



DEVELOPMENT AND EVALUATION OF RELEASE EQUIVALENT SUSTAINED RELEASE FORMULATION OF DEXTROMETHORPHAN HBR USING SIMPLE TECHNOLOGY

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ABSTRACT

Dextromethorphan HBr is a synthetic antitussive compound. Biological half life of this drug is 2 to 4 hours. Due to its shorter half life the dose is upto 4 times a day, thereby reducing patient compliance. Thus to reduce the dose frequency and to improve the patient compliance sustained release tablets of freely water soluble Dextromethorphan HBr. was formulated with non-swellable waxy polymer Compritol888 by dry granulation method.

The matrix tablets of Dextromethorphan HBr were prepared by direct compression of granules, physical mixture of drug and polymer was found compatible after comparative study for three months. Matrix tablets were evaluated for hardness, friability and weight variation. This tablet was capsulated with loading dose of drug. *In vitro* drug release study was performed using USPXXIII apparatus (basket type) in HCl pH 1.2 for two hrs and in phosphate buffer pH 6.8 for remaining 10 hrs.

Dissolution study showed that polymers can sustain the release of drug for up to 12 hrs. Comparison of *In vitro* release of the Dextromethorphan HBr with existing sustained release suspension (Delsym) clearly indicated the advantage of present formulation in terms of release equivalence, patient compliance by using simple dry granulation method.

The equivalent formulation was developed using dry granulation method which showed advantages in the terms of patient compliance, safety, and better transportation over existing suspension formulation. Difference factor (f_1) and similarity factor (f_2) was used as a statistical method in this work.

Key words: Dextromethorphan HBr, Compritol888, Delsym

INTRODUCTION

The goal of any drug delivery system is to promptly provide the required amount of drug to the proper site in the body and to maintain the desired drug concentration. That is determined by, drug blood level which is the concentration of a drug in the blood or plasma. Controlled release systems have been developed and studied the drug pharmacological action and reduce their side effects. The basic concept is that the rate of drug absorption may be adjusted through a controlled rate of drug release from the dosage form. A huge variety of such systems have been proposed over the last two decades; among them, the simplest system is the matrix device, where the drug is dispersed within a polymer network¹.

Dextromethorphan hydrobromide, a centrally acting non-opioid antitussive drug. It is an effective and safe for the control of cough in patients. Dose is 10-30 mg daily in divided dose. Due to its short biological half life of 2-4 hr, it requires multiple dosing (2-3 times a day). Multiple dosing leads to fluctuation in the drug blood level and often dose related adverse effects. Multiple dosing also often results in poor compliance and inefficient therapy². Development of sustained release formulation of Dextromethorphan can minimize the dose related adverse effects, cost and ultimately the patient compliance.

Various types of hydrophilic polymeric materials have been widely used to modify and modulate the drug release from solid

pharmaceutical dosage forms such as Hydroxypropylmethylcellulose, Eudragit and Carboxypolyethylene³⁻⁵. However, a many factors can influence the drug release behaviour from the dosage form such as chemical-physical properties of the raw materials, composition and amount of components in the formulation, and manufacturing variables⁶⁻⁹. A waxy polymer can minimize such problem which are associated with hydrophilic polymer and highly water soluble drug. Example of waxy polymers includes hydrogenated oils, glyceryl stearates, fatty alcohols and microcrystalline wax. These polymers have good advantages as good stability at varying pH values and low incompatibility with wide range of drugs. Matrix delivery system utilizing waxy polymer usually employ a core of drug embedded in the waxy polymer or a core of drug and matrix forming agent¹⁰.

Glyceryl behenate (Compritol888) is a waxy polymer, originally introduced as a lubricant in compressing tablets, which has recently had a wide application as a sustained release polymer¹¹. It is commonly used as a lubricant and binding agent for tablets in concentration of 1-3% and a sustained release excipient in concentration between 10% to 50%¹². A recent study by Feng-Qian Li and Jin-Hong Deng investigated the use of glyceryl behenate as sustained release polymer to prolong the release of Sodium Ferulate¹³.

