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Formulation and evaluation of dextromethorphan polistirex extended release suspension (30MG/5ML)

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ABSTRACT

A Pharmaceutical suspension is a coarse dispersion in which internal phase is dispersed uniformly throughout the external phase. The internal phase consisting of insoluble solid particles having a specific range of size which is maintained uniformly throughout the suspending vehicle with aid of single or combination of suspending agent. The external phase (suspending medium) is generally aqueous in some instance, may be an organic or oily liquid for non oral use.

Keywords: Suspension, Internal phase, External phase

INTRODUCTION

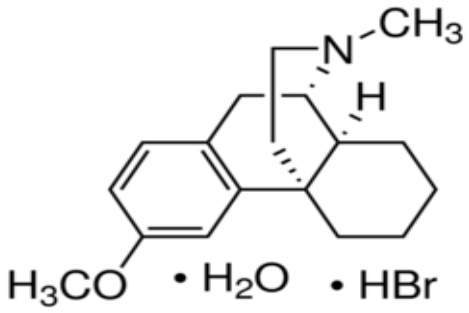
A Pharmaceutical suspension is a coarse dispersion in which internal phase is dispersed uniformly throughout the external phase.

The internal phase consisting of insoluble solid particles having a specific range of size which is maintained uniformly throughout the suspending vehicle with aid of single or combination of suspending agent.

The external phase (suspending medium) is generally aqueous in some instance, may be an organic or oily liquid for non oral use.

DRUG PROFILE

- **Drug name : Dextromethorphan Hydrobromide Monohydrate**
- **Chemical Name:** (9S,13S,14S)-3-methoxy-17-methylmorphinan Hydrobromide Monohydrated. Synthetic analog of codeine and d-isomer of 3-methoxy-N-methymorphinan.
- **Synonyms:** (+)-Dextromethorphan, D-methorphan, Delta-Methorphan.
- **Solubility:** Sparingly soluble in Water, Freely soluble in Alcohol.
- **Melting point:** 116 - 119 °C



- **Molecular formula** : $C_{18}H_{25}NO.HBr.H_2O$
- **Molecular weight** : 370.331 g/mol
- **Bioavailability** : 71%
- **Half-life** : 2 - 4 hours
- **Protein binding** : 60-70%
- **Dosage forms** : Suspension
- **Dose** : 10-20mg.
- **Category** : Anti-Tussive

Mechanism of Action

Dextromethorphan is an opioid-like drug that binds to and acts as antagonist to the NMDA glutamatergic receptor, it is an agonist to the opioid sigma 1 and sigma 2 receptors, it is also an alpha3/beta4 nicotinic receptor antagonist and targets the serotonin reuptake pump. Dextromethorphan is rapidly absorbed from the gastrointestinal tract, where it enters the bloodstream and crosses the blood-brain barrier. The first-pass through the hepatic portal vein results in some of the drug being metabolized into an active metabolite of dextromethorphan, dextrorphan, the 3-hydroxy derivative of dextromethorphan.

MATERIALS USED IN THE WORK

S.No	Materials	Manufacturer
1	Dextromethorphan polistirex (1:1:5)	Aurobindo Pharma Ltd.
2	Propylene glycol	DOW
3	Methyl paraben	Salicylates&Chemicals Pvt Ltd.
4	Citric Acid Anhydrous USP	Merck
5	Sucrose(40/80)	MB sugars
6	High Fructose Corn Syrup (Hi Sweet 55)	Roquette
7	Polysorbate 80	Clariant
8	Xanthan gum	CP Kelco
9	Tragacanth Powder	Fractaram
10	FD&C Yellow No.6	Neelikon
11	Edetate Disodium USP	Merck
12	PEG Coated granules(20%W/W)	Aurobindo Pharma Ltd.
13	ER Coated granules(22%)	Aurobindo Pharma Ltd.
14	Amberlite (sodium polystyrene sulfonate)IRP 69	DOW
15	Polyethylene glycol USNF (Polyglykol 4000 PF)	Clariant
16	Surelease Ethylcellulose Dispersion Type B NF E-7-19040	Colorcon

METHODOLOGY

Preformulation studies

Pre formulation involves the application of biopharmaceutical principles to the physicochemical parameters of drug substances are characterized with the goal of designing optimum drug delivering system.

