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Research Article

FORMULATION AND DEVELOPMENT OF TASTE MASKED DISPERSIBLE TABLET OF CEPHALEXIN MONOHYDRATE USING ION EXCHANGE FIBERS AND RESINS

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ABSTRACT

The primary aim of present work was to formulate and evaluate taste masked dispersible tablets of Cephalexin monohydrate, an antibacterial drug, using ion exchange resins like INDION 224 and ion exchange fibres Smopex 101pp as a taste masking agent and superdisintegrating agents like crospovidone and sodium starch glycolate in different concentrations. Characterization of drug was done by melting point determination, FT-IR spectroscopy and UV-spectroscopy. Drug-resin and fibre complexes were prepared by batch method using the resins and fibre in different ratios. Drug loading study was carried at different pH. INDION 224 and Smopex 101pp showed highest drug loading (86.44% and 90.41%). Hence, further studies were done using INDION 224 and Smopex 101pp. The drug-resin/fibre complexes were studied for micromeritic properties, *in vitro* drug release and taste masking ability by determining threshold bitterness concentration of the drug. The complexes were characterized by drug content, FTIR and DSC studies. Powder blends were prepared and evaluated for various physical properties. Dispersible tablets of drug-resin complex (DRC) and Drug-fibre complex (DFC) were prepared by Direct Compression method using crospovidone and sodium starch glycolate in different concentrations as superdisintegrants. Tablets were evaluated for thickness, hardness, friability, uniformity of weight, dispersion time, uniformity of dispersion, disintegration time, wetting time, wetting volume, content of active ingredient and dissolution studies. All the formulations showed the evaluated parameters within the acceptable limits for dispersible tablets. Finally, formulation F4 was taken as an optimized formulation which was containing 3% of crospovidone and showed the least *in vitro* disintegration time and an excellent drug release. Stability study was also conducted on the optimized batch F4 which showed good results.

Keywords: Cephalexin monohydrate, dispersible tablet, ion- exchange resin, complexation.

INTRODUCTION

Essential factors in assessing the patient's acceptability of pharmaceutical productareappearance, odour and taste. Goodflavour and texture are found to significantly affect acceptance of the product. Oral dosage forms which suffer problems of bitter taste may include chewable tablet, capsule, suspension, lozenges, mouthwashes, dentifrices, syrups and ingestible ointments. Bitter taste is one of the important formulation problems; more than 50% pharmaceutical active ingredients have bitter

taste. So, for the paediatric and geriatric patient compliance,it's required to mask the taste by suitabletechnique. Administration of the bitter drug orally with acceptable level of palatability is key issue for health care providers especially in case of pediatric patients.Over a decade, the demand for development of dispersibletablets has enormously increased as it has significant impacton the patient compliance. Dispersible tablets offer anadvantage for populations who have difficulty in swallowing. It has been reported that dysphasia (difficulty in swallowing) is common among all age groups specific with pediatric, geriatric population along with institutionalized patients and patients with nausea, vomiting and motionsickness complications. DTs with good taste and flavour increase the acceptability of bitter drugs by various groups of population. Cephalexin monohydrate is widely used in the treatment of bacterial infection and it is widely prescribed in pediatric patients. lowering and widening in the melting .Its bitter taste is a major problem in the pharmaceutical industry point range due to low patient compliance and remains a huge challenge. So, present work attempts to mask the bitter taste of Cephalexin monohydrate. After extensive literature survey and market study, it was found that Cephalexin monohydrate is no where available in taste masked DT form with ion exchange fibers. DTs have so many advantages over liquid preparations and conventional tablets available in market.

MATERIALS AND METHODS

Materials

Cephalexin monohydrate obtained from Hindustan Antibiotic private Ltd.Indion204 and Indion 224 from ion exchange india limited,Mumbai. Smopex-101pp,Smopex-102pp from Johnson MattheyTurku,Finaland.Sodium starch glycolate,crosspovidone,micro crystalline cellulose,Mannitol,PVPK-30,Aspartame was procured from Glenmark research center,Sinner.

Preformuation studies

Solubility analysis

In preformulation study,Solubility analysis was done to select the Suitable solvent system to dissolve the drug and also to taste its solubility in dissolution medium which was to be used.

Melting point Determination

Melting point determination of obtained Sample was done which is good indication of purity of sample drug. Since the Presence of even small amount of impurity can be detected by
Lowering and widening of melting point range.

Organoleptic Study

The drug sample was tested for the Organoleptic parameter like apperance,colour,odour and taste and compare with the standard description for Cephalexin monohydrate.

