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FORMULATION OF DEXTROMETHORPHAN HYDROBROMIDE EXTENDED-RELEASE SUSPENSION AND EVALUATION

Pavani Sure[1]*, Dr.N. Sandeepthi[2]

[1]Assistant Professor, Department of Pharmaceutics, Vignan Institute of Pharmaceutical Sciences, Deshmukhi Village, Yadadri Bhuvanagiri Dist., [2]Associate Professor, Department of Pharmaceutics, Vignan Institute of Pharmaceutical Sciences, Deshmukhi Village, Yadadri Bhuvanagiri Dist

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Abstract:

Dextromethorphan hydrobromide is a synthetic anti tussive agents. Biological half-life of this drug is 2-4hrs. Due to its half-life, the dose is employed 4times a day. To reduce the dose frequency and to improve the patient compliance, the extended-release suspension of dextromethorphan polistirex was formulated with PEG coating and Enteric coating. In the present study the extended-release suspension of dextromethorphan polistirex was prepared and physical mixture of the drug and polymer was found to be compatible after the comparative study of three months. The extended-release suspension of dextromethorphan polistirex was evaluated by FTIR, DSC and other parameters. Difference factor (f2) was used as a statistical method in this work.The formulation showed advantages in the terms of patient compliance, safety, and better transportation over existing suspension formulation.

Key words: *Dextromethorphan polistirex, Surelease Dispersion, Delsym.*

Corresponding author:

Pavani Sure,

Assistant Professor , Department of Pharmaceutics,
Vignan Institute of Pharmaceutical Sciences, Deshmukhi Village,
Yadadri Bhuvanagiri Dist.E.mail:nellutla.jhancy@gmail.com

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INTRODUCTION:

Desired Characteristics and Applications Of Pharmaceutical Suspensions

Definition:

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.

Classification:

Based On General Classes:

Oral suspension

Externally applied suspension

Parenteral suspension

1.1.3 Based On Proportion Of Solid Particles

Dilute suspension (2 to10%w/v solid)

Concentrated suspension (50%w/v solid)

Based On Electrokinetic Nature Of Solid Particles

Flocculated suspension

Deflocculated suspension

Based On Size Of Solid Particles

Colloidal suspension (< 1 micron)

Coarse suspension (>1 micron)

Nano suspension (10 ng)

Advantages And Disadvantages :

Advantages:

- Pharmaceutical Suspension can improve chemical stability of certain drug.

E.g.Procaine penicillin G

- Drug in suspension exhibits higher rate of bioavailability than other dosage forms.

Bioavailability is in following order,

Solution > Suspension > Capsule > Compressed Tablet > Coated tablet

- Duration and onset of action can be controlled.

E.g.Protamine Zinc-Insulin suspension

- Suspension can mask the unpleasant/ bitter taste of drug.

E.g. Chloramphenicol

Disadvantages:

- Physical stability,sedimentation and compaction can causes problems.
- It is bulky sufficient care must be taken during handling and transport.
- It is difficult to formulate
- Uniform and accurate dose can not be achieved unless suspension are packed in unit dosage form.

Features Desired In Pharmaceutical Suspensions:

- The suspended particles should not settle rapidly and sediment produced, must be easily re-suspended by the use of moderate amount of shaking.
- It should be easy to pour yet not watery and no grittiness.
- It should have pleasing odour, colour and palatability.
- Good syringeability.
- It should be physically, chemically and microbiologically stable.
- Parenteral/Ophthalmic suspension should be sterilizable.

Applications :

- Suspension is usually applicable for drug which is insoluble or poorly soluble. E.g. Prednisolone suspension
- To prevent degradation of drug or to improve stability of drug.
  E.g. Oxytetracycline suspension
- To mask the taste of bitter of unpleasant drug.
  E.g. Chloramphenicol palmitate suspension
- Suspension of drug can be formulated for topical application e.g. Calamine lotion
- Suspension can be formulated for parentral application in order to control rate of drug absorption.
- Vaccines as a immunizing agent are often formulated as suspension.
  E.g. Cholera vaccine
- X-ray contrast agent are also formulated as suspension.
  E.g. Barium sulphate for examination of alimentary tract.