One of the controlled systems for Dextromethorphan in Pharmaceutical market was Delsym, which is a suspension type of formulation in which release of drug was controlled by the coating of ethyl cellulose on polyethylene 400 pretreated granules of drug. These coated particles of drug were

suspended into a medium for the prolonged action of drug. The objective of the present work is to minimize the formulation difficulties of above procedure of the sustained release formulation of Dextromethorphan. In this project, we have formulated a release equivalent formulation of sustained release of Dextromethorphan utilizing a simple dry granulation of drug with the glyceryl behenate which would provide an extended duration of therapeutic effect with minimum potential for side-effect. Significance of different batches was confirmed by applying dissolution data in statistical manner by using fit factor: difference factor (f_1) and similarity factor (f_2)¹⁴.

MATERIALS AND METHODS

Materials

Dextromethorphan HBr was gifted from Arbro Pharmaceuticals Ltd., (Delhi). The assay of this drug as given in the certificate of analysis was of 98%. Polymer Compritol888 was also gifted from Arbro Pharmaceutical Pvt. Ltd. Lactose, Aerosil, and Magnesium stearate was of Pharmacopoeial grade. All other materials, solvent used were of analytical and / or high performance liquid chromatographic grade. All the excipients were used as supplied without any further purification.

Methods

Preparation of matrix tablets

Four different batches of granules, of Dextromethorphan HBr were prepared by dry granulation method by varying the polymer/diluent w/w ratio, always keeping the drug amount 25 mg constant in each batch. Batch details for the formulation of Dextromethorphan sustained release matrix tablets are given in the table 1.

Table 2: Tablet parameter of Formulated Tablet

Contents (mg)	DXM 1	DXM 2	DXM 3	DXM 4
Dextromethorphan HBr	25	25	25	25
Compritol888	50	55	60	65
Lactose	43	38	33	28
Mg Stearate	1	1	1	1
Aerosil	1	1	1	1

5 mg Dextromethorphan capsulated as a loading dose in the hard gelatin capsule.

Theoretical weight of each tablet = 120 mg.

Compritol888 (glyceryl behanate) and lactose were used as an intragranular excipients and magnesium stearate and aerosil were used an extragranular excipients. After adding all these material the final formulation was mixed for two minutes. Tablets were compressed using single punch tablet machine, at a tablet weight of 120 mg according to classical tableting procedure.

Evaluation of matrix tablets

Average weight and weight variation

The weight variation test was carried out for 20 matrix tablets from each batch in a sartarius digital balance and the average weight was determined, using the following formula as per USP 1995:

Average weight = Total weight of tablets/20

Hardness test

Ten tablets were tested using Monsanto hardness apparatus.

Friability

Twenty tablets were weighed (W1) and rotated for one hundred revolutions in a Roche friabilator. The tablets were then reweighed (W2) and the percentage friability (%F) were calculated with following Eq.

$$\%F = [(W1 - W2 / W1) \times 100]$$

Filling of capsules

Zero No. capsules were used to place the single tablet inside it with

Dextromethorphan (5 mg) as a loading dose. Starch and talc were used as filler in the capsule.

***In-vitro* dissolution studies**

Drug release studies of, marketed available sustained release formulation of Dextromethorphan (Delsym suspension) and formulated capsules were carried out using USP XXIII dissolution apparatus (Type I, basket). The formulated capsule was added to 900ml of 0.1 N HCl (pH 1.2) for the first two hour and Phosphate buffer (pH 6.8) for the remaining ten hours. The temperature of the medium was maintained at 37⁰C and was stirred at 50 rpm. Sample (10 ml) withdrawn at one hour time interval over a period of 12 hrs. After each sampling, equal amount of the medium was added. The sample withdrawn was filtered to remove particulate matter. Dissolution study of all formulated batches were also performed by keeping all the factors same, as release studies of market available sustained release formulation of Dextromethorphan. The absorbance of the sample at different time intervals was measured using a UV visible spectrophotometer (Unicon) at 440 nm.

To compare the dissolution data of the tablets, a statistical method was used which was independent of the dissolution process. This

method established two comparison factors: the difference factor (f1) and the similarity factor (f2). These factors are easily calculated and provided a simple measure of similarity between pairs of dissolution profile but do not provide information on individual batches.

The difference factor (f1) can be calculated by using the following formula

$$f_1 = \left[\frac{\sum (|R_t - T_t|)}{\sum R_t} \right] \times 100$$

Where R_t = amount of drug released from the reference formulation

T_t = amount of drug released from the tested formulation

If the dissolution profiles are superimposed, f_1 reaches a value of 0, whereas the factor value increases when the differences between dissolution profile increases.

