Original Article

NOVEL FORMULATION DESIGN AND IN-VITRO EVALUATION OF EXTENDED RELEASE PELLETS BY COMPLEXATION TECHNIQUE

Hande sayali sakharam[1], Ghangale Gauri Dhondibhau[2], Dr. K Nagasree[3], Gunjal Sachinkumar Dnyaneshwar[4], Kiran Arun Suryavanshi[5], Reshma Shashikant Mindhe[6], Parth Ramesh Gharat[7]

[1]Dnyanvilas College of pharmacy, Pune, Maharashtra - 412105, India

[2,4]Amrutvahini College of pharmacy, sangamner, Maharashtra - 422605, India

[3]Samskruthi College of pharmacy, Ghatkesar, Medchal- Malkajgiri, Hyderabad, Telangana- 501301, India

[5]SMBT Institute of Diploma Pharmacy, Dhamangaon, Tal-Igatpuri, Nashik, Maharashtra -422403, India

[6]Shivneri Institute of Pharmacy, Khanapur, Tal-Junnar, Pune, Maharashtra- 410502, India

[7]Central Ayurveda Research Institute, Bidhan Nagar, Kolkata - 700091, India

Email: handesayali11@gmail.com

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Abstract

This research was undertaken with an aim to formulate dextromethorphan hydrobromide as extended release micropellets. The Preformulation studies were carried out on drug Dextromethorphane Hydrobromide and it was shows that Drug has good flow property. Various ion exchange resins were screened for complexation with the drug and ratio of drug: resin was optimized along with manufacturing process for complexation. The Drug-Resin complex was further coated with suitable hydrophobic release rate retarding polymeric coatings using fluid bed processor. Optimization of % Ethyl Cellulose coat on drug-resin complex was carried out and 23.5% EC coat was selected for preparing final batch of micropellets of the drug Dextromethorphan hydrobromide.

Keywords: Extended Release Pallet, Dextromethorphan Hydrobromide, Drug-Resin complex.

INTRODUCTION

An perfect medicate conveyance framework diminishes the introduction of the sedate to other tissues and in this way is capable for precisely conveying the medicate at a wanted rate and hence minimize its side-effects. Modified-release dosage form is a product that alters the timing and rate of release of drug substance and it refers to both delayed and extended release systems for oral administration. The basic rational for modified release drug delivery is to alter the Pharmacokinetics and pharmacodynamics of pharmacologically active moieties by using release modifying polymers and novel techniques like fluidization, pelletization and thus effectively optimize the bioavailability and resulting blood concentration-time profiles of drugs [1] .Oral modified release dosage form can be broadly classified into two categories: Single-unit and Multiple-unit dosage forms [2]. The single-unit dosage forms include matrix tablet or coated or uncoated tablet or capsules [3]. The multiple-unit dosage forms consist of pellets, micropellets or microencapsulated drug filled in a capsule or compressed into a tablet or suspended in suspension [4]. The individual subunits like pellets release the dose of the active ingredient and the functionality of the entire dose depends on the quality of the subunits.5Multiparticulate dosage forms provide increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying due to which they are preferred over single-unit dosage forms Dextromethorphan hydrobromide is widely used in relief of cough due to bronchial irritation or minor throat irritation [5,6]. The drug has a faint odour, bitter taste and is sparingly soluble in water, freely soluble in alcohol and in chloroform. The pH of the drug lies between 5.2 and 6.5 implying its basic nature. It has a short half-life and is rapidly absorbed from the gastrointestinal tract, where it enters the bloodstream and crosses the blood-brain barrier [7]. Because of shorter half life it requires frequent administration. The objective of the current research is to formulate the robust, stable & extended release taste masked micro pellets of drug Dextromethorphan Hydrobromide having bitter taste and shorter half life of 2 to 4 hrs. Initially attempts were made to mask the bitter taste of drug by means of complexation with ion exchange resin. Complexation with resin not only masks bitter taste of the drug but also delay its release [8,9]. To modify further release of

dextromethorphan its coating was performed using release retarding polymer. These coated micro pellets can be used to formulate extended release dosage forms such as capsule, suspension etc. [10-14].