Table no:1 Formulation table showing various compositions:

S.No	Ingredients	Reference	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
		Delsym(Lot:286006)	ER Coating 15%	ER coating 20%	ER Coating 25%	PEG Coating 15%	PEG Coating 25%	Low viscosity	High viscosity	Low pH	High pH	Optimum batch same as F2
			mg/5ml	mg/5ml	mg/5ml	mg/5ml	mg/5ml	mg/5ml	mg/5ml	mg/5ml	mg/5ml	mg/5ml
I	**Polyethylene glycol coating**											
1	Dextromethorphan Polistirex		90	90	90	90	90	90	90	90	90	90
2	Polyethylene glycol 4000		18	18	18	**13.5**	**22.5**	18	18	18	18	18
3	Purified water(15%w/w solids)		102	102	102	76.5	112.5	102	102	102	102	102
4	Polyethylene glycol coated granules		108	108	108	103.5	127.5	108	108	108	108	108
II	**Extended Release coating**											
5	Polyethylene glycol coated granules		108	108	108	103	127.5	108	108	108	108	108
6	Surelease dispersion		**16.2**	**21.6**	**27**	20.7	25.5	21.6	21.6	21.6	21.6	21.6
7	Purified water(10%w/w solids)		145.8	194.4	243	186.3	226.8	194.4	194.4	194.4	194.4	194.4
8	Extended Release coated granules weight		124.2	129.6	135	124.2	153	129.6	129.6	129.6	129.6	129.6
III	**Suspension**											
9	Propylene glycol		300	300	300	300	300	300	300	300	300	300
10	Methylparaben USNF(Saligin MP)		9	9	9	9	9	9	9	9	9	9
11	Citric Acid Anhydrous USP		6	6	6	6	6	6	6	**5**	**9**	6
12	Sucrose USNF (#40-#80)		600	600	600	600	600	600	600	600	600	600
13	High Fructose Corn Syrup (HI-SWEET 55)		1500	1500	1500	1500	1500	1500	1500	1500	1500	1500
14	Polysorbate 80 USNF		4	4	4	4	4	4	4	4	4	4

15	Xanthan Gum USNF (Xantural 75)		20	20	20	20	20	**15**	**25**	20	20	20
16	Tragacanth		10	10	10	10	10	**5**	**15**	10	10	10
17	Edetate Disodium USP		2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
18	FD & C Yellow no 6		0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12	0.12
19	Orange flavor TR2654/V1		10	10	10	10	10	10	10	10	10	10
20	Extended Release coated granules		124.2									
21	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	QS to 5ml	QS to 5ml

EVALUATION OF SUSPENSIONS:

Physicochemical characterization of the drug polymer mixtures:

Fourier transforms infrared radiation measurement (FT-IR): FT-IR spectra of drug and drug-excepients blend were recorded on an FT-IR spectrophotometer in the frequency range between 4000 and 500 cm-1.

Differential scanning calorimetry (DSC) study: Differential scanning calorimetry study of suspension was performed to determine the drug excipients compatibility study.

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

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. The size of 100 particles were measured and the average particle size of was determined.

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.

pH Stability Study: The formulation was studied for stability of pH. After reconstitution the suspension was stored at 2-8˚C and pH of the suspension was checked for 10 days.

Stability Studies: Short term accelerated stability studies are performed on the optimized formulations packed in HDPE bottles of 30ml capacity. The oral suspension is subjected to stability studies at 40^0C/75%RH in a stability chamber for a period of 1 month**.** Evaluation of the oral suspensions is done initially at the time of charging and at the end of first month. The suspensions are again analyzed for its physical appearance, water content and in vitro drug release profile and HPLC assay.

Drug release: The release studies were carried out at 37± 0.5˚C by using USPII 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. Samples were withdrawn after time interval 0.5min,60min,2hr,3hr,5hr,7hr,10hr,12hr,16hr,20hr and 24hr and replaced with fresh medium and absorbance was measured in HPLC. The concentration was calculated using standard calibration curve.

