Innovare Academic Sciences

International Journal of Pharmacy and Pharmaceutical Sciences

ISSN- 0975-1491 Vol 6, Issue 4, 2014

Original Article

FORMULATION AND *IN VITRO* EVALUATION OF FLOATING MICROSPHERES OF DEXTROMETHORPHAN HYDROBROMIDE

PAVAN KUMAR PERUMANDLA *, SREE PRIYA

Priyadarshini College of Pharmaceutical Sciences, Department of Pharmaceutics, Chowdaryguda, Rangareddy 500088, A.P. India

Email: Pavan_pharma@yahoo.com

Received: 01 Feb 2014 Revised and Accepted: 18 Feb 2014

ABSTRACT

Objective: The aim of the present study was to develop floating microspheres of Dextromethorphan hydrobromide (DXM HBr), which belongs to class antitussive.

Methods: Floating microspheres were prepared for the improvement of bioavailability of Dextromethorphan hydrobromide by retaining in the stomach for prolonged period of time by solvent evaporation technique using polymers like ethyl cellulose (EC) and hydroxylpropyl methyl cellulose (HPMC K4M and K15M) in different ratios.The prepared floating microspheres were evaluated for micromeretic properities, percentage yield, *in vitro* buoyancy, drug entrapment efficiency, *in vitro* dissolution studies.

Results: Results showed that as the concentration of polymer increases it affects the particle size, percentage yield, in vitro buoyancy and drug release from the microspheres. Percentage yield of microspheres was found up to 71.16%. The formulated microspheres were free flowing with good flow properties. Scanning electron microscopy of optimized formulation F3 confirmed spherical structure of microspheres with pores on the rough surface and the particles were of the size range from 112-224 µm. The floating microspheres of optimized formulation(F3), exhibited the prolonged drug release of 99.61% in sustained manner up to 12 hours and remain buoyant more than 12 hours. The drug release mechanism from the floating microspheres was found to be Anamolus type (non-fickian diffusion) and followed Higuchi kinetics.

Conclusion: The developed floating microsphere system is a promising floating drug delivery system for oral sustained administration of Dextromethorphan hydrobromide (DXM HBr).

Keywords: Floating microspheres, Dextromethorphan hydrobromide (DXM HBr), Ethyl cellulose (EC), Hydroxylpropyl methylcellulose (HPMC), Solvent evaporation technique etc.

INTRODUCTION

Oral delivery of the drug is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in the formulation. From immediate release to site-specific delivery, oral dosage form has really progressed. It is evident from the recent scientific and patented literature that an increased interest in novel dosage forms that are retained in the stomach for the prolonged and predicted period of time exists today in academic and industrial research groups[1].

Development of oral controlled-release systems has been a challenge to formulation scientists because of their inability to retain and localize the system in the targeted area of the gastrointestinal tract. These controlled/sustained release preparations using alternative routes have been formulated but the oral route still remains preferable[2]. Single-unit formulations are associated with problem being obstructed in the gastrointestinal tract, which may have a potential danger of producing irritation. But a floating system made of multi-unit forms has relative merits compared to of single-unit dosage preparations. On each subsequent gastric empting, particles will spread out over a large area of absorption sites, increasing the opportunity for drug release profile and absorption in a more or less predictable way[3].

Oral controlled release dosage form shows the drug absorption at desired rate means, to reach effective plasma levels within an acceptable short time period, next to avoid an overshoot in the case of rapidly absorbed drugs and to maintain affective plasma levels over the desired time period[4]. Recent advances indicate that floating microspheres are especially suitable for achieving sustained release oral formulations with flexibility of blending to attain different release patterns, low risk of dose dumping as well as reproducible and increase in the gastric residence time[5]. Floating microspheres are gastro-retentive drug delivery systems based on non-effervescent approach. Hollow microspheres in strict sense, spherical empting particles without core. These microspheres are characteristically free flowing powder consisting of proteins or synthetic polymers. Gastro-retentive floating microspheres are less density systems that have sufficient buoyancy to float over a gastric content and remain buoyant for prolonged period of time[6].

