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Research Paper

Formulation Development and Evaluation of Sustained Release Matrix Tablets of Guaiphenesin

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ABSTRACT

In this study we sought to formulate and evaluate sustained release matrix tablet of guaiphenesin by melt granulation technology. The sustained release tablets were prepared by melt granulation technique using rice bran wax as a drug retardant and dibasic calcium phosphate (DCP) as a channelling agent. Guaiphenesin is an expectorant and has a short plasma half-life of one hour. Because of high frequency of administration and short biological half-life, guaiphenesin was considered as model drug. Sustained release formulation that would maintain plasma levels for 12 hours is sufficient for twice daily dosing of guaiphenesin. The compatibility of drug and wax was examined by differential scanning calorimetry (DSC). The effect of waxes at different (drug: wax) concentrations on the release profile of drug from matrix formulation were studied. Drug release was studied at pH 1.2 for 2 hour and pH 6.8 for 10 hours. A significant retardation in the drug release was observed by increasing the wax concentration. The drug release study revealed that wax concentration of 30% to be optimum. Dissolution study showed 99% drug release within 12 hrs. Kinetic modelling of *in vitro* dissolution profiles revealed the drug release mechanism ranges from diffusion controlled or Fickian transport to anomalous type or non-Fickian transport. These results suggest that the rice bran wax has good release retardant property for highly water-soluble drug such as guaiphenesin.

KEYWORDS: Rice bran wax; Guaiphenesin; Sustained release; Lipid matrix; Melt granulation.

Introduction

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes (Asijia et al., 2012). The popularity of oral route is due to its ease of administration, patient compliance (Aulton, 2007). The conventional dosage form provides prompt release of drug. So, to achieve as well as to maintain the drug concentration within the therapeutically effective range needed for treatment, it is often necessary to take this type of drug delivery system several times a day. Therefore, recently several technical advancements have been made. They have resulted in the development of new techniques for drug delivery. These techniques are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity, or targeting the delivery of drug to a tissue (Asijia et al., 2012). Sustained release system include any delivery system that achieves slow release of drug over an extended period of time (Birajdar et al., 2013). The oral sustained release systems are mainly grouped into three types, e.g. reservoir or membrane controlled system, monolithic matrix system and osmotic pump system (Chien, 2007).

Guaiphenesin is an expectorant and it acts by reducing viscosity of sputum. It is used as expectorant in cough mixtures and tablets (Ding and Robinson, 2007). It has short biological half life (1 hr), high water solubility and therefore frequent administration is required (usually three to four times a day). There is potential need to formulate sustained dosage form.

Thus lipophilic waxes have been employed as matrix carriers for sustained release solid dosage forms. The wax matrices are prepared by fusion and melt granulation methods. These utilize the molten wax as binder (Gren and Nystrom, 1999). Waxes provide good stability at varying pH and effective retarding of water soluble drug in forming a wax matrix system different processing methods like dry blending, wet granulation, melt granulation are used (IP, 2014). Natural waxes have been investigated for sustained release of highly water soluble drugs. Because of easy availability and expected to be relatively inexpensive, biocompatible, biodegradable and eco-friendly (Keen et al., 2013).

Melt granulation is process by which granules are obtained through the addition of either a molten binder or a solid binder which melts during the process (Lachman et al., 1991). Thus melt granulation is one such technique, being a rapid, one pot, solvent free method (Liu et al., 2011). Therefore, melt granulation process gathered increasing interest in the pharmaceutical industry (Parikh, 2005; Ubaidulla et al., 2007; Rosiaux et al., 2014; Syamala et al., 2013). In this study we sought to formulate and evaluate sustained release matrix tablet of guaiphenesin by melt granulation technology.

Materials and Methods

Guaiphenesin was obtained as gift sample from Ajanta pharma Ltd, Mumbai, India, and rice bran wax from Bajaj mills, Warangal (Andhra-Pradesh, India). Dibasic calcium phosphate, Talc, Aerosil, Magnesium stearate were procured from Loba Chemie Pvt. Ltd. (Mumbai, India). All other reagents and chemicals used were of analytical reagent grade.

Purification of Rice bran wax

The crude wax (100gm) was soxhleted with acetone (300 mL) for 30 min at 85 ºC. The mixture in thimble was cooled up to 25ºC and was subjected to decolourization with 2% H_2O_2 at 90 ºC for 1 h and secondary decolourization with NaOCl 15% at 100 ºC for 1 h. The purified wax obtained was then used for further study Rosiaux et al., 2014).