RESULTS & DISCUSSION:

CONSTRUCTION OF STANDARD GRAPH FOR DEXTROMETHORPHAN POLISTIREX:

CALIBRATION OF STANDARD CURVE:

Accurately weighed 100mg Dextromethorphan polistirex in a 100ml standard volumetric flask and dissolved in methanol and the volume was made upto

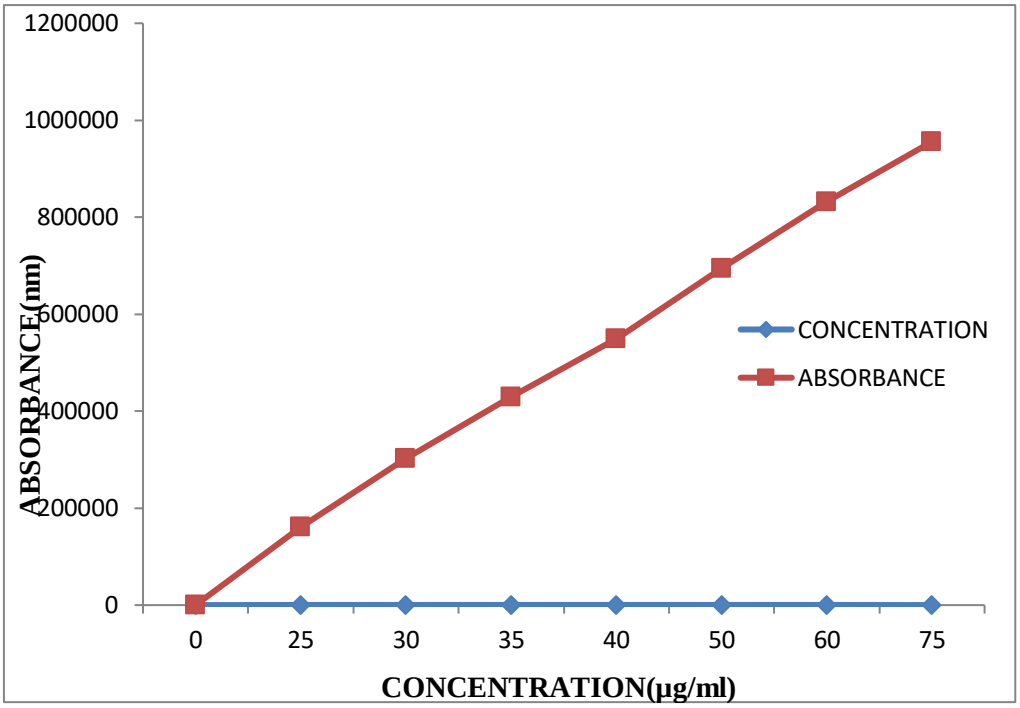
100ml using 0.1N HCl to obtain a stock solution-1(1000µg/ml).From this stock solution -1,10ml was pippetted out into a 100ml standard volumetric flask and made upto the mark using 0.1N HCl (stock solution-2).

From this stock solution-2, aliquots of 0.25ml,0.30ml,0.35ml,0.40ml,0.50ml,0.60ml and 0.75ml,were pipetted out into a series of 10ml standard volumetric flasks and the volume was made upto the mark with 0.1N HCl to get drug concentration in the range of 25 to 75µg/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.

Table 2 Standard Graph values of suspension

CONCENTRATION(µg/ml)	ABSORBANCE(nm)
0	0
25	161349
30	302357
35	429053
40	549050
50	694442
60	831338
75	955838

FIG - 1 CALIBRATION OF STANDARD CURVE



EVALUATION OF SUSPENSIONS:

Physicochemical characterization of the drug polymer mixtures:

Compatibility testing of drug with polymer:

Fourier transforms infrared radiation measurement (FT-IR): Major functional groups present in dextromethorphan polistirex show characteristic peaks in IR spectrum. Figure 4.1 shows peaks observed at different

wave numbers and the functional group associated with these peaks for drug and drug with different polymer. The major peaks are identical to functional group of dextromethorphan polistirex. Hence, it was confirmed that there was no incompatibility between drug and various polymers.