Drug excipient compatibility studies

Drug Excipients Compatibility Studies were carried out by mixing the drug with various excipients in different proportions (in 1:2 ratio were prepared to have maximum likelihood interaction between them) was placed in a vial, and closed with rubber stopper and sealed properly.

Construction of Standard Graph for Dextromethorphan Polistirex

Preparation of 0.1N HCL

Measure 43ml of hydrochloric acid in 5 litre standard volumetric flask and make up the volume using demineralized water.

Calibration of Standard Curve

Accurately weighed Dextromethorphan polistirex which is equivalent to 30 mg of Dextromethorphan Hydrobromide in a 100ml standard volumetric flask and dissolved in methanol. The volume was made upto 100ml using 0.1N Hydrochloric acid to obtain a stock solution-1(1000µg/ml).

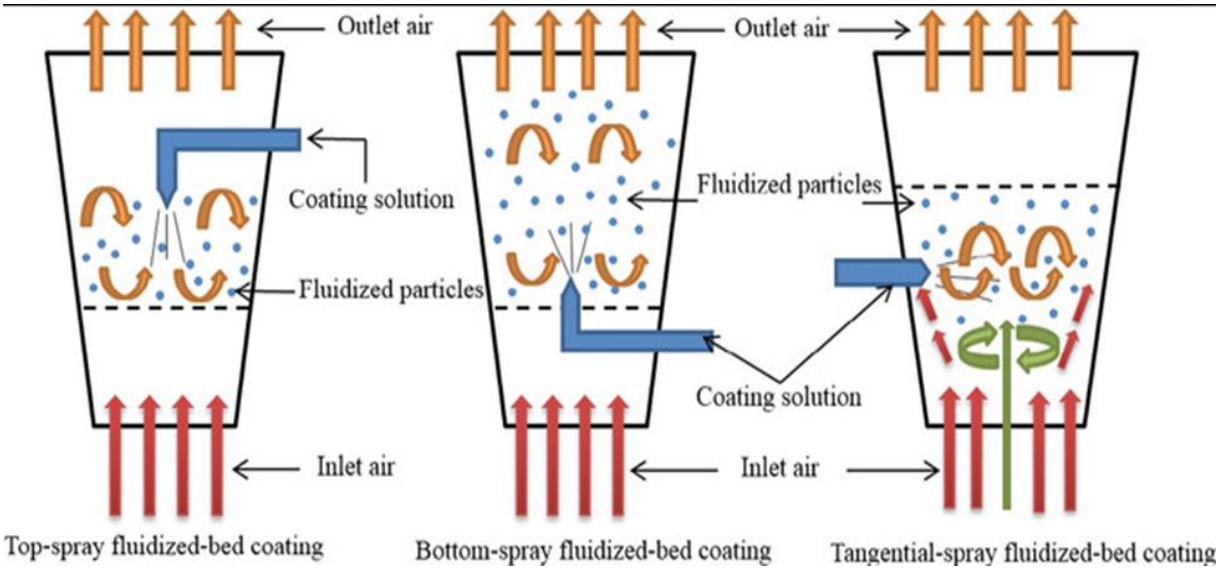
From this stock solution -1,10ml was pippetted out into a 100ml standard volumetric flask and made upto the mark using 0.1N Hydrochloric acid (stock solution-2).From this stock solution - 2,aliquots of 2ml,4ml,6ml,8ml,10ml,and 12ml,were pipetted out into a series of 100ml standard volumetric flasks and the volume was made upto the mark with 0.1N Hydrochloric acid to get drug concentration in the range of 2 to 12µg/ml.The absorbance of the resulting solution was then measured using HPLC against 0.1N Hydrochloric acid as blank. The standard curve was obtained by plotting concentration(µg/ml)values in X-axis and the absorbance values in Y-axis.

