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DEVELOPMENT AND CHARACTERIZATION OF SUSTAINED RELEASE PELLETS OF AMBROXOL HCL

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ABSTRACT

The present research work was carried out with the aim to prepare and evaluate sustain release pellets of Ambroxol HCl, a drug which is used as mucolytic agent. The basic goal is to sustain the drug release upto 24hours. Pellets have been prepared by Wurster process employing different viscosity grades of ethyl cellulose as polymer for sustain drug release and diethyl phthalate, propylene glycol and triethyl citrate as plasticizer in the formulations. Total of 16 formulations have been developed by varying polymer and plasticizer concentrations. Physical compatibility studies revealed that there is no incompatibility between drug and excipients. Micromeritic properties revealed the good flow properties of the pellets. The friability and drug content were within the specified limits. The formulated pellets have low moisture content and are suitable for filling into hard gelatin capsules. From the in-vitro dissolution profile formulation (F11) containing Ethyl Cellulose 50cps and propylene glycol were found to produce the drug release similar to innovator product along with all the parameters, so it is optimized and subjected to stability studies and found that there was no significant change in the properties of the pellets.

KEY WORDS: Sustain release pellets, Ambroxol HCl, Mucolytic agent, Wurster process, Diethyl phthalate, Propylene glycol, Triethyl citrate.

INTRODUCTION

Oral ingestion is traditionally preferred route of drug administration, providing a convenient method of effectively achieving both local and systemic effects. In conventional oral drug delivery systems, there is very little control over release of drug. The effective concentration at the target site can be achieved by intermittent administration of grossly excessive doses, which in most situations, often results in constantly changing, unpredictable and often sub or supra therapeutic plasma concentrations leaving the marked side effects [2, 6].

The term modified-release drug product is used to describe products that alter the timing and/or the rate of release of the drug substance. A modified-release dosage form is defined "as one for which the drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as solutions, ointments, or promptly dissolving dosage forms as presently recognized [10]. Several types of modified-release drug products are recognized of which extended release products are one. A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form are called as Extended-release drug products. Examples of extended-release dosage forms include controlled-release, sustained-release and long-acting drug products [12, 7].

Oral sustained release drug delivery is a system that provides continuous oral delivery of drugs at predictable and reproducible kinetics for a predetermined period throughout the course of GI transit and also the system that target the delivery of a drug to a specific region within the GI tract for either a local or systemic action [1].

Pharmaceutical pellets are agglomerates of fine powder particles or bulk drugs and excipients, small, free-flowing, spherical or semi-spherical solid units, size ranges from

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about 0.5mm to 1.5mm (ideal size for oral administration), obtained from diverse starting materials utilizing different processing techniques and conditions. These pellets are usually designed to release the drug in a sustained manner [4].

Ambroxol is more potent than other mucolytic agents i.e., only 75 mg is sufficient to produce therapeutic effect. Half life of the Ambroxol is 4 hrs. The clearance rate of ambroxol is approximately 53 mL/min. The therapeutic dose is needed to be maintained for 24 hrs [13]. The conventional doses release the entire drug in just few minutes and therefore the therapeutic concentrations are maintained for a short period of time generating a need for administration of another dose. Therefore a sustained release formulation of ambroxol which would release the drug over a time period of 24 hrs is beneficial.

The concept of sustained drug delivery has been explored for the delivery of drugs for prolong period of time for the past few years. This type of drug delivery has proved to provide a solution to several problems encountered in the repeated administration of such drugs. Utilizing the concept of incorporating drug in to the polymer system and extend the drug release for prolong period of time, an attempt was made to design and evaluate sustained release pellets of ambroxol HCl.

MATERIALS AND METHODS

Ambroxol was obtained as gift sample from the Madras Pharmaceuticals Ltd, Chennai. Starch was purchased from Emco Industries, MCC from Anshul Agencies, N.P. Seeds from Lee Pharma, Ethyl cellulose N-7, Ethyl cellulose N-15, Ethyl cellulose N-50 from Deepak Chemicals, Talc from Vishal Agencies.

