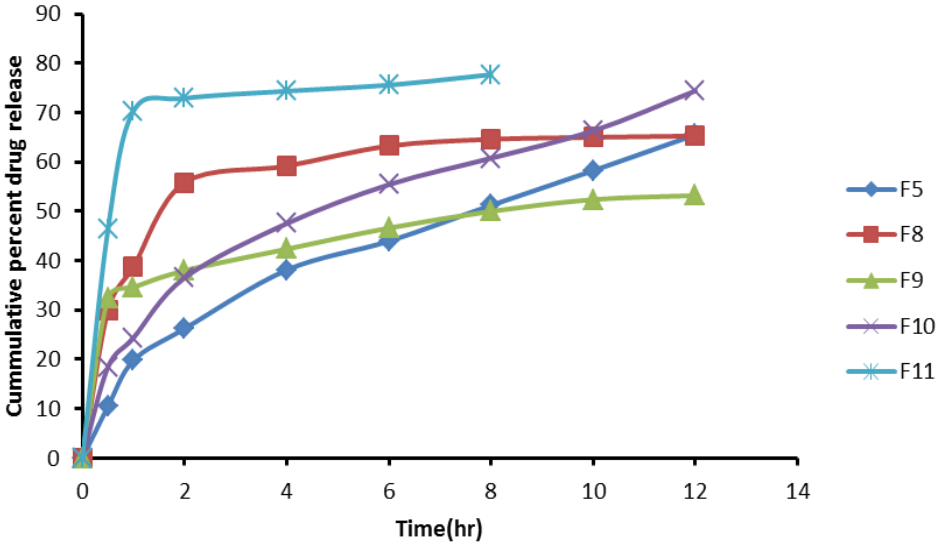

Fig. 8: Dissolution profiles for F5, F8, F9, F10, F11.

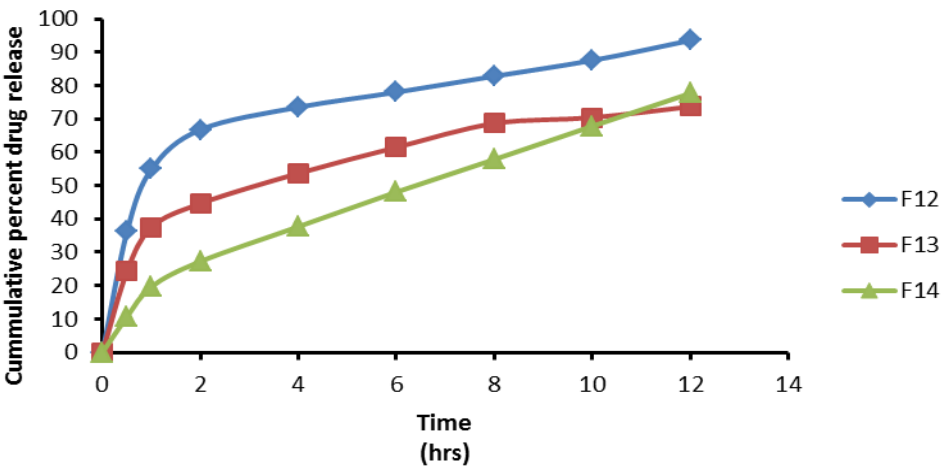

Fig. 9: Dissolution profiles for F12, F13, F14.

DISCUSSION

The linearity was checked in different buffers like distilled water, 1.2pH, 4.6pH, 5.8pH, 6.8pH and 7.4pH buffers in the range of 10, 20, 30, 40 and 50µg/ml. The dissolution as per FDA is 0.1N HCL.

Flow properties of granules, prepared from all the formulations are good as obtained from the bulk density, tapped density, Hausner's ratio and compressibility index values indicated.

Solubility studies were determined for Guaiphenesin in different buffers like distilled water, 0.1N HCl, 4.6 pH, 5.8 pH, 6.8 pH and 7.4 pH phosphate buffers. The drug showed its highest solubility in 0.1N HCl.