TECHNOLOGY

Fbp coating

Fluidized bed processing

- Types of FBP according to the position of the spray gun:
- Top spray
- Bottom spray
- Tangential spray



Bottom spray coating

The Wurster bottom spray method makes it possible to attain high - quality results in coating in coating pellets and particles. The combination of the nozzle positioned directly in the product bed and the controlled product motion made possible by the inner partitions results in an extremely quick and thus economical process

FORMULATION DEVELOPMENT

Manufacturing formula: PEG coating (20%W/W)

S.NO	Ingredients	B.No.	mg/5ml	Qty/Batch(g)
1	Dextromethorphan Polistirex (1:1:5)	DMPP0118001	78	600
2	Polyethylene Glycol 4000 (Polyglycol 4000 PF)	DEA4006387	15.6	132
3	Purified water		15%w/w Solids	748

- **Step 1.0 Coating solution preparation:**
- Step 1.1 PEG 4000 was dissolved in purified water under stirring and stirring continued for another 15min.
- **Step 2.0 PEG coating (20%w/w):**
- Step 2.1 Dextromethorphan Polistirex was sifted through mesh #60 and loaded into FBP bowl and pre-wared at an inlet temperature of 35°C for 5mins.
- Step 2.2 Coating solution of step 1.1 was sprayed onto pre-warmed material.
- LOD of Dextromethorphan Polistirex 2.86% w/w.

Process Parameters

S.NO	Parameters	Observation
	Machine Parameters	
	Filter bag	Anti-static
	Plate	'A'
	Mesh	50 microns
I	**Process Parameters**	
	Inlet temperature(°C)	51-56
	Product temperature(°C)	34-38
	Atomization air	1.1-1.3
	Fluidization	31-39 CFM
	Peristaltic pump speed	05-08 rpm

Manufacturing formula:ER coating (19%W/W)

S.NO	Ingredients	B.No.	mg/5ml	Qty/Batch(g)
1	PEG Coated granules(20%w/w)	-	93.60	350.00
2	Surelease dispersion (EthylCellulose dispersion Type B NF E-7-19040 clear)	IN535438	17.784	292
3	Purified water		10%w/w solids	438.90

- 10% extra quantity was taken considering process lossess.
- Surelease dispersion is 25%w/w dispersion. Hence, 292.60g of surelease dispersion contains 73.15g of solid content.

Purified water quantity calculation

Purified water required quantity (10%w/w) is 658.35 g, but 292.6 g surelease dispersion contains

219.45 g of water. Therefore 438.90 g of purified water was taken.

Coating solution preparation

Step 1: Surelease dispersion and purified water were taken in to a beaker and kept under slow stirring for 20 min.

Step 2: Coating dispersion of step 1 was passed through #60 mesh.

Extended-Release Cating(19%w/w)

Step 3: PEG coated (20%) granules were sifted through mesh #60 and loaded into FBP bowl and pre-warmed at an inlet temperature of 50°C for 5mins.

PREPARATION OF SUSPENSION

- **Step 1.0:** Xanthum gum, Tragacanth powder and Sucrose(160g) were taken in to a blender and mixed for 10min.
- **Step 2.0:** Step 1.0 material was added into 1000.00g (25% of final batch size) of hot purified water under stirring was continued for another 60min and cooled the solution to room temperature.
- **Step 3.0:** Propylene glycol was taken in a beaker and heated at 50-60°C, Methyl paraben was dissolved in it under stirring till clear solution is formed and cooled the solution to room temperature.
- **Step 4.0:** Polysorbate 80 was dissolved in 200.00g (5% 0f final batch size) of purified water under stirring for 15min.
- **Step 5.0:** Citic acid Anhydrous, Sucrose (320 g), FD&C yellow No.6 and Orange Flavor TR 2654/V1 were dissolved one by one in 600.00g (15% of final batch size) purified water under stirring was continued for another15min.
- **Step 6.0:** Disodium EDTA was dissolved in 200g (5% of final batch size) of purified water under stirring and mixed for 15min.
- **Step 7.0:** High fructose corn syrup was taken in a beaker and kept under stirring. Step 2.0,Step 3.0, step 4.0, step5.0, and step 6.0 contents were added into it one by one under stirring and stirring was continued for 30min.
- **Step 8.0:** PEG coated granules (20%W/W) and Extended-Release coated (29%W/W) granules were added to step 7.0 contents and continued stirring for 20min.
- **Step 9.0:** Step 8.0 contents were kept aside overnight.
- **Step 10.0:** Final volume of the suspension was made up to 4.4kg (specific gravity: 1.10) using purified water (350ml consumed) and suspension was stirred for another 20mn.