MATERIALS & METHODS

Preformulation studies

Preformulation studies were carried out in order to maximise the chances in formulating an acceptable, safe, efficient, stable dosage form. Physical characteristics of dextromethorphan hydrobromide were studied.

Assay of the drug by HPLC analysis

An HPLC system (pump, chemstn software) along with C18, column5µm, 150 × 4.6 mm (Water-Symmetry) was used to carry out assay of drug dextromethorphan hydrobromide. 20ul injections of standard and sample were prepared using the mobile phase consisting of Acetonitrile: Ammonium phosphate- Octanesulfonic acid buffer in the ratio of 30:70 v/v. 5.75g of Ammonium phosphate and 5.41g of Octanesulfonic acid was weighed in a suitable container and diluted to 1000ml with water. It was further adjusted to pH 2.5 with Phosphoric acid and filtered through 0.45 um milipore filter to give 50nM Ammonium phosphate 25mM 1- Octanesulfonic acid buffer with pH 2.5. 300 ml of acetonitrile was mixed with 700 mL of ammonium phosphate-Octanesulfonic acid buffer, stirred and sonicated for 10 minutes respectively and allowed to cool at room temperature. Flow rate was1.7mL/min and the retention and run times were 15 minutes and 25 minutes respectively. The detection was carried out at 280nm.

FORMULATION OF DEXTROMETHORPHAN HYDROBROMIDE MICROPELLETS

Preparation of Drug-Resin complex

Complexation with ion exchange was selected as a strategy for taste masking of drug Dextromethorphan Hydrobromide. The detailed development with respect to manufacturing formula and procedure is given below.

Selection of resin grade

There are 4 trials carried out for selection of appropriate resin grade. In these trials, drug-resin complexes were formulated with different grades of Sodium polysterene Sulfonates such as Grade “Z”, Grade “W”, Grade “Y” and Grade “V”and corresponding batches were analyzed for impurities. 100g of Dextromethorphan Hydrobromide was dissolved in 2L of purified water at room temperature under stirring which was continued for 45 minutes till clear solution was obtained. Batch quantities of individual resin were added to the drug solution prepared slow speed stirring. After stirring of drug resin complex slurry, it was filtered using #200 (ASTM, 75µ) sieve. The insoluble drug resin complex was separated from the filtrate. The resultant wet mass of drug resin complex was dried at not more than 50°C product bed temperature. The Drug-resin complex obtained after processing above batches was characterized for impurities.

Optimization of ratio of drug to resin in Drug-Resin complex

Optimization of drug: resin ratio was carried out by evaluation of ratio ‘1:3’, ratio ‘1:1’ and ratio ‘2:1’, the composition of the batches to be evaluated for optimization is given in below table 2. The batch quantity of selected resin was added to drug solution under stirring. During stirring of drug resin complex slurry, samples were withdrawn at 20, 40, 60, 80,100, 120 and 180 minute time points. The samples were allowed to stand undisturbed and the insoluble drug resin complex was separated from the medium by using 200 (ASTM, 75 µ) sieve. The filtrate obtained was analyzed for content of free/ uncomplexed drug. The Drug-Resin complex obtained after filtration was dried at a product bed temperature of not more than 50ºC. The dried Drug-Resin complex obtained in all batches was sifted through # 120(ASTM, 125µ) sieve. The sifted complex was analyzed for drug release profile (dissolution) to evaluate the impact of different ratios of drug: resin. The drying operation was continued till LOD below 8% was obtained. The drying parameters are provided in below table 1.

Table 1: Drying parameters for Drug-Resin complex

Drying time (minutes)	Inlet air temperature (°C)	Product bed temperature (°C)	LOD achieved (% w/w)
240 minutes	40-55	25-60	6.33

Table 2: Composition of batches manufactured to optimize drug: resin ratio

Formulation Details [Drug: Resin]	Ratio A (1:3)		Ratio B (1:1)		Ratio (2:1)	
Ingredients	mg/unit	% w/w	mg/unit	% w/w	mg/unit	% w/w
Drug	30	25.00	30	50	60	66.66
Sodium polysterene Sulfonate	90	75.00	30	50	30	33.33
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Theoretical weight of drug-resin complex (mg)	120	100	60	100	90	100

Physical characterization of Drug-Resin complex

Light brown coloured micro pellets of Drug-Resin were obtained. Physical characterization tests of drug-Resin complex were performed and mentioned in result and discussion section.