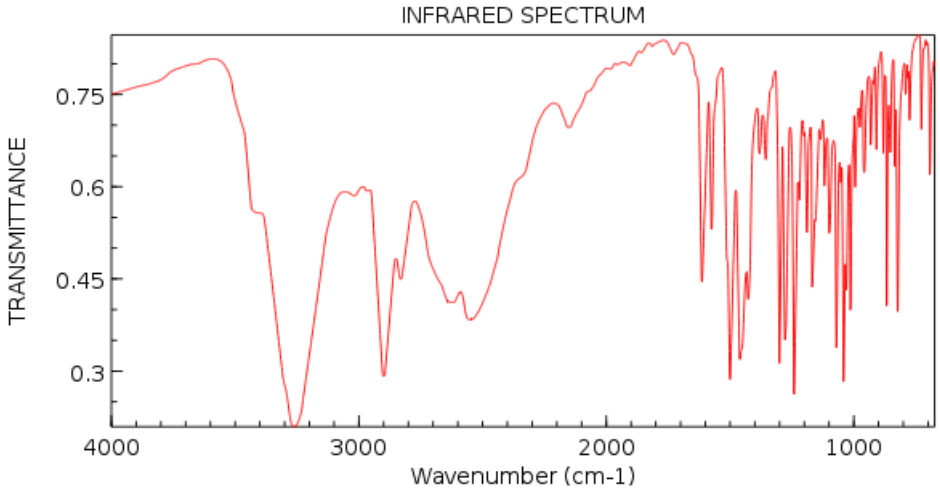


Fig 2 FT-IR SPECTRUM OF PURE DRUG

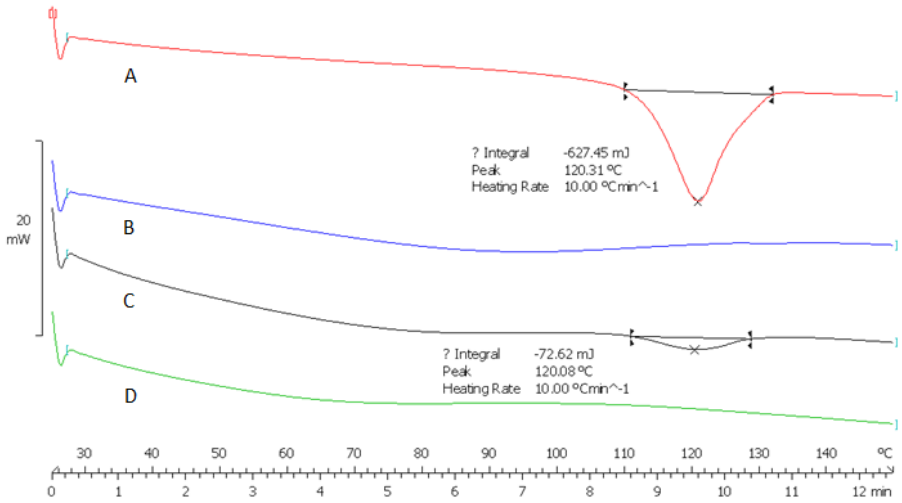


Figure 3: DSC thermograms of pure drug and 1:2 drug- excipient mixture.

Table no.3 Values of sedimentation volume (%) suspension using different suspending agent
Sedimentation volume (%)

Formulation	24hours	1week	1month	2months	3months
F1	4.9	5	6	7.5	8.9
F2	5.5	6	7.9	8.9	9.2
F3	5.9	6.6	7.7	8.9	10
F4	7	7.9	8.9	10	11
F5	5.5	6.9	8.5	10	11.5
F6	10	11	12	12.9	13.8
F7	12.8	13.9	14	14.5	15.8
F8	8.5	9.4	10	11	12.9
F9	7.1	8.2	9.5	10.7	13
F10	5.5	6	7.9	8.9	9.2

Table no.4. Viscosity values of different formulations for 3 months period
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

Table no 5: Particle size determination

	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 shows (table no.4.2.4) pH 3.51 was relatively a stable formulation.