The prepared formulations were subjected to in-vitro dissolution studies in 900mL of 0.1N HCl as per FDA guidelines. The results were assessed with the help of release kinetics the formulations F1, F2, F3 and F4 were formulated by wet granulation technique. The F1 formulation with polymer concentration of Carbopol 934 P NF (5%w/w) and HPMC E5 (10%w/w) found to have release percent of approximately 60%. The polymer concentration showed high retarding effect. So the polymer condition was changed to Carbopol 934 P NF (7.5%w/w) and HPMC E5 (7.5% w/w) in F2 formulation. The release percent was found to be 84% to clearly visualise the effect of Carbopol 934 P NF, the F4 formulation was formulated to contain only Carbopol 934 P NF (15%w/w) and the release percent was found to be only 70% in 12 hours.

The data was fitted into release kinetic profiles. The formulations were found to follow first order release kinetics. Higuchi's plot for all the wet granulation formulations showed diffusion model of release and extending the 60% data Peppas plot indicated the release to be by fickian transport. The value for 'n' values for F1, F2, F3 and F4 were 0.433, 0.454, 0.478 and 0.474.

Wet granulation technique is also used to prepare tablets in order to compare the data obtained with direct compression technique. The formulation F5, the release was observed to be approximately 65% in 12 hours. The rate controlling polymers used were Carbopol 934 P NF (5%w/w) and HPMC K4M (15% w/w). The formulations F6 and F7, which were prepared using direct compression technique, the tablets were dispersed in 0.5 hours. The rate- controlling polymer used was Carbopol 934 P NF (20% w/w) only. In F7 acacia gum was also added to increase the release. Therefore, F8 formulation was formulated with polymer concentration of Carbopol 934 P NF (10% w/w) and HPMC K4M (10% w/w). The release was similar F5 (65%). On fitting the data into release kinetics, the formulations found to follow up first order kinetics. Higuchi's plot for all the formulations showed diffusion model and on extended to Peppas, it showed Fickian type of transport. The 'n' values for F5 and F8 formulations were 0.481 and 0.444.

The formulations F9, F10 and F11 with polymer concentration of Carbopol 934 P NF and HPMC K4M were Carbopol of 5% w/w and HPMC K4M of 15% w/w, 10% w/w and 5% w/w respectively. The release percent was found to be approximately 53%, 74% and 77% respectively for F9, F10, F11 formulations. F11 formulation tablet got dispersed in 8 hours.

The data was fitted into release kinetic profile. The formulations were found to follow first order release kinetics. Higuchi's plot for all the formulations showed diffusion model of release and on extending the 60% data in the Peppas plot indicated the release to be by Fickian transfer. The 'n' values for F9, F10 and F11 were 0.482, 0.435 and 0.440.

The F12 formulation with polymer concentration of Carbopol 934 P NF (5% w/w) and HPMC K4M (7.5% w/w) showed better release profile with approximately release of 94% in 12 hours. Higuchi's plot showed that the release is diffusion model and Peppas plot (n = 0.491) showed that the release is Fickian transport. The formulation was also formulated in wet granulation method (F13), which showed significant difference in release. Similarly, final formulation was formulated (F14) with change in diluent, which showed significant difference in release. The diluent used was Avicel 101. The release kinetics was found to follow first kinetics. Higuchi's plot explains the release mechanism to be diffusion. On extending to Peppas plot, it showed the release was by Fickian in F12 and Anomolous in F14 formulation. The 'n' values for F12, F13 and F14 were 0.491, 0.460 and 0.551.

SUMMARY AND CONCLUSION

Solubility parameters were estimated in different buffers like distilled water, 1.2pH, 4.6pH, 5.8 pH, 6.8 pH and 7.4 pH buffers. The drug was found to have its highest solubility in 0.1 N HCl.

Of all the formulations formulated F12 was considered as best formulation as the cumulative percent release mean is approximately 94%. The final formulation which is formulated by direct compression method, is compared with formulation formulated by wet granulation technique and also checked in with change in diluent. Both of them showed significant difference in release rate. All the evaluation test and dissolution test were done in triplicate. The rate constant and regression values are also reported for all formulations. All the values were within the limits. Finally the Guaiphenesin drug release is extended to12hrs with the help of Carbopol 934P NF and HPMC polymers.

Solubility studies showed that the drug is more soluble in acidic medium. With powder flow properties it is known that the pure drug has poor flow properties but the granules in wet granulation formulae and the powder blend in direct compression formulae showed good flow properties. Hardness is maintained at 7kg/cm^2

approximately which is required for sustained release tables (6-8kg/cm^2) Friability and weight variation were within the limits. Dissolution studies showed that F12 is best formulation with cumulative percent drug release mean is approximately 94%.

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