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PharmTech
International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.2, No.1, pp 502-506, Jan-Mar 2010

DEVELOPMENT AND EVALUATION OF ORAL RECONSTITUTABLE SYSTEMS OF CEPHALEXIN

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ABSTRACT: Cephalexin, a cephalosporin antibiotic was chosen as the model drug candidate to obtain a dosage form with improved stability, palatability and attractive paediatric elegance, cost effective and with ease of administration. The present work was carried out to design and develop oral reconstitutable system of Cephalexin as dry suspension, to be reconstituted with water and then given to children. It was also aimed at determining the influence of different processing conditions like powder mixture, granulation and combination product on the properties of the drug product. All the formulations showed good organoleptic properties with enhanced sedimentation and rheological behavior with T90% within two hours. The powder mixture gave a rapid release of 10 – 30 minutes.
KEYWORDS: Cephalexin, oral reconstitutable system, dry suspension.

INTRODUCTION AND EXPERIMENTAL

Conventional oral suspensions can be administered immediately but an important category of oral solutions and suspensions that requires mixing prior to administration is more acceptable and stable. These are dry mixtures or dry syrups that require addition of water at the time of dispensing. The reconstituted system is the formulation of choice when the drug stability is a major concern. After reconstitution, these systems have a short but acceptable life if stored at the refrigerated temperatures. The required properties can be maintained before and after reconstitution. Reconstitutable oral systems have adequate drug stability during the shelf life. It also reduces the weight of the final product because the aqueous vehicle is absent and consequently the transportation expenses may be reduced.[1,2]

The objective of the present study is to design and develop oral reconstitutable suspensions of Cephalexin for paediatric population with age group 5 to 15 years with adequate drug stability, enhanced acceptance and palatability, ease of administration and rapid drug release. Cephalexin is a cephalosporin antibiotic which is marketed as oral tablets and suspensions.[3-10] It works by interfering with the bacteria's cell wall formation, causing it to rupture, and killing the bacteria. Cephalexin is active against a wide range of Gram positive and Gram negative organisms and is used to treat urinary tract infections, respiratory tract infections, and skin and soft tissue infections. Hence it was chosen as the model drug candidate to present in a more stable and palatable dosage form with attractive paediatric elegance. This technology can also be used to obtain quick relief and for administration of bitter drugs meant for children.[1,2,11,12]

Materials and Methods

Cephalexin was purchased from Research Fine Chemical Industries. Acacia, tragacanth, sodium starch glycolate were purchased from S D Fine Chemicals Ltd.; PVP was purchased from Loba Chemie Pvt. Ltd. All other chemicals were of analytical grade and were purchased from Merck India.

Preparation of oral reconstitutable systems of Cephalexin:

1. Powder mixture

Powder mixture of Cephalexin (Dose 125mg/ 5ml) was prepared using suspending agents, sweetener, preservative, buffer, flavorant and anticaking agent by conventional technique. All ingredients were passed through 200# and then mixed by geometric dilution (Table 1). Dose of powder mixture: 3.4g of the powder to 5 ml equivalent to 0.125g of Cephalexin.

2. Granulation

Powder mixture of Cephalexin (Dose 125mg/ 5ml) was prepared using suspending agents, sweetener, preservative, buffer, flavorant and anticaking agent by conventional technique. All ingredients were passed through 200# before mixing. The drug was dry blended with the other ingredients by geometric dilution. Wet granulation was the usual process for making the granulation. The solid ingredients were blended and massed using isopropyl alcohol. The wet mass was formed into granules using 18#. The formed granules were dried in the oven and passed through 20# after drying (Table 2). Dose of granulations: 3.4g of the granulations to 5ml equivalent to 0.125g of Cephalexin.

3. Combination Product:

Powdered and granulated ingredients were added. Heat sensitive ingredients were added after drying of the granulation. The general method included granulating first some ingredients then the remaining ingredients were blended with the dried granules before filling into the container. Half the amount of diluents was granulated and the remaining half was added after granulation to the dried granules. For making the granulation, the drug was dry blended with the other ingredients. Wet granulation was the usual process for making the granulation. The solid ingredients were then blended and massed using isopropyl alcohol. The wet mass was formed into granules using 18#. The formed granules were dried in the oven and passed through 20# after drying (Table 3). Dose of combination product: 3.4g of the granulations to 5ml equivalent to 0.125g of Cephalexin.

Physical characteristics of Oral Reconstitutable Systems:

Oral reconstitutable systems of Cephalexin was evaluated for organoleptic properties, pH, microscopy, flow properties, rheological and sedimentation behavior, drug content and *in vitro* drug release.

Flow properties:

Flow properties such as angle of repose, bulk density, tap density and porosity of powder mixture, granulations and combination product were carried out.