Formulation table showing various compositions

TRAIL NO	1	2	3	4	5	6	7	8
UNIT FORMULA	mg/5ml							
PEG COATING								
Dextromethorphan Polistirex	90	90	90	90	90	90	90	90
Polyethylene glycol 4000	18	18	18	18	18	18	18	18
Purified water(15%w/w solids)	102	102	102	76.5	112.5	102	102	102
Polyethylene glycol coated granules weight								
ER COATING								
PEG Coated granules	108	108	108	108	108	108	108	108
Surelease(20% dispersion)	16.2	27	21.6	21.6	21.6	21.6	21.6	21.6
Purified water	QS	QS	QS	QS	QS	QS	QS	QS

TRAIL NO	1	2	3	4	5	6	7	8
BASE SUSPENSION								
Propylene glycol	150	150	150	150	150	150	150	150
Methylparaben USNF(Saligin MP)	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
Citric Acid Anhydrous USP	6	6	6	3	9	6	6	6

Sucrose USNF (#40-#80)	600	600	600	600	600	600	600	600
High Fructose Corn Syrup (HI-SWEET 55)	1500	1500	1500	1500	1500	1500	1500	1500
Polysorbate 80 USNF	4	4	4	4	4	4	4	4
Xanthan Gum USNF (Xantural 75)	20	20	20	20	20	15	25	20
Tragacanth	5	5	5	5	5	3	7	5
Edetate Disodium USP	2.5	25	2.5	2.5	2.5	2.5	2.5	2.5
FD & C Yellow no 6	0.115	0.115	0.115	0.115	0.115	0.115	0.115	0.115
Masker Citrus Flavour	10	10	10	10	10	10	10	10
Purified Water	QS to 5ml	QS to 5ml	QS to 5ml	QS to 5ml	QS to 5ml	QS to 5ml	QS to 5ml	QS to 5ml

EVALUATION OF SUSPENSIONS

- **Viscosity measurement:** The viscosity of the samples was determined using the Brookfield viscometer at 50 revolution/min (Spindle ≠ S62).
- **Particle size measurement:** The particle size of dextromethorphan polistirex in the prepared suspensions was measured by Malvern.
- **Sedimentation volume:** Sedimentation volume (F) is a ratio of the final volume of sediment (Vu) to the original volume of sediment (Vo) before settling. 50ml of each suspension were transferred to 50 ml measuring cylinders and the volume of sediment formed was noted at every 24 hr for 7 days. The sedimentation volume F (%), was calculated using the formula: F = 100 Vu/ Vo.
- **Determination of pH:** The determination of pH is an important tool as the formulation is reconstituted and used. By checking this we ensure any noticeable change during its use and storage.
- **Drug release:** The release studies were carried out at 37± 0.5°C by using USP II at 50rpm.A 500ml volume of 0.1N HCL of the release media. A 5.00 ml of suspension was placed inside the vessel at time zero.
- transferred to 50 ml measuring cylinders and the volume of sediment formed was noted at every 24 hr for 7 days. The sedimentation volume F (%), was calculated using the formula: F = 100 Vu/ Vo.
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RESULTS & DISCUSSION