Drug–Excipients compatibility studies

The identification of possible incompatibilities between drug and excipients is one of the basic tasks to be dealt with in preformulation studies. The desired level of stability is often difficult to achieve because the active principle may interact with the other substances of the formulation which do not have a specific pharmaceutical activity. Sometimes, this interaction is fundamental for a proper functioning of the drug delivery system (e.g. to speed up dissolution, or controlling release). Most often, the negative effects of the Drug-Excipient interaction in the solid state is mediated by water and enhanced by an increased temperature. Even traces of water may play a major role in degradation of water-soluble drugs through an increased mobility of Drug-Excipient which enhances their reactivity. Therefore drug-excipient compatibility studies were performed for the selected drug and polymers.

Formulation of Ambroxol SR pellets

Preparation of core pellets

The inner core pellets were prepared by using conventional coating pan method. The binder solution was prepared by dissolving PVP K-90 in IPA with vigorous stirring. The Ambroxol drug powder, starch and microcrystalline cellulose (MCC) were weighed as mentioned in table-1 and were subjected to milling & passed through sieve to get fine powder. Further, the Ambroxol drug powder was blended with starch and MCC for 15 mins. The NP seeds were loaded in the coating pan and wetted with the help of binder solution using the spray gun at air pressure of 1.5 kg/cm^2. The blended powder mixture was charged to the wet non-pareil (NP) seeds by dusting method. The method involved the disposition of successive layers of drug excipients blend on the NP seeds with the help of binder solution until the blend was completely charged. The pellets were dried at 40 ºC by tray dryer and sieved through sieve no 12#18.

Preparation of Sustained Release pellets

The sustained release pellets were prepared by using fluidized bed coater. The process parameters were set up as in given in table-2. Ethyl cellulose (EC) was dissolved in mixture of Iso-propyl alcohol (IPA) and methylene Dichloride (MDC) with vigorous stirring. Add Diethyl phthalate (DEP) and Talc to above solution with continuous stirrings. Load the drug coated pellets into the fluidized bed coater and spray the above coating solution as per process parameters. After completion of process pellets were dried and sieved through sieve no 12#18. The coating composition of the pellets is given in table -3 and 4. In formulations F1-F10 Diethyl phthalate is used as a plasticizer and in formulations F11-F16 Propylene glycol (PG) and triethyl citrate (TEC) are used as plasticizer and the same process is used to prepare the pellets.

Evaluation

The prepared formulations are subjected to evaluation for their micromeritic properties like Angle of Repose, Bulk Density, Tapped Density and Carr's Index [3].

Angle of Repose

The angle of repose of pellets was determined by the fixed funnel and free standing cone method. The accurately weighed pellets were taken in a funnel. The height of the funnel was adjusted in such a manner that the tip of the funnel just touched the apex of the heap of the granules. The pellets were allowed to flow through the funnel freely onto the surface. The diameter of the pellets cone was measured and angle of repose was calculated using the following equation.

$$\tan \theta = h/r$$

where h = height of the pellets heap, r= radius of the pellets heap, θ is the angle of repose.

Determination of Bulk Density and Tapped Density

Bulk density of a compound varies substantially with the method of crystallisation, milling or formulation. It is of great importance when one considers the size of a high

dose capsule product or the homogeneity of a low dose formulation in which there are large differences in drug and excipient densities. In addition to bulk density, it is frequently desirable to know the true density of pellets for computation of void volume or porosity of pellets. An accurately weighed quantity of the pellets (W) was carefully poured into the graduated cylinder and volume (V_0) was measured. Then the graduated cylinder was closed with lid and set into the tap density tester (USP). The density apparatus was set for 100 tappings and after that the volume (V_f) was measured and continued operation till the two consecutive readings were equal. The bulk density and the tapped density were calculated using the following formulae.

Bulk density = W/V_0

Tapped density = W/V_f

where, W= Weight of the pellets, V_0 = Initial volume, V_f = final volume

Compressibility index or Carr's Index

Compressibility index is an important measure that can be obtained from bulk and tapped densities. In theory, the less compressible a material is the more flow able it is. The compressibility of the powder was determined by the Carr's compressibility index.