Table no.6 pH values of different formulations for 3 months period

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

pH Stability Study: The Optimised suspension(F2) was stored at 2-8˚C and pH of the suspension was checked for 10 days as shown in table no 7.

Table 7: pH values of formulation (F2)

DAYS	pH
Day 1	3.51
Day 2	3.50
Day 3	3.52
Day 4	3.55
Day 5	3.48
Day 6	3.3sfd2
Day 7	3.55
Day 8	3.46
Day 9	3.50
Day 10	3.50

Table No. 8: Accelerated Stability Study Report

PERIOD	Dissolution (%)	pH	Assay (%)
INITIAL	88	3.51	98.42
1st MONTH	87.2	3.50	98.27
2nd MONTH	87.1	3.52	97.2

Drug release: All the formulations showed acceptable properties as shown in table 4.7. 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.

Table No.9: 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

FIG-4 Invitro dissolution data for formulation F1 by using different percentage of ER coating

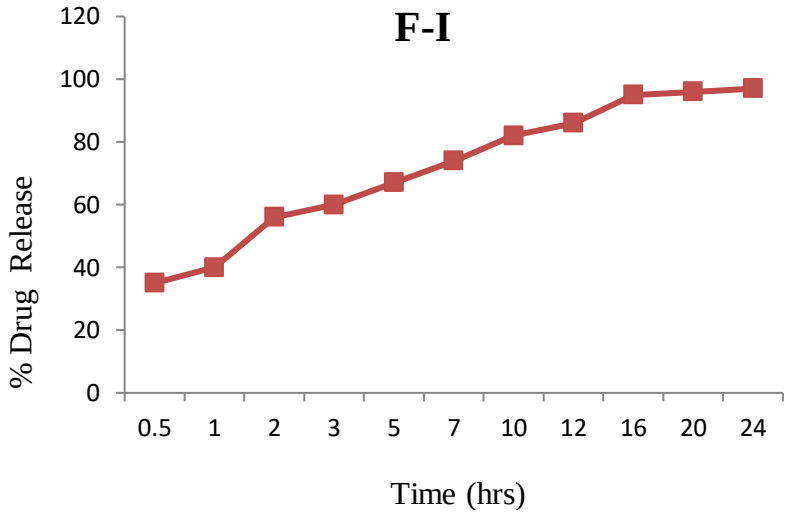
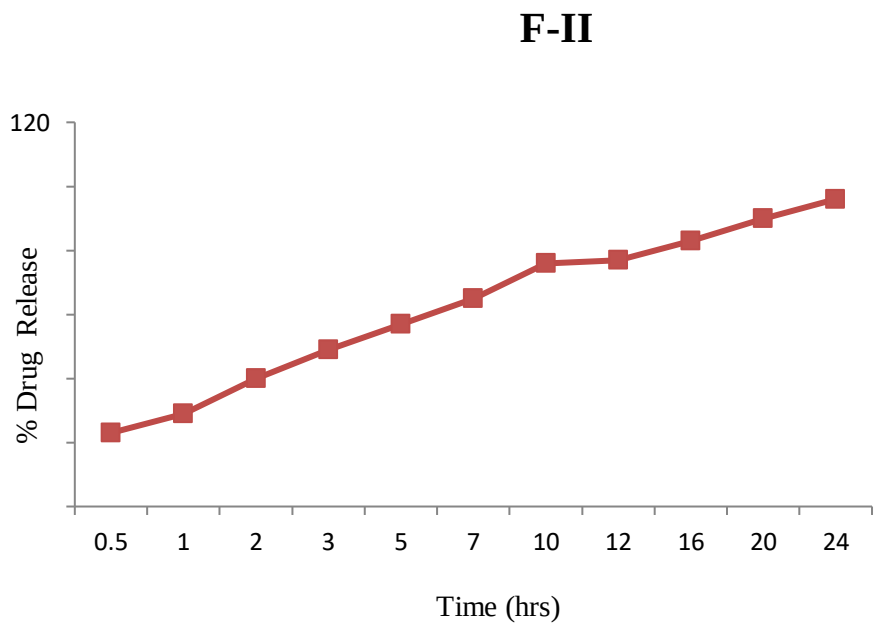