Gastric emptying of dosage form is extensively variable process and ability to prolong and control the emptying time is valuable asset for dosage forms, which reside in the stomach for a long period of time than a conventional dosage forms. Several difficulties are faced in designing controlled released system for better absorption and enhanced bioavailability. Conventional oral dosage forms like tablets, capsules provides specific drug concentration in systemic circulation without offering any control over drug delivery and also cause great fluctuations in plasma drug levels. Also single unit dosage forms have been extensively studied, these single unit dosage forms have the disadvantage of a release all or nothing during empting process while the multi-unit particulate system pass through the GIT to avoid the vagaries of gastric emptying and thus release the drug more uniformly. The uniform distribution of these multi-unit dosage forms along the GIT could result in more reproducible drug absorption and reduced risk of local irritations. This floating dosage forms enhances bioavailability being locally active in the stomach and or upper part of the intestine[7]. The present study involves formulation and *in-vitro* evaluation of floating microspheres of Dextromethorphan HBr under gastro retentive drug delivery system for improving bioavailability by prolonging the gastric retention time. Dextromethorphan is the drug which is used to treat the dry cough because of pollutants, chemical agents etc. In the present study the Dextromethorphan HBr is chosen to incorporate into the polymers like ethyl cellulose, HPMC K4 M and HPMC K 15M. DXM is poorly absorbed from the GIT and has a short elimination half life of 3-6 hours. DXM oral bioavailability is of 11%.

So DXM was chosen to formulate into a controlled release dosage form in the form of floating microspheres.

MATERIALS AND METHODS

Dextromethorphan HBr was obtained from Mylan Laboratories Ltd. Hyderabad, A.P, India. Polymers EC, HPMC K4M, HPMC K15M, and solvents like Ethanol and Dichloromethane were obtained from vijay enterprises, Hyderabad, A.P, India. And all other ingredients are of analytical grade.

Selection of vehicles

The solubility of Dextromethorphan HBr was checked in various solvents like water, ethanol, dichloromethane, methanol. Studies revealed that DXM was freely soluble in ethanol, dichloromethane, methanol and sparingly soluble in water. The solubility was confirmed by analyzing the sample by quantitative determination by UV spectroscopy. Wave length scan was done at 278 nm.

Preparation of floating microspheres of Dextromethorphan HBr

Floating microsphere of DXM HBr was prepared by 'emulsion solvent evaporation technique'. Accurately weighed drug and polymers in different ratios are dissolved in the solvents like ethanol and dichloromethane (1:1 ratio) as shown in table 1.

The solution was poured in 100ml of water containing 0.01 ml of tween 80 and 5 ml n-hexane during stirring to form a homogenous solution, which is maintained at 40˚C temperature and at agitation speed of 800 rpm for one hour to allow the volatile liquid to evaporate. The microspheres formed were filtered and air dried for 24 hours at room temperature[8].

Formulation design

Formulation design for Dextromethorpahn HBr floating microspheres using different ratios of drug and polymers as shown in table 1

Table 1: Formulation design of DXM HBr floating microsphere:

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
DXM (mg)	60	60	60	60	60	60	60	60
EC (gm)	0.5	1	1.5	2	0.5	1	1.5	2
HPMC K4M (gm)	0.3	0.3	0.3	0.3	-	-	-	-
HPMC K15 M (gm)	-	-	-	-	0.3	0.3	0.3	0.3
Ethanol:DCM (ml)	10:10	10:10	10:10	10:10	10:10	10:10	10:10	10:10
Tween 80 (ml)	0.01	0.01	0.01	0.01	0.01	0.01	0.01	0.01

Drug polymer interaction (FTIR) study

Infrared spectroscopy was conducted using a Shimadzu Fourier transformed infrared spectrophotometer (FTIR) and the spectrum was recorded in the wave length region of 4000-400 cm^{-1}. The procedure consisted of dispersing a sample (drug alone, drug and excipient physical mixture and floating microspheres of optimized formulation F3) in KBr and compressed into disc by applying a pressure of 5 tons for 5 minutes in a hydraulic press. The pellet was placed in the light path and the spectrum was obtained.