FTIR Spectroscopic Studies

FTIR absorbtion spectrum of the drug sample was recorded by KBR dispersion technique over the range 400 to 4000 cm^{-1}.and it was compared with the standard FTIR Spectrum of pure drug.

Selection of Resin and Fibers

Resin and fibers were selected on the Basis of nature of drug and requirement.Thereforecation exchange resin and fibers were selected.Strongcation exchanger like Smopex 101pp and indion 224 were selected to obtained drug resin and fiber complex ofcephalexin monohydrate.

Compatibility Studies

Fourier Transform Infrared Spectroscopic (FTIR) analysis

FT-IR spectral studies were carried out using ATR (Bruker) to check the formation of complexes between drug and resins/fibers. The FT-IR spectrum of drug with resin and fiber was compared with the FT-IR spectrum of pure drug and pure resin spectrum. Scanning was done from 4000 to 400 cm^{-1}.

Preparation of Taste Masked Product

The drug resin complexes were prepared by batch process. An accurately weighed amount of Cephalexin monohydrate (100 mg) was dissolved in 20 ml distilled water. Then known weight (100mg) of ion exchange resin and fibers was added to the solution separately and stirred on magnetic stirrer. Time to reach equilibrium was determined by periodically measuring concentration of drug solution. DRC and DFC thus formed was filtered and washed with 10 ml of distilled water. The drug content in the final filtrate was analyzed by UV-spectroscopy at 260nm. The amount of drug adsorbed was determined by the difference between amount of drug present in stock solution and amount remaining in filtrate at the end of equilibrium.

DRC and DFC were dried overnight in a hot air oven at 50^{O}C and then stored in tightly closed in desiccators.

Selection of Drug: Resin Ratio

Two batches were prepared containing drug–resin and drug-fiber complexes in the ratio of 1:1 and 1:2. The slurry was stirred for 2 hours. DRC and DFC obtained were separated by filtration,washed with copious quantity of deionized water and drug contents were determined.

Effect of pH on Drug Loading

A series of 100ml of dispersion containing 1mg/ ml Cephalexin monohydrate was prepared. pH of these solutions were adjusted to 2, 3, 4, 5, 6 and 7 using 0.1N HCl; ion exchange resin (100mg) and ion exchange fiber (100mg) separately was added to each beaker and stirred for 2 hours. Resinate thus formed was filtered and washed with 10 ml distilled water. The drug content in the finalfiltrate was analyzed by UVspectroscopy at 260nm.

DSC analysis of Taste Masked Products

Differential Scanning Calorimetric (DSC) analysis was performed for pure cephalexin monohydrate,Smopex 101pp and resinate (1:11 ratio) using a Mettler Toledo DSC 823e instrument operated with STARe programme under pressure of nitrogen gas with flow rate of 40ml/min and heating rate of 10^{o}C per minute in the temperature range of 30^{o}C to 300^{o}C.
Each sample was accurately weighed (3 mg) in an aluminum pan, crimped and hermetically sealed.

Evaluation of Taste Masked Products

The taste masked products were evaluated for the micromeritic properties like angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio and also for drug content.

Taste Evaluation of the Taste Masked Products

Evaluation of taste was done in two parts -

a)Determination of Threshold Bitterness Concentration

Various concentrations (10-50 mcg /ml) of drug wereprepared in phosphate buffer pH 6.7. Mouth was rinsed tasted by swirling it in the mouth mainlytasted by swirling it in the mouth mainly near the base of the tongue for 30 seconds. If the bitter sensation was no longer felt in the mouth after 30 seconds, the solution was spat out and waited for 1 minute to ascertain whether this is due to delayed sensitivity. Then mouth was rinsed with safe drinking water. The next highest concentration should not be tasted until at least 10minutes had passed. The threshold bitter concentration is the lowest concentration at which a material continues to provoke a bitter sensation after 30 seconds. After the first series of tests, mouth was rinsed thoroughly with safe drinking water until no bitter sensationremained. Interval of at least 10 minutes was observed between two tests.

b) *In Vitro* Evaluation of Taste of Resinates

An accurately weighed (equivalent to100 mg drug) taste masked product and 10 ml of pH 6.7 phosphate buffer (0.1 M) was taken in series of volumetric flask and stirred at 50 rpm. The stirring was stopped at different time intervals such as 0,10, 30,60 and 120 sec., dispersion was filtered, and the concentration of cephalexin monohydrate in filtered resinate was determined. Time forresinate to achieve drug concentration corresponding to threshold bitterness in 10 ml phosphate buffer was recorded.