Preparation of Guaiphenesin Sustained Release Tablet by Melt Granulation

Matrix tablets of guaiphenesin were prepared by melt granulation method as per formule given in Table 1. Wax granules were prepared by melting wax by heating at a temperature of around 85 ºC. Then to this molten mass drug and other diluents were added under mixing & then allowed to solidify at room temperature and pulverized in mortar and sized through a 16 mesh sieve. Prior to compression aerosil, talc, and magnesium stearate was mixed with each batch of granules for 5 min. A rotary tableting machine (Karnavati Engg. Ltd. Rimek Minipress 2D), equipped with 14-mm flat faced circular punches, was used to prepared tablets at a constant compression force.

TABLE 1

Composition of sustained release matrix tablets of Guaiphenesin for formulations(F1-F6).

Ingredients (mg)	F1	F2	F3	F4	F5	F6
Guaiphenesin	600	600	600	600	600	600
Rice bran wax	45	90	135	180	225	270
Dibasic calcium phosphate	247	202	157	112	67	22
Magnesium stearate	3	3	3	3	3	3
Talc	2.5	2.5	2.5	2.5	2.5	2.5
Aerosil	2.5	2.5	2.5	2.5	2.5	2.5
Total	900	900	900	900	900	900

Product Evaluation

Pre Compression Evaluation

Angle of Repose

The angle of repose is one of the important parameter for evaluation of granules to check flow property of granules. The angle of repose of prepared granules was determined by using funnel method. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation

$$\text{Tan } \theta = h/r \qquad \text{.....(1)}$$

Where,

h = height of cone

r = radius of the powder cone

Bulk density

The ratio of mass (weight) to the volume is known as the bulk of material. The bulk density of a powder depends on particle shape as the particles become more spherical in shape bulk density are increased. Bulk density was determined by pouring pre-sieved drug excipient blend into graduated cylinder and measuring the volume and weight "as it is" it is expressed in g/mL and was calculated by using formula

$$Db = M/v \qquad \text{.....(2)}$$

where,

M = Mass of particles and

V = Total volume of packing

Tapped Density

Tapped density was determined by placing granules into graduated cylinder. The cylinder was then placed in the apparatus and parameters were set to carry out the test. Volume occupied by the sample after tapping were recorded and tapped density was calculated by following formula

$$TD = \text{Weight of powder/Tapped volume} \qquad \text{.....(3)}$$

Compressibility Index

An important measure that can be determined from bulk density is the percent compressibility and it is determined by using formula,

$$\text{Carr's Index} = [(TBD - BD) \times 100/TBD] \qquad \text{.....(4)}$$

Hausner's ratio

It is calculated by formula:

$$\text{Hausner's ratio} = \text{Tapped density/Bulk density} \qquad \text{.....(5)}$$

Percent Moisture Content

Moisture content of the granules was determined by dry weight basis. 0.5 g granules were weighed and kept in a desiccators containing activated silica at room temperature. Granules were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight by using formula,

$$\% \text{ moisture content} = \frac{\text{Weight of water in sample}}{\text{Weight of dry sample}} \times 100 \qquad \text{.....(6)}$$

Motic Microscopy

The size of the formulated granules was investigated by optical microscopic image analysis. The image analyser consisted of an optical microscope (magnification 10x) linked to a computer and a digital camera. The digitalized images were analysed by image analysing software. The maximum (d max) and minimum (d min) diameter, circumference and area were recorded for 100 granules.

Post Compression Evaluation

Hardness

The hardness of the tablets was measured in terms of kg/cm^2 using simple Monsanto hardness tester.

Thickness

Variation in thickness may cause problem in packaging & should be controlled within ± 5% of a standard value. Tablet thickness was measured by Vernier calliper scale.

Weight Variation

The weight of tablet is routinely measured to ensure that the tablets contains proper amount of drug. 20 tablets from each batch were selected randomly weighed and average weight was calculated. The % deviation of each tablet from the average weight was calculated.

Friability

From each batch, 20 tablets were selected randomly and weighed. These pre weighed tablets were subjected to friability testing using Roche friabilator for 100 revolutions. Tablets were removed, de-dusted and weighed again. Following formula was used to calculate the friability

$$\% \text{ Friability} = 1 - (\text{loss in weight/initial weight}) \times 100 \quad \text{.....(7)}$$

Drug Content

Twenty tablets were weighed individually and powered in mortar pestle and an amount equivalent to 100 mg of Guaiphenesin was extracted with 100 mL of phosphate buffer (pH 6.8) and sonicated for 10 min. The solution was filtered through Whatmann filter, and the content of Guaiphenesin in the solution was determined by measuring absorbance on double beam UV spectrophotometer at 273 nm after suitable dilution.