FIG-5 Invitro dissolution data for formulation F2 by using different percentage of ER coating



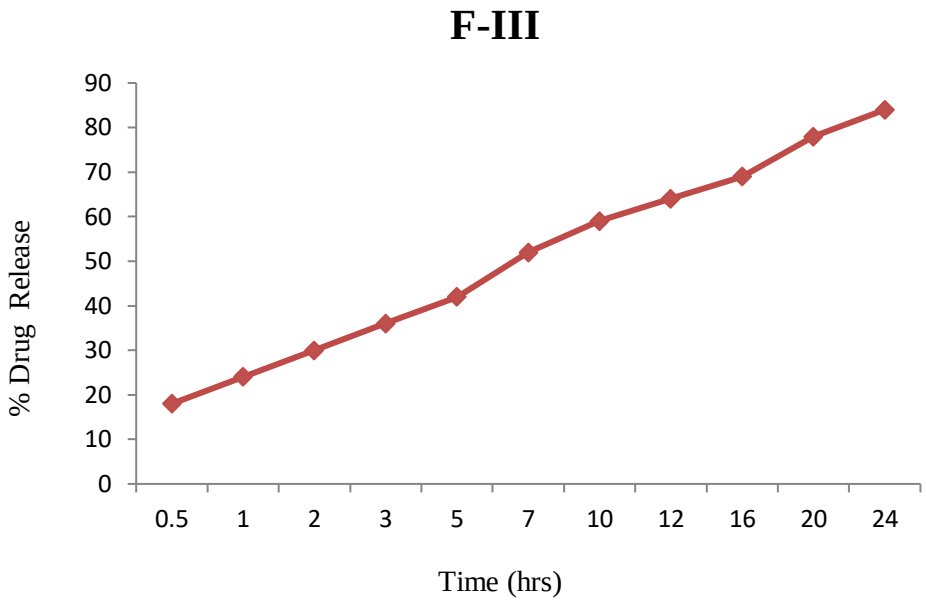


FIG-6 Invitro dissolution data for formulation F3 by using different percentage of ER coating

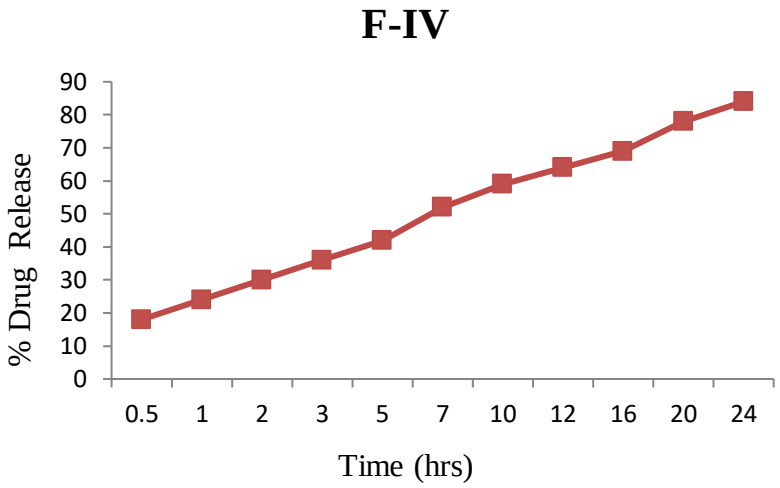


FIG-7 Invitro dissolution data for formulation F4 by using different percentage of PEG coating