Chemical characterization of Drug-Resin complex

The chemical characterization of Drug-Resin complex was performed with respect to tests like assay and dissolution.LOD was performed by the oven method at 105°C for 1 hour.

Solvation coating on Drug-Resin complex

The main ingredients for solvation coating were PEG and purified water. Compositions of trials performed to optimize the concentration of solvating solution are given in below table 3. Two concentrations of solvating solution were evaluated for processability and their observations are presented accordingly. Drug-Resin complex was loaded in to the coating bowl of fluidized bed coater. The product bed was heated to achieve a temperature of 25-35°C by setting appropriate temperature (30-90°C) for inlet air. The machine parameters, process parameters and coating parameters recorded during solvation coating are given in table 4.

Table 3: Composition of coating solution for trials performed to optimize the solid content of solvating solution

Ingredients	Batch A	Batch B
Polyethylene glycol	38.36	27.78
Purified water	61.64	72.22
Theoretical total	100.00	100.00

Ethyl cellulose coating on Drug-Resin complex

Ethyl cellulose is a commonly used release rate controlling polymer. The mechanism of controlling the drug release by application of ethyl cellulose films is by diffusion. Ethyl cellulose coating solution was prepared by dissolving Dibutylsebacate

used as a plasticizer followed by Ethyl Cellulose NF22 having viscosity between 18-22 cps in a mixture of IPA: DCM (90:10) under stirring for 5 minutes. The stirring was continued for 30 – 40 minutes after which a clear solution was obtained. This solution was sifted through # 80(ASTM, 180µ) sieve. The dried and sifted Drug-Resin complex was considered as the product bed for EC coating. The Drug-Resin complex was coated with Ethyl cellulose solution such that 4% weight gain was obtained on product bed. The manufacturing formula for 4% w/w of coated drug-resin complex is given in table 5.

Table 4: Machine parameter and process parameter

Machine Parameters	Observations
Nozzle diameter (mm)	0.8
Internal diameter of silicon tubing (mm)	4
Wurster column height (mm)	20
Bottom sieve size (# size)	# 250
Peristaltic pump (rpm)	3-4
Coating attachment	Bottom spray
Process parameters	
Inlet air temperature (°C)	26 – 41
Product bed temperature (°C)	26-30
Spray atomization air pressure (bars)	1.00
Exhaust Temperature(°C)	26-28
Spray rate (g/ min)	1.4-2.05

Table 5: Batch compositions in terms of 4 %w/w of Coated Drug-Resin complex

Ingredients	Quantities
Drug-Resin complex	96.15
Ethyl cellulose N 22	3.51
Dibutylsebacate	0.34
Isopropyl alcohol	q.s.
Dichloromethane	q.s.
Theoretical total	100.00

Optimization of % Ethyl Cellulose coat on drug-resin complex.

In order to achieve extended release formulation for 24 hours, the micropellets were coated with different level (%) of Ethyl cellulose such as 4%, 18%, 20.5%, 23%, 25% and 28% and effect of this on assay, LOD and dissolution profile was studied.

RESULTS AND DISCUSSION

Table 6: Physical Characteristics of the drug

Test	Results
Description	White crystalline solid or powder
Taste	Bitter in taste
Odour	Faint odour
Bulk density	0.55 gm/mL
Tap density	0.8 g/cc

Compressibility index	10
Particle size distributions	99.0% on 80 mesh
Angle of repose (°)	-
LOD at 105°C for 5 minutes (%)	4.98%
pH	Between 4 to 5
Residue on ignition	NMT 0.1%
Solubility	Sparingly soluble in water, freely soluble in alcohol and in Chloroform
Hygroscopicity	Non-hygroscopic

Table 7: Slope and Linearity of Dextromethorphan Hydrobromide

Slope (m)	Intercept (b)	Y=m*x + b	Y-intercept at 100% level (%)
201.89	31.04	11975.03	0.26

Table 8: Assay of the drug by HPLC analysis

Actual Conc. (µg/ml)	Mean Area (mAU*min)	Correlation coefficient	Coefficient Determination [R^2]
1.8	370.762	1.0000	0.9999
14.8	3047.197		
29.6	5978.671		
59.2	12025.872		
71.0	14325.795		