Dissolution Study

For any formulation drug release from the dosage form is the foremost parameter to be measured. Drug release is evaluated by the *in-vivo* dissolution test apparatus. The *in vitro* dissolution studies were conducted using USP II apparatus. The dissolution media is comprised of 0.1 N Hydrochloric acid for the first 2 h and phosphate buffer (pH 6.8) until 12 h (900 mL) kept at 37.0 ± 0.5 ºC and 50 rpm. An aliquot of 5 mL sample was withdrawn and replaced with another 5 mL of fresh dissolution medium at various time intervals. The contents of Guaiphenesin in sample were determined by measuring at 273 nm in a UV-Visible spectrophotometer (Jasco V-630). The absorbance values were transformed to concentration by reference to a standard calibration curve obtained experimentally. The release study was performed in triplicate.

Analysis of Release Data

The release data obtained were treated according to zero order (cumulative drug release versus time), First order (log cumulative percentage of drug remaining versus time), Higuchi (cumulative percentage of release versus square root of time), Korsmeyer-Peppas (log cumulative percentage of drug release versus log time) equation models (Aulton, 2007).

Results and Discussion

Drug and excipient compatibility by using DSC

Drug and excipient (Rice bran wax) study was done by using Differential Scanning Calorimetry. The outcome results were shown in Fig 1. From the DSC of pure drug and rice bran wax it was observed that there is endothermic peak around 80 ^{o}C and 80.79 ^{o}C. This shows that there is no major difference in onset temperature and peak temperature, when compared with pure drugs thermogram and rice bran wax thermogram. Fig.1 shows that no interaction was found between drug and wax.

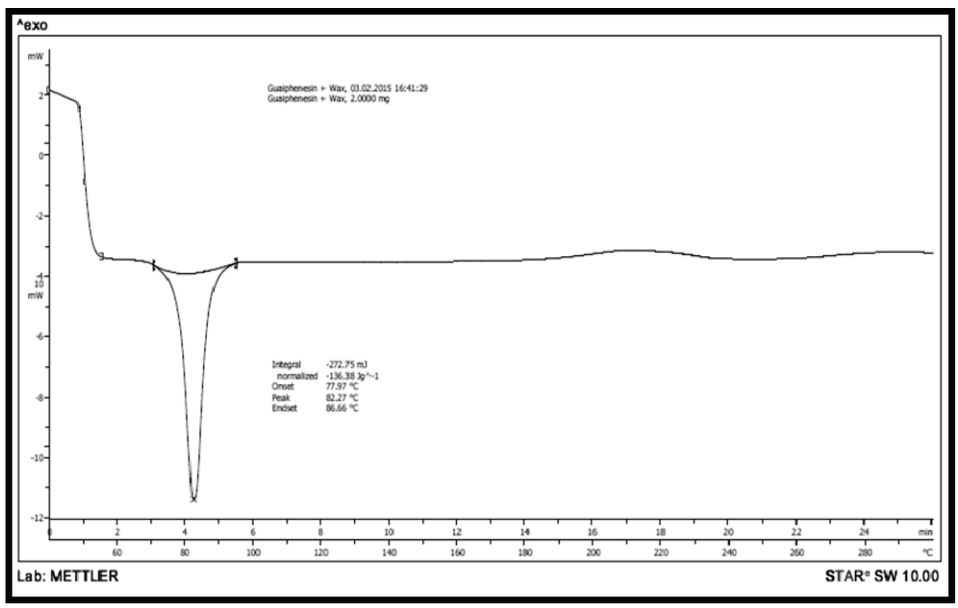

Fig. 1. DSC thermogram of Rice bran wax and Guaiphenesin.

TABLE 2

Evaluation data for matrix granules for formulation F1-F6.

Formulation code	Angle of Repose	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Hausne'r Ratio (HR)	Car's index (%)	Particle size (µm)	Moisture content (%)
F1	11.4 ± 0.05	0.416 ± 0.001	0.494 ± 0.003	1.184 ± 0.012	15.71 ± 0.71	454.33 ± 2.08	0.50
F2	12.40 ± 0.0057	0.384 ± 0.001	0.459 ± 0.0079	1.21 ± 0.06	16.31 ± 1.63	573.7 ± 3.14	0.55
F3	17.59 ± 0.095	0.412 ± 0.0025	0.459 ± 0.0079	1.17 ± 0.02	14.50 ± 0.96	676.9 ± 0.96	0.60
F4	17.7 ± 0.01	0.402 ± 0.002	0.482 ± 0.0025	1.14 ± 0.05	13.49 ± 0.35	694.0 ± 0.63	0.56
F5	23.79 ± 0.089	0.383 ± 0.001	0.464 ± 0.002	1.16 ± 0.01	14.54 ± 0.73	785.5 ± 0.55	0.80
F6	25.64 ± 1.14	0.332 ± 0.0032	0.449 ± 0.003	1.15 ± 0.01	13.66 ± 0.89	837.33 ± 1.60	0.54

TABLE 3

Evaluation data for matrix tablets for formulation F1-F6.