Particle size determination

Determination of average particle size of DXM floating microspheres was carried out by optical microscope in which objective micrometer and ocular micrometer was employed. From each batch 100 DXM floating microspheres were spread on a clean slide and size was compared with the ocular micrometer readings[8].

Micromeritic properties

Micromeritic properities such as carr's index % (% **Ic**) and Hausner's ratio (HR) were characterized by using the following equation:

$HR = \rho t/\rho b$

$\% \mathbf{Ic} = (\rho t - \rho b/\rho t) \times 100$

Where ρt = tapped density, ρb = bulk density

The angle of repose (θ) of the microspheres, which measures the resistance to particle flow, was determined by the fixed funnel method, using the following equation[7]:

$\tan \theta = h/r$

where **h** is the height of the heap that formed after making the microspheres flow from the glass funnel and **r** is the radius.

Percentage yield

The prepared floating microspheres of all batches were accurately weighed. The weight of the prepared microspheres were calculated by the total amount of all excipients and drug used in the preparation of the microspheres, which gives the percentage yield of floating microspheres. It was calculated by using the following equation[8]:

$$\text{Percentage yield} = \frac{\text{Actual yield of the product} \times 100}{\text{Total weight of excipients and drug}}$$

Drug entrapment efficiency

100 mg of floating microspheres were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting with ethanol. The extract was transferred to a 100 ml volumetric flask and the volume was made up using 0.1N HCl solution. The solution was filtered and dilutions were made and the absorbance was measured against blank solution spectrometrically at 278nm. The amount of drug entrapped in the floating microspheres was calculated by using the formula[5]:

$$\text{Percentage Drug entrapment} = \frac{\text{Actual drug content} \times 100}{\text{Theoretical drug content}}$$

In-vitro buoyancy

The floating microspheres about 100 mg were spread over the surface of the dissolution medium of 500 ml stimulated gastric fluid (pH1.2), which was placed in USP dissolution apparatus type II (rotating paddle). The medium temperature was maintained at 37±5°C and was agitated by paddle at 100 rpm for 12 hours. After agitation the microspheres that floated over the surface of the medium and those that settled down at bottom of the flask were recovered separately and dried. The percentage buoyancy of the floating microspheres were calculated by using the formula[9]:

$$\text{Buoyancy } \% = \frac{W_f}{W_f + W_s}$$

Where W_f and W_s are the weight of the floating and settled microspheres respectively

In-vitro drug release

The drug release study from the floating microspheres was performed using USP type-II apparatus (rotating paddle) in 500ml of 0.1N HCl dissolution media (pH1.2) at 50 rpm at 37± 0.5°C. 5 ml of the sample was withdrawn at different time intervals for 12 hours and the same volume of fresh buffer was replaced to maintain sink conditions. Withdrawn samples were analysed spectrometrically at 278 nm by using UV visible spectrophotometer[10].

Scanning electron microscopy

The floating microspheres of DXM HBr were morphologically studied under scanning electron microscope (SEM), Hitachi 53700N model. The microspheres of DXM HBr were placed on an electron microscope brass stud and coated with gold in an ion sputter. The picture of microspheres were taken by random scanning of the stud at an accelerating voltage of 25-15 KV and particle shape and surface morphology were determined.

Accelerated stability studies

In order to determine the change in evaluation parameters like physical appearance, drug entrapment efficiency, *in vitro* drug release profile on storage, stability studies of optimized batch F3 was carried out at accelerated storage conditions at temperature 40±2˚C and 75±5% RH in a humidity chamber for 1 month. Sample was withdrawn after 30 days and evaluated for changes in physical appearance, drug entrapment efficiency and *in vitro* drug release profile[10].