Carr's index (%) = [(TD – BD) x 100]/BD

Where, TD is Tapped density, BD is bulk density.

Friability

About 10 gm of samples was weighed and mixed with 25 glass spheres (5 µ diameter) and friability testing of pellets was performed for 10mins at 25 RPM by using electrolab friabilator. Limits: N.M.T. 1%

Moisture content

Moisture content was determined by Karl Fischer Test. About 35ml of the Methanol was taken in titration flask of Karl Fischer Titrator and it was titrated with Karl Fischer reagent to end point. Pellets were grinded to fine powder in a dry mortar and about 500mg of the sample was quickly transferred to the titration flask and dissolved by stirring and titrated with Karl Fischer reagent to end point.

Water% = V x F x 100 / weight of sample in mg

Where, F = factor of Karl Fischer Reagent, V = Volume in ml of Karl Fischer reagent consumed for sample titration.

Limits: N.M.T. 5%

Assay

About 10 gm of pellets were grinded to fine powder in a dry mortar and a quantity of powder equivalent to 75mg of Ambroxol HCl was transferred into 100ml volumetric flask. To this 50ml of methanol was added and sonicated to dissolve the drug and diluted to volume with methanol and mixed thoroughly. The solution was filtered through whatman filter paper and 2ml of filtered solution was transferred into 100ml volumetric flask and diluted to volume with DM water. The absorbance of the solution was measured at 245 nm and drug content was determined [9, 5]

***In-vitro* Dissolution Studies**

The dissolution of ambroxol hydrochloride sustained release pellets was studied by using USP apparatus 2 (Paddle method). Ambroxol hydrochloride sustained release pellets equivalent to 75 mg of Ambroxol hydrochloride was placed in 900 ml of 0.1 N HCl medium at 37°± 0.5°C with a rotation of 50 rpm for 1 hour. At the end of 1 hour the media was removed and drug content was determined spectrophotometrically at 244 nm. Then 900 ml of phosphate buffer pH 6.8 was placed in each vessel and rotated at 50 rpm at 37°± 0.5°C for 24 hours. 10 ml samples were drawn every one hour and replaced by fresh medium to maintain the volume constant and drug content was determined spectrophotometrically at 244 nm using UV-Visible Spectrophotometer [11, 13].

Stability studies

From the prepared sustained release Ambroxol HCl pellets formulations, F_{11} which showed appropriate % release was selected for stability studies. The capsules containing filled weight 202.702mg which is equivalent to 75mg of Ambroxol HCl was subjected to stability studies which was carried out at 40 ºC/75%RH for 2 months and evaluated at the end of 1st and 2nd month for Physical observance, Moisture content, Dissolution and Drug content [8].

RESULTS AND DISCUSSION

Results of Compatibility study

From the data given in table-5, it is clear that Ambroxol is compatible with all the excipients used for the process.

Physical characterization

The micromeritic properties of the prepared pellets are evaluated and the results are given in the table-6 and 7. Angle of repose values of all the formulations was found to be less than 30, which indicates good flow properties of the prepared pellets. Bulk density and tapped density values obtained were used to calculate the % compressibility index and values found to be in the range of 10.22 ±3.1 to 21.34 ±3.7, which indicates fair to passable nature of the pellets.

Pellets were evaluated for the moisture content, assay and friability and the results are presented in table-8 and 9. The moisture content in the formulations was less than 2%, the drug content was in the range of 97.62 to 103.23 % and friability was less than 1%, all the values represent that the results obtained were within the specified limits.

***In-vitro* dissolution studies**

The initial three formulations of Ambroxol HCl SR

pellets were formulated with Ethyl cellulose 7cps (N-7) with concentrations of 2%, 3% and 5% respectively. However satisfactory results were not obtained with these polymers and it was decided to proceed further with high viscosity polymers which would effectively sustain the release of drug.

The next three formulations of Ambroxol HCl SR pellets were formulated with Ethyl cellulose 15cps (N-15) with concentrations of 2%, 3% and 5% respectively. However satisfactory results were not obtained with these polymers and it was decided to proceed further with high viscosity polymers which would effectively sustain the release of drug.