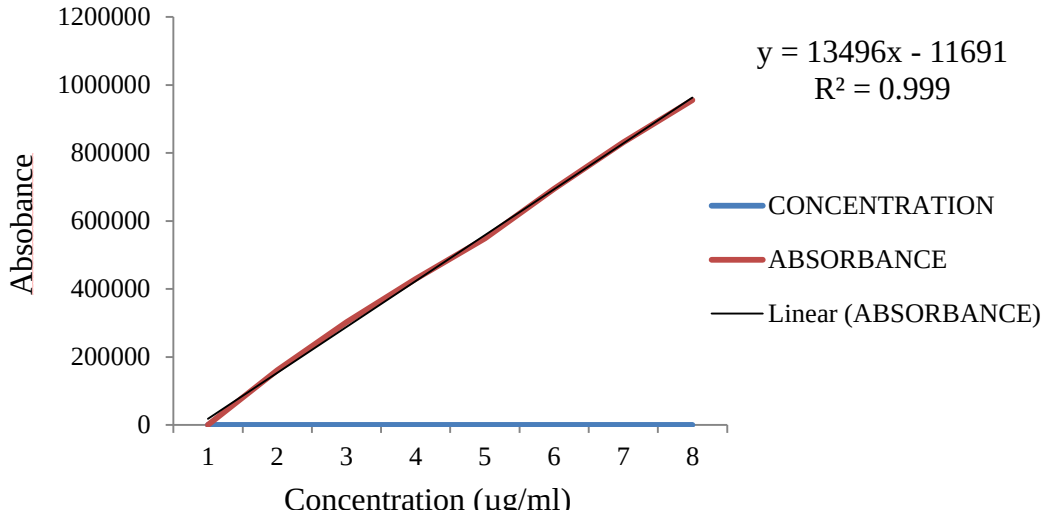
Construction of Standard Graph for Dextromethorphan Polistirex

Calibration of Standard Curve

- Accurately weighed Dextromethorphan polistirex which is equivalent to 30 mg of Dextromethorphan Hydrobromide in a 100ml standard volumetric flask and dissolved in 0.1N HCl and the volume was made upto 100ml using 0.1N HCl to obtain a stock solution-1(1000µg/ml).From this stock solution -1,10ml was pippetted out into a 100ml standard volumetric flask and made upto the mark using 0.1N HCl (stock solution-2).
- From this stock solution-2, aliquots of 2ml,4ml,6ml,8ml,10ml,and 12ml,were pipetted out into a series of 100ml standard volumetric flasks and the volume was made upto the mark with 0.1N HCl to get drug concentration in the range of 2 to 12µg/ml.The absorbance of the resulting solution was then measured using

HPLC against 0.1N HCl as blank. The standard curve was obtained by plotting concentration(µg/ml)values in X-axis and the absorbance values in Y-axis.

Concentration	Absorbance
0	0
25	161349
30	302357
35	429053
40	549050
50	694442
60	831338
75	955838



Viscosity measurement

The formulation F6 & F7 fails to measure the viscosity during 24 hrs to 3mnths. When the concentration of suspending agent decreased in F6 a slight decrease in viscosity was found, when the concentration of suspending agent increased in F7 a slight increase in viscosity was found. When solution kept for long time the viscosity of F3, F4 and F5 has decreased from 390-380, 380-375 & 375-370 respectively. The change in viscosity in case of F2 was relatively a stable formulation.

Viscosity (50rpm) in cps

Formulation	24hours	1week	1month	2months	3months
F1	350.7	355.5	360	365	359.9
F2	360.8	363	361	370	365
F3	390	388	387.9	384.5	380.1
F4	380.5	380	377	379	375.5
F5	375.2	375.1	372	374	370
F6	250.8	245.8	240.9	249.1	243.5
F7	550	545	540.9	539.8	519.5
F8	408.6	400	399	385	401
F9	400.2	401.2	402.5	400.3	405.1
F10	360.8	363	361	370	365

Particle size analysis: The particle size of dextromethorphan polistirex suspensions was measured and the average particle size was determined.

	PARTICLE SIZE (μ)		
Formulation	**D(V,10%)**	**D(V,50%)**	**D(V,90%)**
F1	45	125	223
F2	49	126	224
F3	50	125	224
F4	47	124	221
F5	48	121	225
F6	46	129	227
F7	45	128	226
F8	48	125	228
F9	50	124	220
F10	49	126	224

pH: By decreasing and increasing the concentration of citric acid in formulation F8 and F9 showed a more or less constant pH value (2.5& 4.5) ,it fails to measure the pH.The change in the concentration of citric acid in
F2 (pH 3.51) was relatively a stable formulation.