Formulation code	Hardness (kg/cm^2)	Thickness (mm)	Weight variation (mg)	Friability (%)	Drug content (%)
F1	6.3 ± 0.28	170.69 ± 0.050	901.6 ± 0.15	0.19	98.85
F2	6.2 ± 0.40	172.93 ± 0.032	901.3 ± 0.32	0.11	99.96
F3	6.4 ± 0.25	172.32 ± 0.025	901.4 ± 0.10	0.099	97.50
F4	6.5 ± 0.36	173.51 ± 0.015	900.7 ± 0.73	0.098	96.40
F5	7.1 ± 0.15	173.69 ± 0.040	901.2 ± 0.15	0.12	98.12
F6	7.8 ± 0.10	173.93 ± 0.026	901.0 ± 0.55	0.15	98.25

Characterization of Granules

The prepared matrix granules were evaluated for various parameters like angle of repose, bulk density, tapped density, Hausners ratio, particle size, moisture content. Results were shown in Table 2.

Characterization of tablets

Tablets were prepared by using melt granulation technique and were evaluated for various parameters like hardness, thickness, weight variation, friability, drug content. Results were shown in Table 3.

In vitro Drug Release Profile for Formulations

The *in-vitro* drug release studies for prepared formulations were conducted for period of 12 h using USP apparatus II (rotating paddle) set at 50 rpm and a temperature of 37±0.5 ºC formulation was placed in the pH 1.2 acidic medium which was replaced with 6.8 pH phosphate buffer for remaining 10h. At specified interval 5 mL samples were withdrawn from the dissolution medium and replaced with fresh medium to keep the volume constant. The absorbance of the sample was analysed at 273 nm by using UV-visible spectrophotometer. Result was shown in Table 4 & 5.

TABLE 4

In-vitro dissolution data of matrix tablets for formulations F1-F3.

Time (hr)	Formulations (% Cumulative drug release)		
	F1	F2	F3
1	40.5 ± 0.010	33.25 ± 0.21	30.66 ± 0.63
2	65.40 ± 0.050	60.31 ± 0.03	41.05 ± 0.55
3	85.5 ± 0.025	81.8 ± 0.21	61.15 ± 0.97
4	97.55 ± 0.080	93.48 ± 0.57	74.26 ± 0.58
5	-	96.83 ± .27	93.17 ± 0.24
6	-	-	97.48 ± 0.56

TABLE 5

In vitro dissolution data of matrix tablets for formulations F4-F6.

Time (hr)	Formulations (% Cumulative drug release)		
	F4	F5	F6
1	29.5 ± 0.69	29.26 ± 0.66	15.23 ± 0.24
2	40.79 ± 0.25	35.88 ± 0.57	22.16 ± 0.42
3	50.98 ± 0.68	45.44 ± 0.69	30.15 ± 0.65
4	65.31 ± 0.70	53.46 ± 1.24	37.25 ± 0.34
5	74.69 ± 0.49	63.59 ± 0.87	45.5 ± 0.76
6	83.55 ± 0.82	72.71 ± 1.16	53.4 ± 0.60
7	91.93 ± 1.01	82.78 ± 0.51	65.35 ± 0.34
8	96.45 ± 0.77	92.13 ± 1.0	72.2 ± 1.50
9	-	98.26 ± 0.21	80.40 ± 0.58
10	-	-	89.55 ± 0.61
11	-	-	93.15 ± 0.27
12	-	-	98.99 ± 0.40

Table 4 and 5 gives the result of the *In-vitro* dissolution data with their standard deviation values.

In-vitro drug release depends on several factors, such as the manufacturing process, the type of excipients and amount of drug. In this work the effect of some diluents on guaiphenesin release was also studied. The results of dissolution studies on formulations F1 to F6 of rice bran wax (5 to 30%) are shown in Fig 2. In table 4 the F1, F2 and F3 released 65.40%, 60.31%, 41.05% of guaiphenesin at the end of 2 hr and 97.55%, 93.48% and 74.26% respectively at the end of 4 hr. F4, F5 and F6 composed of rice bran wax (20 to 30%) the release profile of these formulations are shown in Fig 2. Formulations F4, F5, F6 released 40.79%, 35.88% and 22.16% of guaiphenesin at the end of 2 hrs and 96.45%, 92.13% and 72.2% at the end of 8 hrs respectively.