***In Vitro* Drug Release Profile**

The *in vitro* dissolution study of cephalexin monohydrate taste masked products wascarried using 0.1N HCL as a dissolution medium in Type II USP dissolution apparatus at 37°C ± 0.5°C for 60 minutes. At 10 min. interval aliquots of medium (5 ml) were taken, filtered and absorbance was measured by UV spectroscopy at 260nm. The medium was replaced with equal volume of fresh dissolution fluid after each sampling.

Formulation of Dispersible Tablet of Taste Masked Chloroquine phosphate

Compositions of seven different formulations of Cephalexin monohydrate tablets were prepared as given in table1. Different concentrations of the superdisintegrants, i.e.Crospovidoneand Sodium starch glycolate were used. All ingredients were passed through sieve no. 120, and then weighed accurately and mixed thoroughly (except magnesium stearate). Tablets were prepared by direct compression method. Prepared granules lubricated with magnesium stearate. All the four blends were evaluated for various parameters like angle of repose, bulk density,

tapped density, % compressibility and Hausner ratio, drug content etc.

Evaluation of Chloroquine phosphate Dispersible Tablets

The tablets from all the batches were evaluated for different parameters as follows:

Appearance

Tablets were evaluated for organoleptic properties.

Thickness

Thickness of tablets was determined using Verniercaliper, three tablets from each batch were used and an average value was calculated.

Weight Variation

Twenty tablets were selected and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight.

Hardness

Tablets were selected at random from each formulation and hardness was checked using Monsanto Hardness Tester.

Friability

Pre-weighed sample of tablets was placed in the Roche Friabilator tester, which was then operated for 100 revolutions. Tablets wereddusted and reweighed; tablets should not lose more than 1% of their initial weight.

Content of Active Ingredient[5, 7]

Drug content of all the batches was determined. For this purpose six tablets were weighed and crushed with pestle in a small glass mortar. The fine powder was weighed to get 700mg (equivalent to 250 mg of Cephalexin monohydrate) and was placed in 1M HCl (250ml) and stirred at 100 rpm for one hour. The solution was filtered and analyzed for content of cephalexin monohydrate by UV spectrophotometer.

Uniformity of Dispersion

Two tablets were placed in 100 ml of water and stirred gently until completely dispersed. A smooth dispersion was obtained which passes through a sieve screen with a nominal mesh aperture of 710 μm (sieve number 22).

Wetting Volume

The tablet was placed in the canter of the Petri dish and with the help of 5 ml pipette; distilled water was added drop wise on the tablet. The volume required to completely disintegrate the tablet was noted as the wetting volume.

Wetting Time

A piece oftissue paper (12cmx10.75cm) folded twice was placed in a Petri dish (10 cmDiameter) containing 10 ml of water. Containing Eosin, a water soluble dye, was added to Petri dish. A tablet was carefully placed on the surface of the tissue paper and allowed to wet completely. The time required for water to reach upper surface of the tablet was noted as a wetting time.

Dispersion Time

Tablet was added to 10 ml of water and time required for complete dispersion was measured. Three tablets from each formulation were randomly selected and dispersion time was performed.

Disintegration Time

The disintegration time of tablet was measured in water ($37^{O}C$) according to U.S.P. Disintegration test apparatus. Three trials for each batch were performed.

***In vitro* Dissolution[4]**

The in vitro dissolution study was performed in the U.S.P. apparatus type II. Aliquot equal to 5 ml of dissolution medium was withdrawn at specific interval and replaced withFresh medium for maintaining sink condition. Sample wasfiltered and absorbance of filtered solutions determined by UV spectroscopy at 343 nm. Dissolution rate was studied for all formulations.

Accelerated Stability Study

Accelerated stability studies were carried out on optimized formulation F3 for one month period as prescribed by ICH guidelines for accelerated study at 40 ± $2^{o}C$ and RH 75 ± 5 %. The tablets were analyzed for physical characterization, dissolution and drug content and compared with the same before accelerated stability study.