The last three formulations of Ambroxol HCl SR pellets were formulated with Ethyl cellulose 50cps (N-50) with concentrations of 2%, 3% and 5% respectively. Satisfactory results were obtained with this polymer, hence there is no need to proceed with high viscosity polymers.

The formulations of Ambroxol HCl SR pellets of Ethyl cellulose 50cps (N-50) with concentrations of 3% were optimised.

From the above results, formulation F11 (3% W/V EC 50 cps with 5%W/V PG as a plasticizer) was the best among the other formulations of Ambroxol HCl SR pellets of Ethyl cellulose as coating polymer as the drug release in this formulation is exactly equal to the innovator drug release.

Stability Studies

From the prepared sustained release Ambroxol HCl pellets formulations, F_{11} which showed desired % release was selected for stability studies. The capsules containing filled weight 202.702mg which is equivalent to 75mg of Ambroxol HCl was subjected to stability studies which was carried out at 40 ºC/75%RH for 2 months and evaluated at the end of 1^{st}, 2^{nd} months for Physical observance, Moisture content, Dissolution and Drug content. The results are given in the table-12.

No significant change was observed in the percentage drug dissolved after a storage period of 1 month at 40^0C / 75 % RH and 2 months at 40^0C / 75 % RH for Ambroxol SR pellets 202.7 mg. No significant change was observed in the assay value of Ambroxol SR pellets 202.7 mg, after a storage period of 1 month at 40^0C / 75 % RH and 2 months at 40^0C / 75 % RH. From the above data it was evident that there was no significant change in the physical and chemical parameters of Ambroxol SR pellets 202.7 mg during the stability studies conducted at 40°C & 75%RH for1 month period and 2 months at 40°C & 75%RH.

Table 1. Composition of Drug loaded Pellets

Ingredients	Quantity (gms)
Ambroxol HCl	500
Starch	330
MCC	200
N.P. Seeds	450
PVP K – 90	20
IPA	Q.S

Table 2. Process parameters of fluidized bed coater

Machine	Fluidized bed coater
Inlet air temperature	55 ºC
Outlet air temperature	45 ºC
Air flow	1.5 kg/cm^2
Spray rate	24 gm/min
No. of Spray gun	01
Spray direction	Bottom spray

Table 3. Composition of SR coated pellets with DEP as plasticizer

Ingredients (gms)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}
Drug Pellets	100	100	100	100	100	100	100	100	100	100
Ethyl Cellulose 7cps	2	3	5	-	-	-	-	-	-	-
Ethyl Cellulose 15cps	-	-	-	2	3	5	-	-	-	-
Ethyl Cellulose 50cps	-	-	-	-	-	-	2	3	5	3
Talc	2	2	2	2	2	2	2	2	2	2
DEP	0.2	0.3	0.5	0.2	0.3	0.5	0.2	0.3	0.5	0.5
IPA(ml)	472	472	472	472	472	472	472	472	472	472
MDC(ml)	900	900	900	900	900	900	900	900	900	900

Table 4. Composition of SR Coated Pellets with Propylene glycol and triethyl citrate as plasticizer

Ingredients (gms)	F_{11}	F_{12}	F_{13}	F_{14}	F_{15}	F_{16}
Drug Pellets	100	100	100	100	100	100
Ethyl Cellulose 50cps	3	3	3	3	3	3
Talc	2	2	2	2	2	2
Propylene glycol	5	7.5	10	-	-	-
TEC	-	-	-	1.5	2.5	3.5
IPA(ml)	472	472	472	472	472	472
MDC(ml)	900	900	900	900	900	900

Table 5. Results of Compatibility study

Name of the Excipient	Ratio API: Expt	Initial Observation	Final observation		conclusion
			30°C		
			2nd week	4th week	
API (ambroxol)	N/A	White colour	White colour	White colour	Compatible
API+ Starch	1 : 1	White colour	White colour	White colour	Compatible
API +MCCP	1 : 1	White colour	White colour	White colour	Compatible
API + PVP K90	1 : 1	White colour	White colour	White colour	Compatible
API + EC	1 : 1	White colour	White colour	White colour	Compatible
API + Talc	1 : 1	White colour	White colour	White colour	Compatible
API + MDC	1 : 1	White colour	White colour	White colour	Compatible
API + TEC	1 : 1	White colour	White colour	White colour	Compatible
API + PG	1 : 1	White colour	White colour	White colour	Compatible
API + IPA	1 : 1	White colour	White colour	White colour	Compatible
API + DEP	1: 1	White colour	White colour	White colour	Compatible