The similarity factor (f_2) can be calculated by using the following formula

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$

Where n = number of experimental data

If the dissolution profiles are superimposed, f_2 reaches a value of 100, whereas the factor value decreases when the difference between dissolution profiles increases

RESULT AND DISCUSSION

In the present study, experimental design methodology was exploited for systematically evaluating the effect of polymer/diluent ratio on drug release from matrix tablets, with the aim of identifying the most significant factor in determining its release rate and establishing their best level for optimizing the considered experimental responses. For this purpose, lipophilic waxy polymer Compritol888 was used for the sustained release matrix tablet if Dextromethorphan HBr, because this polymer have some good characteristics as direct compressibility, binding property and insolubility in water.

The formulated tablets of each batches of Dextromethorphan provided good weight uniformity. It was found that, average weight for all four batches was between 119.2-200.2mg since theoretical weight of each tablet was 120mg. In case of hardness no change was seen in different batches but there was change in friability by varying the polymer/diluent ratio. The tablet passes the hardness and friability test in accordance with the Pharmacopoeial limits (Table 2).

Table 2: Tablet parameter of Formulated Tablet

S. No.	Evaluation Procedure	DXM 1	DXM 2	DXM 3	DXM 4
1	Average weight (mg)	119.2	119.5	200.8	200.3
2.	Weight variation (%)	±5.5	±4.8	±4.8	±4.2
3.	Hardness (kg/cm ²)	2-3	2-3	2-3	2-3
4	Friability (%)	0.13	0.23	0.22	0.16

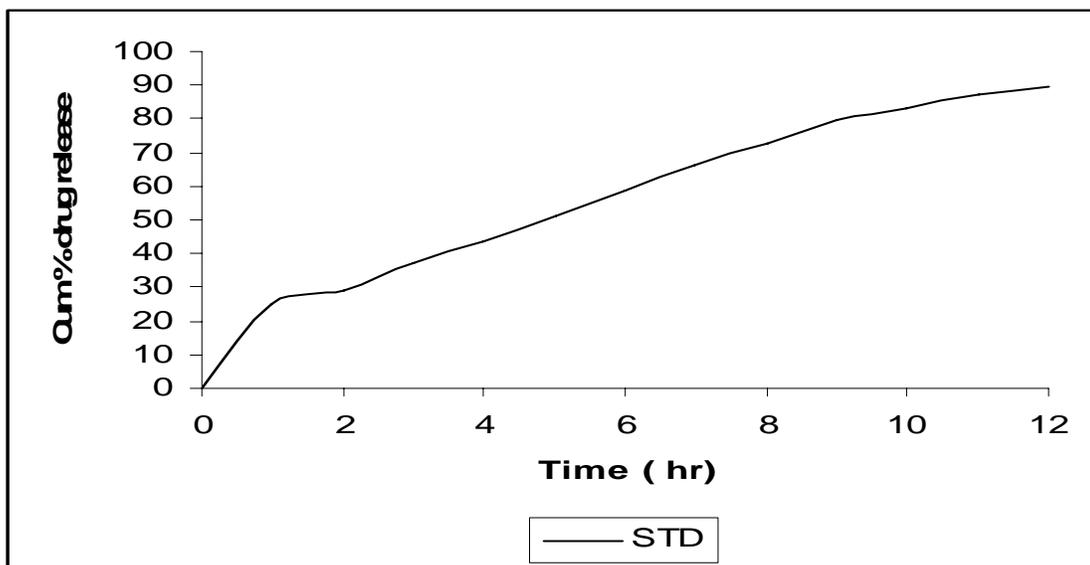
Marketed available formulation, showed the 25% release of drug with in an hour. The amount of drug release increases with

the time and after 12 hour nearly 90% drug have released from the formulation (Fig. 1). Because it is a release equivalent

study and it was difficult to get 25% amount of drug in an hour with the same matrix tablet so, we placed the tablet in

the capsule with 5 mg Dextromethorphan to find out the same release pattern as discussed above.