Table 1: Composition of taste masked dispersible tablets of Cephalexin monohydratewith corresponding formulations(cephalexin:smopex-101 complex)

	F1	F2	F3	F4
DFC	523	523	523	523
crosspovidone	14	35	14	35
SSG	14	14	56	56
PVPK30	14	14	14	14
Mannitol	10.5	10.5	10.5	10.5
Mag.Stearate	3.75	3.75	3.75	3.75
Aspartame	3.50	3.50	3.50	3.50
Mcc	117.25	96.25	75.25	54.25
Total	**700mg**	**700mg**	**700mg**	**700mg**

Table 2: Composition of taste masked dispersible tablets of Cephalexin monohydrate with corresponding formulations(cephalexin:Indion224 complex)

	F1	F2	F3	F4
DRC	533	533	533	533
crosspovidone	14	35	14	35
SSG	14	14	56	56
PVPK30	14	14	14	14
Mannitol	10.5	10.5	10.5	10.5
Mag.Stearate	3.75	3.75	3.75	3.75
Aspartame	3.50	3.50	3.50	3.50
Mcc	107.25	86.25	65.25	44.25
Total	700mg	700mg	700mg	700mg

Table 3: Evaluation of formulation (Cepha:Smopex101pp)

Evaluation Parameter	Formulations			
	F1	F2	F3	F4
Hardness(kg/cm²)	2.75±0.6	2.72±0.4	2.73±0.2	**2.70±0.3**
Thickness (mm)	4.81±0.4	4.89±0.5	4.80±0.4	**4.88±0.5**
Friability(%)	0.59	0.62	0.59	**0.50**
Dispersion Time (Sec)	29±2.30	26±2.92	25±1.45	**23±3.62**
%weight variation	704±1.56	702± 0.56	702±0.46	**700±0.030**
Wetting time (sec)	36±1.86	38±2.08	34±0.654	**32±1.660**
Wetting volume	4.4±0.754	4.5±1.65	4.4±0.546	**4.2±0.22**
Uniformity of dispersion	Passes	Passes	Passes	**Passes**
Disintegration time(Sec)	30±0.452	28±0.654	25±1.76	**24±0.87**

Table 4:Evaluation of formulation(Cepha:Indion 224)

Evaluation Parameter	Formulations			
	F1	F2	F3	F4
Hardness(kg/cm²)	2.79±0.93	2.74±0.89	2.78±0.45	2.82±0.32
Thickness (mm)	3.89±0.4	3.82±0.5	3.85±0.4	3.87±0.5
Friability(%)	0.60	0.59	0.53	0.51
Dispersion Time(Sec)	28±1.60	27±2.12	24±1.38	22±1.43
%weight variation	702±1.67	706± 0.46	703±0.86	702±0.43
Wetting time (sec)	35±1.57	36±1.93	34±0.14	30±0.94
Wetting volume(ml)	4.9±0.64	4.3±1.25	4.4±0.65	4.0±0.35
Uniformity of dispersion	Passes	Passes	Passes	Passes
Disintegration time(Sec)	28±0.84	28±0.98	25±1.34	23±0.99

After evaluating the formulations on the parameter of hardness ,disintegration time, thickness, Friability,Weight variation,Dispersion time,Wetting volume,Wetting volume formulation **F4** is selected as best formulation

Table 5:Percent cumulative drug release from formulation (F4)

Time	Cumulative Percent drug release			
	DRC(0.1 N HCl)	DRC (SGF)	DFC(0.1N HCl)	DFC (SGF)
5	32.18±0.48	33.18±0.65	36.20±0.46	39.37±1.35
10	42.90±1.72	43.14±1.45	46.35±0.34	50.20±0.89
15	56.20±1.84	57.60±1.37	61.90±0.87	63.80±1.68
20	74.40±0.56	75.14±0.78	79.13±1.56	83.60±1.63
25	82.90±0.97	83.88±0.91	87.40±1.45	89.20±0.17
30	95.10±0.54	96.18±1.68	96.80±0.49	98.90±0.78

Table 6: Evaluation of optimized batch F4 after stability study (cepha: Smopex 101pp)

Formulation code	Hardness	Thickness	% Drug Release
F4	2.69 ±0.39	4.87±0.57	97.80±0.62

Table 7: Evaluation of optimized batch F4 after stability study (cepha: Indion 224)

Formulation code	Hardness	Thickness	% Drug Release
F4	2.81±0.72	3.86±0.78	95.40±0.53

DISCUSSION

Preformulation study revealed that Cephalexin monohydrate sample was found to be Slightly soluble in water, practically insoluble in ethanol, chloroform, and ether, soluble in solutions of dilute alkalis.The melting point of the obtained drug sample was found to be 326°C, which is within the given standard range 325-327°C. The physical state, colour, odour and taste of the drug sample were found to be crystalline,white,Characteristics and bitter respectively, indicating its compliance with IP standards. The FTIR spectrum of the drug sample was found to be similar to the standard spectrum of Chloroquine phosphate. It was observed that the FTIR spectra shows the occurrence of complexation. The study of drug-resin complexes prepared using INDION 224 and Smopex-101pp showed that Cephalexin monohydrate: INDION 224 (1: 1) gave the best drug loading as 86.44 % and Smopex-101pp also gave better loading efficiency i.e. 90.41% at 2 hrs. Hence, it was selected for the further studies. It was observed that with increasing pH up to 6, the loading of drug on resin increased but above pH 6 loading decreased.