Table 6. Micrometric properties of the pellets of F1-F10 formulations

Formulations	Angle of repose (Ɵ)	Bulk Density (gm/ ml)	Tapped density (gm/ml)	Compressibility Index (%)
F1	25.7±1.2	0.74±0.05	0.86±0.04	13.95± 1.2
F2	26.4±1.5	0.72±0.12	0.81±0.03	12.19±0.1
F3	28.9±1.3	0.69±0.08	0.87±0.04	20.68±2.1
F4	24.3±1.4	0.75±0.06	0.89±0.03	15.73±0.5
F5	28.2±2.1	0.78±0.02	0.89±0.02	12.35±0.4
F6	24.7±1.3	0.79±0.09	0.88±0.03	10.22±3.1
F7	29.3±2.2	0.69±0.03	0.87±0.02	20.69±2.7
F8	25.4±1.4	0.64±0.02	0.85±0.12	14.10±0.45
F9	29.5±2.5	0.67±0.03	0.84±0.07	20.23±2.4
F10	27.3±1.9	0.70±0.04	0.89±0.09	21.34±3.7

Table 7. Micrometric properties of the pellets of F11-F16 formulations

Formulations	Angle of repose (Ɵ)	Bulk Density (gm/ ml)	Tapped density (gm/ml)	Compressibility Index (%)
F11	26.4±1.2	0.74±0.05	0.86±0.01	13.95±1.5
F12	27.9±2.6	0.75±0.09	0.89±0.06	15.73±1.5
F13	28.5±0.9	0.78±0.06	0.90±0.09	13.33±0.9
F14	30.5±1.9	0.79±0.12	0.91±0.04	13.18±0.5
F15	29.4±2.5	0.78±0.21	0.91±0.05	14.28±1.5
F16	29.7±3.1	0.79±0.13	0.90±0.08	12.22±2.1

Table 8. Evaluation parameters of F1-F10 formulations of Ambroxol SR pellets

Formulations	Moisture Content (%)	Assay (%)	Friability (%)
F1	2.2±1.1	97.62±1.21	0.34±0.03
F2	2.1±0.7	101.97±0.86	0.42±0.03
F3	2.2±0.3	97.81±1.85	0.32±0.05

F4	2.5±0.6	98.25±0.96	0.35±0.06
F5	2.5±0.5	98.62±1.02	0.44±0.04
F6	2.4±0.7	102.45±1.05	0.38±0.06
F7	2.6±0.3	98.52±0.45	0.26±0.05
F8	2.4±0.4	98.45±0.06	0.27±0.03
F9	2.5±0.1	101.56±1.42	0.24±0.02
F10	2.6±0.7	103.23±1.56	0.34±0.03

Table 9. Evaluation parameters of F11-F16 formulations of Ambroxol SR pellets

Formulations	Moisture Content (%)	Assay (%)	Friability (%)
F11	2.5±0.7	98.2±1.5	0.24±0.03
F12	2.8±1.2	101.5±1.5	0.22±0.03
F13	2.7±1.8	97.6±1.6	0.32±0.05
F14	2.6±1.9	98.5±2.1	0.45±0.06
F15	2.4±1.5	103.6±0.71	0.44±0.04
F16	2.6±1.6	102.6±0.6	0.38±0.06

Table 10. *In-vitro* dissolution profile of F1-F10 formulations of Ambroxol SR pellets