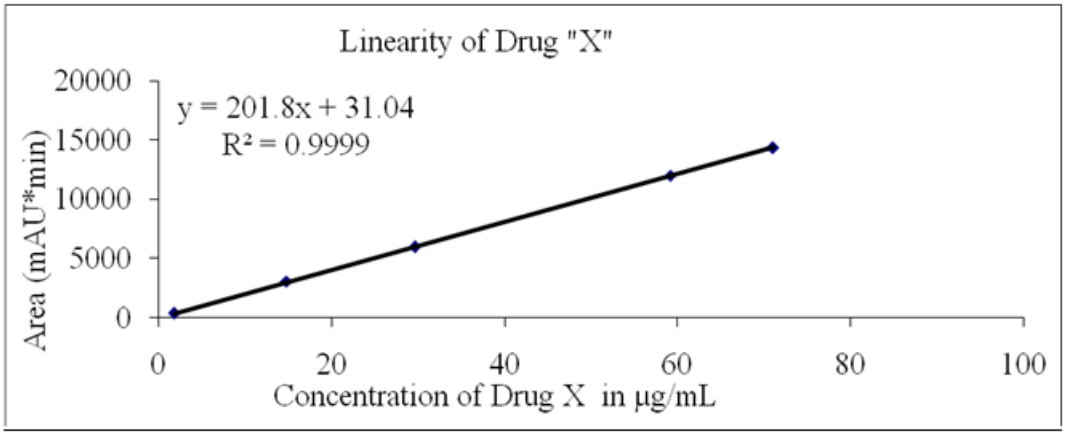

Fig. 1: Linearity of Dextromethorphan Hydrobromide

Table 9: Selection of resin grade

Formulation details	% Total impurity
Drug: Resin (Grade "Z")	0.00
Drug: Resin (Grade "W")	0.35
Drug: Resin (Grade "Y")	0.06
Drug: Resin (Grade "V")	0.29

The total % Impurity levels for drug resin complex manufactured with Amberlite IRP 69" were not detected. Resin with grade "IRP 69" was selected for complexation with the drug.

Table 10: Dissolution of drug resin complexes with different ratios of drug: resin

Time (hrs)	Ratio A (1:0.5)	Ratio B (1:1)	Ratio C (1:3)
% of Drug released			
0.5	88.0	48.9	43.1
1	99.3	57.9	48.2
3	105.5	61.3	50.1

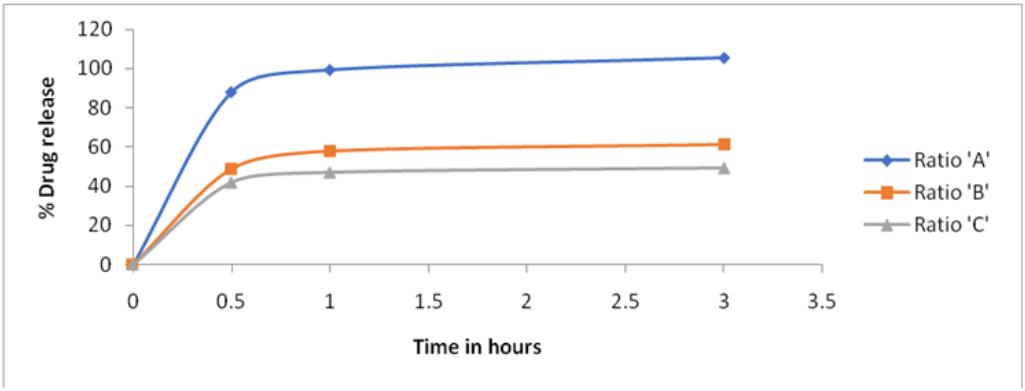

Fig. 2: Dissolution of drug resin complexes with different ratios of drug: resin

The drug: resin ratio was optimized as ratio '1:3' for further development of Drug-Resin complex based on dissolution profile.

After completion of 120 minutes of stirring, it was seen that drug content of slurry remained constant with respect to content of free/uncomplexed Dextromethorphan Hydrobromide i.e no further complexation occurs. The stirring time required for drug-resin complex formation was optimized as 120 minute (2 hours) after addition of resin to drug solution.