RESULTS AND DISCUSSION

Drug polymer interaction (FTIR) study

For the FTIR spectra obtained for the pure drug DXM HBr alone, physical mixture of DXM, EC and HPMC K4M and optimized floating microspheres of formulation F3, the peaks obtained were nearly at same ranges showing that the drug and polymers were compatible with each other.

Particle size determination

The mean particle size of microspheres as determined by optical microscopy by using stage micrometer and ocular micrometer is shown in table 2. With the increase in the EC concentration the particle size increased from F1 to F4, F5 to F8. This is because the viscosity of the polymer increases with increasing polymer concentration, which in turn decrease the stirring efficiency. The polymer rapidly precipitates leading to hardening and avoiding further particle size reduction during solvent evaporation.

Table 2: Mean particle size of DXM HBr floating microspheres:

Formulation code	Mean particle size (µm)
F1	112±2.10
F2	140±8.45
F3	210±2.35
F4	210±1.10
F5	112±4.22
F6	154±6.33
F7	168±1.11
F8	224±2.62

Micromeretic properities

All formulations F1 to F8 of floating microspheres were evaluated for variable micromeritic parameters such as bulk density, tapped density, % compressibility index, Hausner's ratio and angle of repose.

The % compressibility index was in the range of 21-27 which indicating passable flow properties.

The values for Hausner's ratio for all the formulations F1-F8 was nearly 1.25 which indicating good flow property.
The values of angle of repose for formulations F1-F8 was found to be in the range of 26˚-27˚ which indicating the good flow potential.

Percentage yield

The percentage yield of all the batches from F1-F8 was found more than 60% and shown in the table 3

Table 3: Percentage yield of DXM HBr floating microspheres

Formulation code	% Yield
F1	63.02±0.64
F2	64.48 ±0.23
F3	70.43 ±1.36
F4	71.61±0.78
F5	60.46±1.02
F6	66.10 ±1.32
F7	69.35±1.12
F8	71.61±1.63

Drug entrapment efficiency

The entrapment of DXM HBr was increased as the concentration of the polymer EC was increased because of the increase in the viscosity of the solution.

The entrapment efficiency was increased from F1 to F4 and F5 to F8 because of increase in the EC concentration. A maximum of 86.66% drug entrapment efficiency was obtained in floating microspheres of F3 formulation. The values are shown in the table 4.

***In-vitro* buoyancy**

The floating efficiency of the DXM HBr floating microspheres was assessed by placing them in 0.1N HCl dissolution media, to stimulate the gastric fluid. The microspheres floated over the surface of dissolution media for prolonged period of time without any apparent gelation. The pores on the microspheres surface also helps in the floating which was confirmed by SEM. So as the concentration of EC increased from F1-F5 and F5-F8 the number of pores increased because of which buoyancy percentage also increased.

Buoyancy percentage of the microspheres for formulations F1-F4 was in the range of 74.31% to 91.02% and for formulations F5-F8 was 66.62% to 89.01% for 12 hours as shown in the table 4:

***In-vitro* drug release**

The dissolution studies on all the formulation from F1-F8 were carried out by using dissolution apparatus of type-II (rotating paddle) in which 500 ml of 0.1N HCl dissolution media was used.