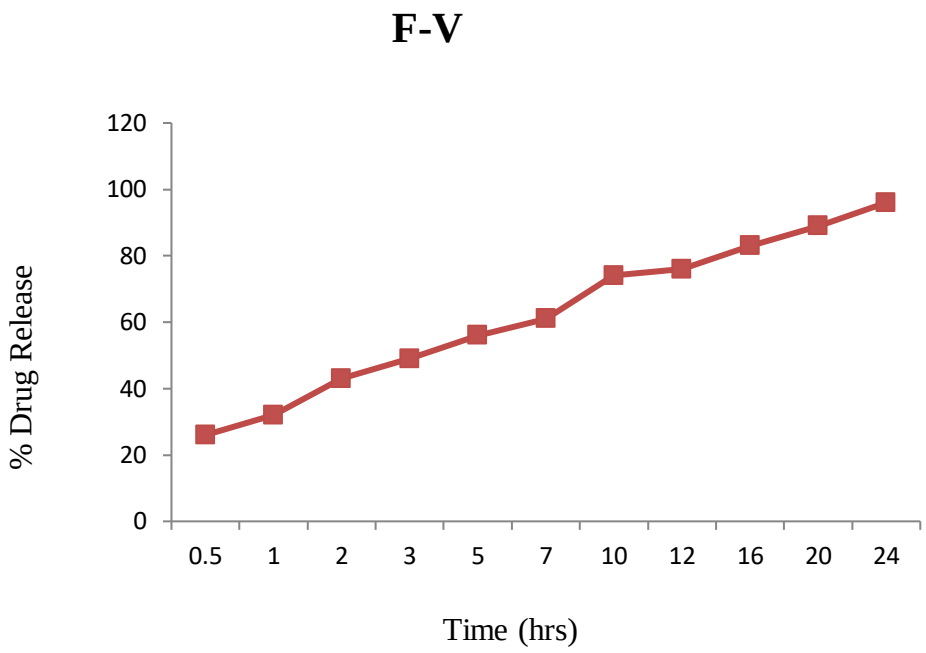


FIG-8 Invitro dissolution data for formulation F5 by using different percentage of PEG coating

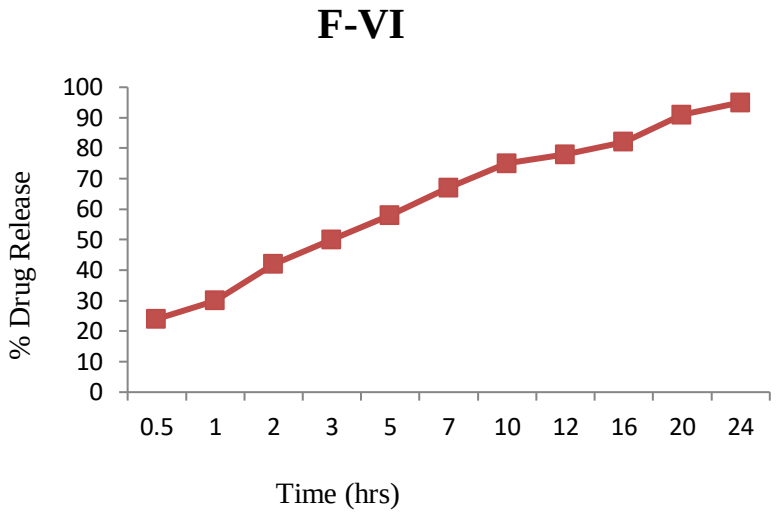


FIG-8 Invitro dissolution data for formulation F6 by using different concentrations of xanthan gum and tragacanth

DISCUSSION AND CONCLUSION:

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.

The bitter taste of drugs remains a big challenge to the pharma sector especially when it deals with oral pharmaceutical to paediatric population. In the present work the taste masking of the drug employed various techniques like masking with sweetener and flavour, drug particle coating with PEG and enteric coating and finally complexation with Dextromethorphan Polistirex. Of this, inclusion complex formation with Dextromethorphan Polistirex proved to be highly efficacious, cost effective and simple method. The complex is thought to separate inside the gastric environment thus releasing the drug. The drug is better absorbed from the upper part of intestine.

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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