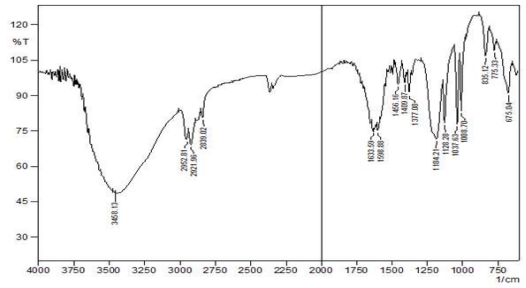

Fig. 1: FTIR spectrum of cephalexin monohydrate

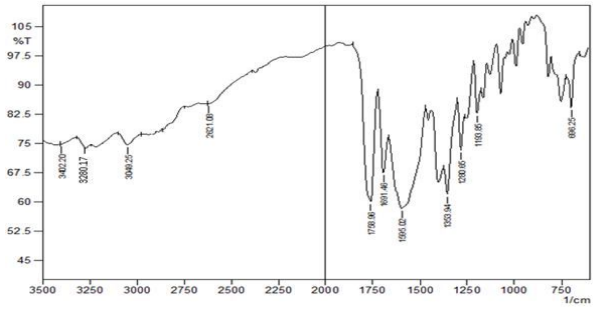

Fig. 2: FTIR Spectra of Smopex

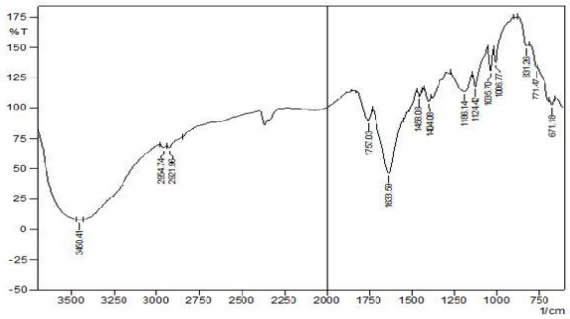

Fig. 3: FTIR Spectra of cephalexin:Smopex 101pp Complex

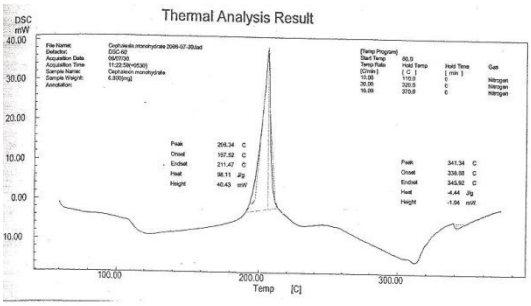

Fig. 4:DSCcurve of Cephalexin monohydrate

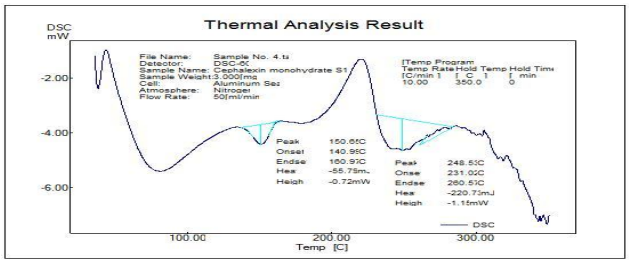

Fig. 5: DSC curve of cepha:S 101pp Complex

CONCLUSION

Overall, the results suggested that ion exchange resins form a suitable tool to mask the bitter taste of drug like Cephalexin and improvepediatric patient compliance. Also, the results indicated that taste masked dispersible tablets of Cephalexin monohydrate can be formulated successfully by using INDION 224 and Smopex 101pp as a taste masking and Crosspovidone and SSG as a superdisintegrating agent, respectively. And this approach may be an alternative for the conventional method. The present study demonstrated potentials for rapid absorption, improved bioavailability, effective therapy and patient compliance.It was also concluded that ion exchange fibers shows more complexation with drug as compared to ion exchange resin.And also shows more drug release.

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