The optimized formulation F3 showed the maximum drug release up to 99.66% at 12th hour and the drug release shown by all other formulations are shown in table 5 and 6:

Table 4: Percentage Drug entrapment and % *In vitro* Buoyancy of DXM HBr floating microspheres

Formulation code	% Drug entrapment	% *In vitro* Buoyancy
F1	68.15±2.13	74.31±1.36
F2	79.98±1.21	86.14±2.21
F3	86.66±2.33	91.02±1.78
F4	86.15±1.24	90.91±2.79
F5	67.63±0.68	66.62±1.14
F6	77.91±2.26	74.47±0.63
F7	82.55±1.32	82.25±1.16
F8	85.63±1.08	89.01±2.54

Table 5: *In vitro* release data of Dextromethorphan hydrobromide floating microspheres with EC and HPMC K4M

S.No	Time (hrs)	Cumulative percentage drug release up to 12 hrs			
		F1	**F2**	**F3**	**F4**
1	0.5	36.31±0.21	21.07±0.66	19.83±0.13	19.52±0.23
2	1	42.05±0.13	26.46±0.21	23.22±0.22	23.07±0.16
3	2	53.46±0.22	32.94 ±0.33	31.17 ±0.11	29.99±0.22
4	3	66.89±0.11	39.56±0.01	37.73 ±0.32	36.80±0.47
5	4	72.29±0.32	45.29 ±0.37	44.36±0.66	43.44±0.02
6	5	79.79±0.16	53.63±0.03	52.70±0.44	49.92±0.13
7	6	86.95±0.22	62.42±0.11	59.96±0.19	57.63±0.55
8	7	93.44±0.15	68.72±0.36	65.97± 0.11	63.31±0.45
9	8	96.68±0.42	78.93±0.77	74.76±0.15	69.52±0.03
10	9	99.30±0.66	85.57±0.32	83.56±0.43	76.15±0.32
11	10	-	91.28±0.21	89.58±0.19	86.34±0.66
12	11	-	99.15±0.13	95.44±0.34	89.27±0.23
13	12	-	-	99.61±0.69	96.45±0.43

Table 6: *In vitro* release data of Dextromethorphan hydrobromide floating microspheres with EC and HPMC K15 M:

S.No	Time (hrs)	Cumulative percentage drug release up to 12 hrs			
		F5	**F6**	**F7**	**F8**
1	0.5	32.94±0.66	28.47±0.54	21.68±0.13	19.83±0.11
2	1	38.04±0.21	34.49±0.32	29.39±0.14	26.62±0.16
3	2	45.13±0.47	41.74 ±0.62	36.65 ±0.43	34.95±0.32
4	3	57.63±0.21	48.84±0.33	45.29 ±0.02	44.67±0.22
5	4	65.50±0.42	56.09 ±0.38	53.00±0.42	47.29±0.66
6	5	71.83±0.09	64.58±0.43	63.50±0.33	52.23±0.14
7	6	76.46±0.26	72.65±0.39	65.81±0.42	57.63±0.56
8	7	81.55±0.22	77.39±0.53	69.21± 0.32	62.57±0.55
9	8	87.11±0.31	82.48±0.46	71.52±0.34	67.07±0.21
10	9	94.21±0.33	88.19±0.64	76.62±0.45	72.29± 0.31
11	10	99.76±0.01	92.36±0.32	81.71±0.43	79.70±0.21
12	11	-	95.83±0.31	87.42±0.54	83.87±0.44
13	12	-	97.68±0.22	91.12±0.22	87.11±0.11

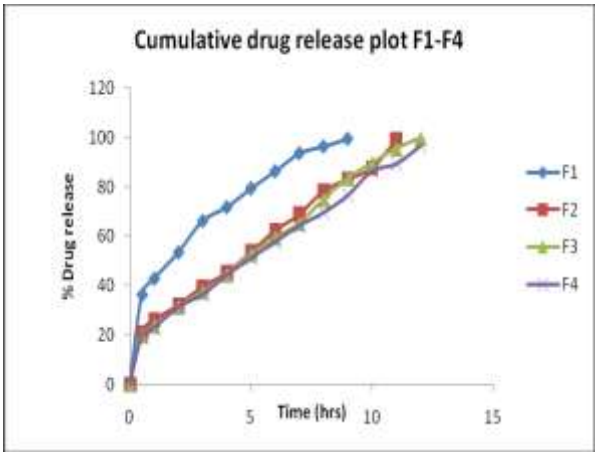

Fig 1: Comparative *in vitro* release plot of DXM floating microspheres of formulations