Formulation	**24hours**	**1month**	**2months**	**3months**
F1	3.56	3.55	3.51	3.52
F2	3.51	3.50	3.55	3.54
F3	3.49	3.48	3.50	3.42
F4	3.50	3.45	3.49	3.52
F5	3.53	3.52	3.57	3.55
F6	3.56	3.51	3.50	3.58
F7	3.56	3.55	3.51	3.52
F8	2.5	2.61	2.51	2.43
F9	4.5	4.7	4.45	4.53
F10	3.51	3.50	3.55	3.54

- **Sedimentation volume:** The sedimentation volume of F1 to F10 was found to be 5%,5.5%,5.9%7%,6%,11.5%,12.8% 8.5%,6.5% and 9% respectively at the end of 24 hours. The formulation F1,F2,F3,F4,F5,F8,F9,&F10 have shown good porability.
- **Sedimentation Volume(%)**

Formulation	**24hours**	**1week**	**1month**	**2months**	**3months**
F1	5	4.9	4.8	4.5	4.4
F2	5.5	5.12	5.1	4.93	4.8
F3	5.9	5.6	5.7	5.4	5
F4	7	6.9	6.8	6.5	6.3
F5	6	5.99	5.8	5.6	5.4
F6	11.5	114	11.2	10.9	11.5
F7	12.8	12.9	12.7	12.5	12.8
F8	8.5	8.4	8.1	8	7.9
F9	7.1	7.2	7.5	7.7	7.6
F10	5.5	5.12	5.1	4.93	4.8

- **Drug release:**The result of the drug release study indicating that F1 and F2 released 97 and 96 at the end of 24hrs, respectively. Formulation F3, F4, F5,F6,F7,F8, and F9 released 84,97,96,9597,97, and 96 at the end of 24hrs. The results indicated that F2 gave higher drug release rate among all the formulations. Hence, F2 formulation is the optimized formulation.

Dissolution Study Report

TIME (hr)		Dissolution Data In 0.1N HCL 500 mL/ 50 rpm paddle									
	REFERENCE	**I**	**II**	**III**	**IV**	**V**	**VI**	**VII**	**VIII**	**IX**	**X**
0.5	25	35	23	18	27	26	24	24	24	27	25
1	30	40	29	24	32	32	30	29	30	32	32
2	42	56	40	30	41	43	42	40	42	40	44
3	48	60	49	36	49	49	50	47	47	48	47
5	55	67	57	42	56	56	58	57	57	54	54
7	63	74	65	52	65	61	67	64	64	63	64
10	73	82	76	59	74	74	75	75	75	74	75
12	75	86	77	64	77	76	78	76	76	76	77
16	82	95	83	69	81	83	82	84	84	81	82
20	88	96	90	78	89	89	91	89	89	89	89
24	95	97	96	84	97	96	95	97	97	96	96
F_2		48	83	47	87	90	80	87	87	89	88

DISCUSSION

The suspension F1 to F9 was prepared by adding different concentration of xanthum gum and tragacanth powder. These formulations were evaluated for various quality parameters to determine their stability such as sedimentation volume, viscosity, particle size, pH and drug release for 3 months time in regular intervals. The data obtained from the determination of sedimentation rates revealed that the formulations F1 to F9 indicates stable suspensions. When the concentration of suspending agent increases in suspensions a slight increase in viscosity was found. When kept the suspension for long time, the change in viscosity indicating that F2&F9 was relatively a stable formulation. The particle size of the suspension was evaluated, and in 10% of the sample having 45-50µ size, in 50% of the sample having 121-129µ size, and in 90% of the sample having 220-228µ size. The pH values of all the formulations were complied as per U.S.P requirements. Suspensions formulation F2 gave higher drug release rate among all the formulations. Hence, F2 formulation is the optimized formulation.

CONCLUSION

Formulation trails F1 – F9 were taken to evaluate ER coating build up, PEG coating build up, viscosity modifier effect, pH effect on dissolution. Batch with 20% ER & 20% PEG coating buildup exhibits similar dissolution profile as marketed formulation & viscosity & pH effect was not there on dissolution profile. However, optimum viscosity & pH were chosen similar to marketed formulation. Scale-up batch was taken similar to optimized formulation F2 & Reproducible results were produced. Hence, F2 formulation is the optimized formulation. The equivalent formulation which is developed shows advantages in the term of patient compliance, safety, and better transportation over existing suspension formulation.

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