Fig. 1: *In vitro* Drug release profile of the market available preparation of Dextromethorphan (Delsym Suspension)



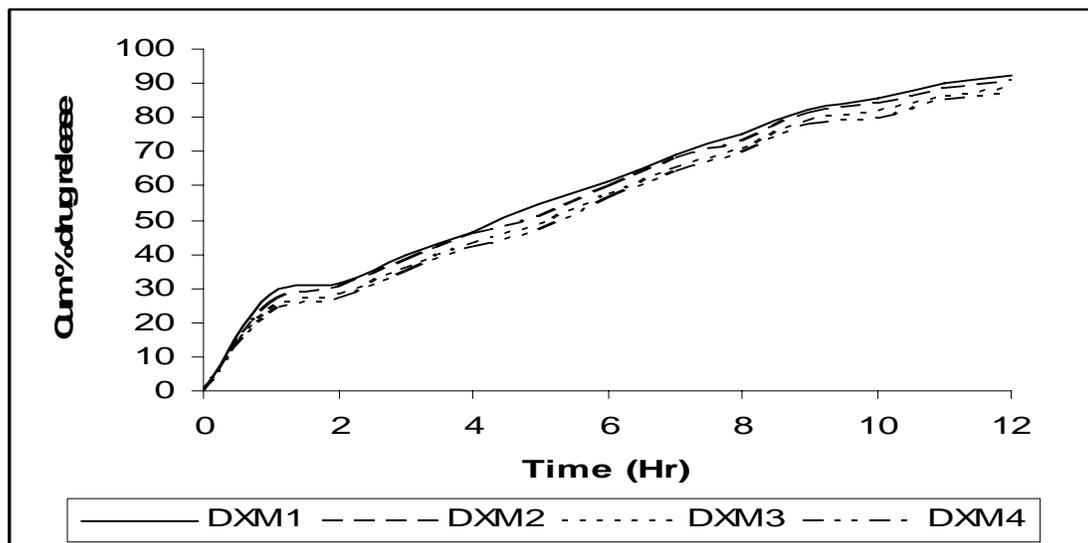
All the four formulated batches of Dextromethorphan were found to release 25% of drug in an hour and rest amount of

drug was released upto 12 hour in a sustained manner (Table 3, Fig. 2).

Table 3: Invitro drug release profile of the formulated Capsule containing sustained release matrix tablet of Dextromethorphan

Time	Cum % drug released			
	DXM 1	DXM 2	DXM 3	DXM 4
0	0	0	0	0
1	28.11	25.65	23.67	22.44
2	31.75	30.63	28.11	27.07
3	39.55	38.01	35.87	34.69
4	46.15	45.78	43.21	41.78
5	54.44	50.79	48.46	46.88
6	61.32	59.91	57.72	56.23
7	68.98	67.68	65.24	63.92
8	74.94	73.20	70.99	69.43
9	82.56	81.12	79.06	77.96
10	85.89	84.06	81.94	79.76
11	90.05	88.35	86.18	84.95
12	92.17	90.60	88.16	87.16

Fig. 2: *In-vitro* drug release profile of the formulated capsule containing sustained release matrix tablet of Dextromethorphan



Dissolution data of all the four batches clearly showed that percentage drug release was decreased by increasing the amount of polymer (Compritol888) while by increasing the amount of diluent (lactose) the percentage drug release decreased. The order of percentage drug release for all the four batches was found to be as DXM 1 < DXM 2 < DXM 3 < DXM 4.

As a function of fit parameter f1 and f2 obtained values, batch DXM 2 is selected as a batch with greater release equivalence to the market available formulation (table 4).

Table 4: f1 and f2 data corresponding to the indicated batches

Batch No	F1	F2
DXM 1	4.44	51.43
DXM 2	1.67	71.90
DXM 3	2.08	67.58
DXM 4	4.33	52.02

CONCLUSION

The present study showed that a sustained release formulation of water soluble Dextromethorphan HBr can also be prepared by using simple dry granulation method with a waxy polymer Compritol888. Dry granulation method is a very simple and useful tool in making of matrix tablets. A release equivalent formulation was developed to retain the release of drug up to 12 hours.

Moreover, this study also showed the effect of Compritol/lactose ratio on the release pattern of the drug. Formulation with higher amount of Lactose showed the rapid dissolution of drug although, Compritol888 retained drug release from the matrix tablets. The equivalent formulation which is developed by simple dry granulation method showed advantages in the term of patient compliance, safety, and better transportation over existing suspension formulation.

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