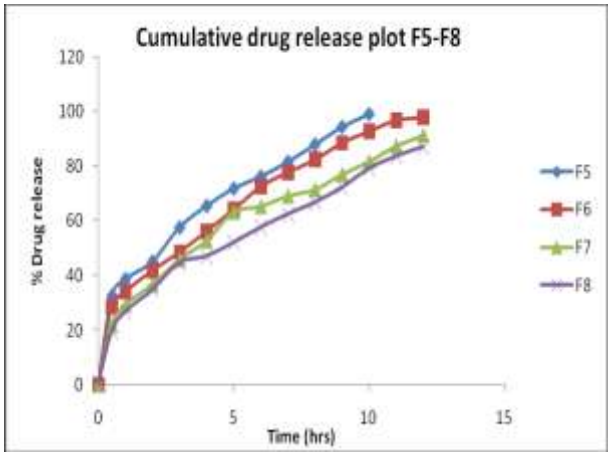

Fig 2: Comparative *in vitro* release plot of DXM floating microspheres of formulations

Kinetics of drug release

The data obtained from the *in-vitro* dissolution studies were fitted to various kinetic models like zero order, first order, higuchi model and korsemeye-peppas model. The optimized formulation F3 followed anomalous type (Non-fickian transport) and *in-vitro* drug release was found to have followed Higuchi kinetics.

Scanning electron microscopy

The scanning electron microscopy (SEM) of DXM HBr microspheres of optimized formulation F3 were spherical shape with rough surface and with pores on them as shown in the figure 3:

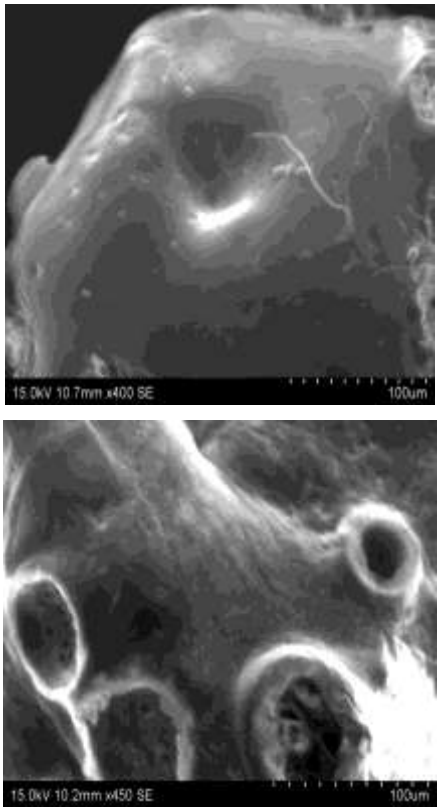

Fig: 3: Scanning electron microscopy of DXM HBr floating microspheres of optimized formulation F3.

Accelerated stability studies

The accelerated stability studies performed for 30 days of optimized formulation F3 in humidity chamber at 40±2˚C and 75±5% RH showed that there was no change in physical appearance as it appeared white in colure as before, no much change in the drug entrapment which was 86.62% and *in vitro* drug release was found to be 99.56%.

CONCLUSION

In this study the floating microspheres of DXM HBr were successfully prepared by 'emulsion solvent evaporation technique'. The concept of formulating floating microspheres of DXM HBr offers a suitable, practical approach to achieve a prolonged therapeutic effect by continuously releasing the medication over an extended period of time by prolonging the gastric residence time, thus improving the oral bioavailability of the drug. It would be faster and more economical to alter beneficially the properties of the exisiting drug than developing new drug entities, hence this formulation will be boon to novel drug dosage form.

ACKNOWLEDGEMENT

Author is thankful to Priyadarshini college of pharmaceutical sciences for providing the requirements to carry out the project work.

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