Time (hrs)	Cumulative % drug release						
Batch	0	1	2	4	8	12	24
Innovator	0	21.6±2.1	26.7±3.5	47.8±1.9	60.3±3.5	88.8±2.7	94.3±2.2
F1	0	29.5±3.6	40.3±2.9	53.9±3.8	69.1±1.9	93.4±2.1	100±0.1
F2	0	27.3±3.7	39.2±2.3	50.7±3.8	67.9±4.8	91.2±1.9	100±0.8
F3	0	25.3±3.9	37.1±2.5	48.3±4.8	65.7±4.7	89.3±3	100±1.0
F4	0	25.4±3.7	34.2±2.3	44.3±3.8	58.3±4.8	89.1±1.9	100±1.5
F5	0	23.3±3.0	33.1±4.8	42.7±2.0	56.1±4.5	88.5±4.0	100±2.5
F6	0	21.7±3.7	31.8±2.3	40±3.8	53.8±4.8	87.3±1.9	98.1±1.5
F7	0	23.5±1.8	30.5±2.8	50.6±4.0	63.7±2.6	87.5±3.0	96.5±2.1
F8	0	20.2±1.8	27.5±2.8	48.5±2.4	61.4±2.6	86.5±3.0	94.5±2.7
F9	0	19.3±1.8	23.5±2.8	43.1±2.4	57±2.6	82.2±3.0	89.7±2.7
F10	0	31.5±2.1	42±3.5	55.9±1.9	72.5±3.5	96.6±2.7	100±2.3

Table 11. *In-vitro* dissolution profile of F11-F16 formulations of Ambroxol SR pellets

Time (hrs)	Cumulative % drug release						
Batch	0	1	2	4	8	12	24
F11	0	20.8±4.2	26.7±2.8	47.2±3.8	59.9±4.9	87.2±4.3	93.1±2.8
F12	0	19.4±1.8	23.2±3.5	45.7±3.7	54.2±4.5	83.7±2.9	90.1±2.8
F13	0	18.7±3.6	22.4±2.9	44.2±3.8	55.7±1.9	80.7±4.1	89.8±4.0
F14	0	23.5±2.5	32.5±4.6	50.3±3.5	63.1±4.5	89.2±4.5	96.6±3.7
F15	0	22..5±1.8	30.7±4.6	50.9±3.8	62.7±2.9	86.5±2.5	93.1±3.1
F16	0	20.1±1.8	28.5±4.6	45.5±3.8	57.6±2.9	86.5±2.5	92.5±3.1

Table 12. Characterisation of stability studies of optimized formulations

Test	Specifications	Initial	After 1 month	After 2 months
Description	White/Off-white coloured pellets	Complies	Complies	Complies
Identification	The retention time of major peak in the chromatogram of the assay preparation corresponds to that in the chromatogram of the standard preparation as obtained in the assay.	Complies	Complies	Complies
Dissolution (In purified water)	NLT 80% release after 12 hours	96.1%	95.7%	95.6%
Related Substances (%)	NMT 1.0%	Complies	Complies	Complies
Assay (By UV-V)	NLT 95.0 percent and NMT 105.0 percent	99.1±2.1%	98.7±1.9%	98.6±3.5%
Dissolution		93.1±2.8%	91.5±3.1%	89.3±4.0%

CONCLUSION

Ambroxol Hcl pellets were prepared in this study by Wuster by using EC 7 cps, EC 15 cps and EC 50 cps as SR polymers. As the pellets were prepared by Wurster process only a little amount of moisture was expected. The loss on drying of pellets was determined as 2.5%w/w, which indicates that the layering processes as well as the raw materials were suitable to manufacture stable pellets having low moisture content. The values of micrometric study indicate that they were suitable to fill the pellets in empty hard gelatine capsule shell. All the formulations showed the percentage drug content of 100±5%. After 12th hour the percentage drug release from the formulations were above 80% for the formulations containing EC7cps 2%,3%,5%; EC15cps 2%,3%,5% and EC50cps 2%,3%,5%. The burst release of Ambroxol HCl from formulations with EC 50cps is comparatively lower than the one with EC 7cps, due to the fact that EC 50cps is more viscous and release retarding capacity is more when compared to EC 7cps. Formulation F11 was identified to be the best as it matches well with the innovator. The optimized formulation was subjected to at stability studies for 2months, which shows that slower decrease of the dissolution as well as assay values, which is in the limits.

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