The wax ratio (F1 to F6) on release profiles of guaiphenesin was studied and decrease in drug release was observed when the concentration of rice bran wax was increased (Fig 2). It may be due to the slower penetration of dissolution medium in matrices due to

lipophilicity of waxy substances. In the formulations F1 to F3 containing different concentration of rice bran wax (i.e. 5%, 10%, 15% respectively) release of guaiphenesin get less retarded than those formulations of F4 to F6 which may be due to higher lipophilicity of waxes. From the release study it was observed that, the F6 formulation containing (30%) rice bran wax shows drug release 98.99% in 12 hrs which is effective percent drug release for sustained release formulation of guaiphenesin.

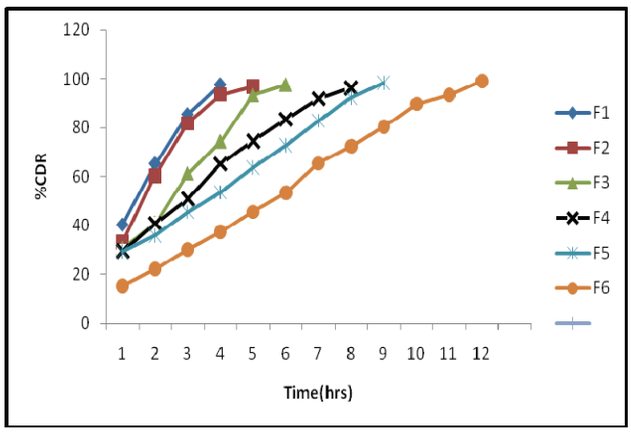

Fig. 2. The dissolution profile of matrix tablets (F1-F6) of Guaiphenesin containing Rice bran wax from 5% to 30%.

Evaluation of drug release kinetics

The formulation batches were evaluated for drug release kinetics using Zero order, First order, Higuchi model, Korsmeyer-Peppas model and R^2 values of the formulations were shown in Table 6.

TABLE 6

Dissolution models for matrix tablets (F1 to F6) of Guaiphenesin.

Formulation code	R^2				N
	Zero order	First order	Higuchi	Korsmeyer peppas	Korsmeyer peppas
F1	0.977	0.919	0.967	o.990	0.642
F2	0.990	0.989	0.966	0.970	0.582
F3	0.981	0.902	0.976	0.979	0.580
F4	0.985	0.940	0.992	0.991	0.682
F5	0.989	0.902	0.973	0.957	0.525
F6	0.995	0.914	0.976	0.987	0.602

Stability studies

The stability of optimum formulation revealed that no significant changes in the physical & chemical parameters when stored at temperature and humidity conditions of 40°C/75% RH are shown in Table 7. No significant reduction in the content of the active drug was observed over a period of three months.

TABLE7

Results of accelerated stability studies of optimized formulation(F6).

Test	Initial	1 Month	2 Month	3 Month
Description	Light Brownish Biconvex oval shape tablet	Light Brownish Biconvex oval shape tablet	Light Brownish Biconvex oval shape tablet	Light Brownish Biconvex oval shape tablet
Weight Variation	907mg to 900mg	895mg to 910mg	909mg to 908mg	897mg to 910mg
Thickness	173.95mm	173.95mm	172.95mm	172.95mm
Hardness	7.7kg/cm^2	7.7kg/cm^2	7.7kg/cm^2	7.7kg/cm^2
Friability	o.099%	0.17	0.16%	0.16%
Drug Content	98.16%	98.45%	98.42%	98.40%
***In-vitro* drug release (After 12 Hrs.)**	98.19%	98.15%	97.50%	98.09%

Conclusions

In this study we attempted to prepare sustained release tablet of Guaiphenesin using different waxes as release retardant polymer. DSC study shows compatibility between drug and wax. Preformulation study shows good flow property of granules prepared by melt granulation. Among all batches F6 batch containing 30% wax concentration shows optimum release i.e., 98.99% in 12 hr. Finished formulation exhibited sustained drug release with zero-order release kinetics and showed the anomalous drug release, indicating that diffusion coupling with erosion mechanism. The above study suggests that the Rice bran wax has good release retardant property for tablets. The matrix tablets of Guaiphenesin can be successfully developed using Rice bran wax in combination with dibasic calcium phosphate.

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