Table 11: Physical characterization of Drug-Resin complex

Parameters	Observations
Bulk Density (g/ml)	0.5360
Tapped Density (g/ml)	0.7216
Angle of repose (°)	25.17
Flow rate (g/sec)	7.62
Particle size distribution (Sieve analysis method)	
Mesh size	**% Retained**
On 60 # (> 250 µ)	0.00
On 80 # (> 180 µ)	1.02
On 100 # (> 150 µ)	2.17
Below 100 # (< 150 µ)	96.81

The physical characterization of Drug-Resin complex showed that majority of particles were below # 120 (ASTM, 125 µ) sieve. The angle of repose value suggests good flow properties.

Table 12: Chemical characterization of Drug-Resin complex

Parameters	Observations	Acceptance criteria
Assay (on dried basis)	15 % w/w	Dried complex should contain 12 – 18 % w/w
LOD	7.00 % w/w	NMT 8 % w/w

Table 13: Dissolution profile of Drug Resin Complex:

Time (hrs)	% drug released
0.0	0.0
0.5	43.1
1.0	48.2
3.0	50.1

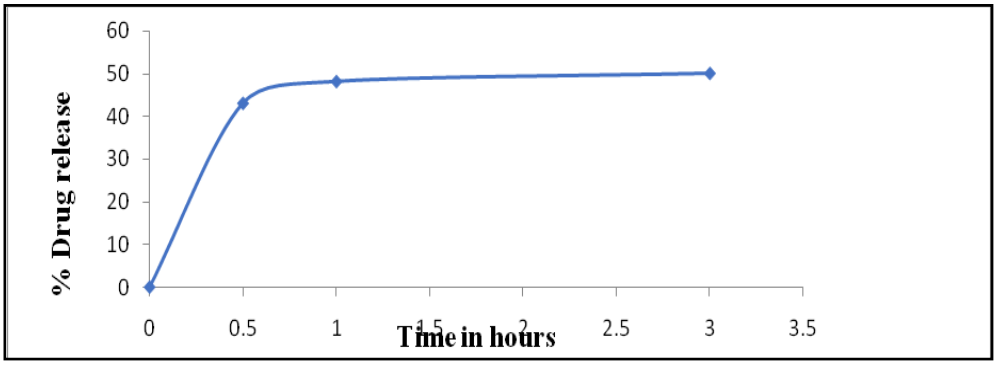

Fig. 03: Dissolution profile of drug-resin complex

The release kinetics/ dissolution behaviour of Drug-Resin complex shows 42% drug release in first 0.5 hrs and approximately 50% of drug release at the end of 3 hrs.

Table 14: Data on optimization of % Ethyl Cellulose coat on drug-resin complex

EC Coat %	4.0	18.00	20.5	23.00	25.5	28.00
LOD %	7.18	6.20	6.60	6.20	6.7	6.90
Assay%	15.04	16.10	15.79	15.35	15.52	14.55
Dissolution % drug release at 12 hrs.	80.1	67.18	65.9	62.4	61.5	54.8

The dissolution profile of this 25.5% EC coated drug resin complex shows that 61.5 % of drug was released within 12 hours. From above data it can be concluded that 28% EC coating can cause more drug retardation as compare to 23.5% EC coating this is due to over coating. Based on results of dissolution profile of all above conclusion, 23.5 % EC coated micro pellets were selected as a final optimized formulation. Thus micropellets of dextromethorphan hydrobromide were prepared.

CONCLUSION

The study was undertaken with an aim to formulate dextromethorphan hydrobromide as extended release micropellets. The Preformulation studies were carried out on drug. Micromeritics like bulk density, tap density, particle size analysis of Dextromethorphane HBR were carried out and it was shows that Drug has good flow property. Various ion exchange resins were screened for complexation with the drug and ratio of drug: resin was optimized along with manufacturing process for complexation. The Drug-Resin complex was further coated with suitable hydrophobic release rate retarding polymeric coatings using fluid bed processor. Optimization of % Ethyl Cellulose coat on drug-resin complex was carried out and 23.5% EC coat was selected for preparing final batch of micropellets of the drug Dextromethorphan hydrobromide. Thus it can be concluded that micropellets of dextromethorphan hydrobromide are successful in providing extended drug release.

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