Rheological behavior:

The rheological behavior of the reconstituted suspensions was determined using Brookefield viscometer (Model – RVT).

Sedimentation behavior:

- **Redispersibility:** The redispersibility was determined by studying the number of strokes to redisperse the formed sediment in 10ml of reconstituted suspensions, at the end of 7 days of storage (not more than 100 strokes to redisperse the formed sediment ≡ Redispersibility).
- **Sedimentation Volume Ratio (SVR):** During the seven day study sedimentation behavior of formulations was studied for sedimentation volume (F) and degree of flocculation (β).

Drug content:

One dose (3.4 g of the formulation to 5 ml) is equivalent to 0.125g of Cephalexin. The drug was extracted with 100 ml of distilled water and the solution was filtered through nylon filter membrane (0.22 μm). 0.1 ml of the solution was further diluted to 10 ml with distilled water and absorbance of the solution was read at λmax 260 nm on Hitachi U-2800 UV spectrophotometer. The drug concentration was extrapolated from the calibration curve in distilled water.

***In vitro* drug release:**

The *in vitro* dissolution studies were carried out using USP apparatus Type II at 100 rpm. The dissolution medium consisted of 900 ml distilled water maintained at $37^0C \pm 0.5^0C$ The drug release at different time intervals was measured for two hours using Hitachi U-2800 UV spectrophotometer.

RESULTS AND DISCUSSION

All the formulations designed as powder mixture, granulations and combination product were palatable and organoleptically acceptable without any bitterness after reconstitution in distilled water (Table 4). Angle of repose decreased in granulations but remained the same in powder mixture and combination product. Porosity was similar in powder mixture, granulations and combination product. Granulations showed enhanced flow properties compared to powder mixture and combination product (Table 5). Granulations and combination product showed quite similar rheological behavior. All formulations showed good sedimentation behavior except a few. All formulations showed T90% within two hours. Powder mixture gave a rapid release of 10-30 minutes (Table 6).

In conclusion, oral reconstitutable suspensions of Cephalexin were successfully developed as powder mixture, granulations and combination product.

Formulations were palatable and organoleptically acceptable without any bitter taste of the drug after reconstitution. Formulations also showed an improved drug release in powder mixtures with T90% between 10-30 minutes. Also the study helped at determining the influence of different processing conditions like powder mixture, granulations and combination product on the properties of the drug product. Thus a highly palatable formulation technique which can avoid bitter taste of drugs with enhanced ease of administration can be used within the existing machinery. It can also be concluded that this method may also be used to administer other bitter drugs especially for children for quick relief.

Table 1 shows Formulations of Cephalexin prepared as powder mixtures

Formulations	F-I (%)	F-II (%)	F-III (%)
Cephalexin	2.5	2.5	2.5
Sucrose	62.5	62.5	62.5
Tragacanth	1	-	-
Acacia	-	1	-
Polyvinyl pyrrolidone	-	-	1
Sodium citrate	0.2	0.2	0.2
Citric acid	0.4	0.4	0.4
Sodium benzoate	0.2	0.2	0.2
Aerosil	0.5	0.5	0.5
Sunset Yellow	q.s.	q.s.	q.s.
Lemon Flavor	q.s.	q.s.	q.s.

Table 2 shows Formulations of Cephalexin prepared as granulations

Formulations	F-IV (%)	F-V (%)	F-VI (%)
Cephalexin	2.5	2.5	2.5
Sucrose	62.5	62.5	62.5
Tragacanth	1	-	-
Acacia	-	1	-
Polyvinyl pyrrolidone	-	-	1
Sodium starch glycolate	1	1	1
Sodium citrate	0.2	0.2	0.2
Citric acid	0.4	0.4	0.4
Sodium benzoate	0.2	0.2	0.2
Aerosil	0.5	0.5	0.5
Sunset Yellow	q.s.	q.s.	q.s.
Lemon Flavor	q.s.	q.s.	q.s.

Table 3 shows Formulations of Cephalexin prepared as combination product

Formulations	F-VII (%)	F-VIII (%)	F-IX (%)
Cephalexin	2.5	2.5	2.5
Sucrose	62.5	62.5	62.5
Tragacanth	1	-	-
Acacia	-	1	-
Polyvinyl pyrrolidone	-	-	1
Sodium starch glycolate	1	1	1
Sodium citrate	0.2	0.2	0.2
Citric acid	0.4	0.4	0.4
Sodium benzoate	0.2	0.2	0.2
Aerosil	0.5	0.5	0.5
Sunset Yellow	q.s.	q.s.	q.s.
Lemon Flavor	q.s.	q.s.	q.s.

Table 4 shows Evaluation data for drug content and organoleptic properties of Cephalexin formulations

Formulations	Drug Content (%)	Organoleptic properties			
		Color	Odor	Taste	Appearance
F-I	99.0 ± 0.4	Yellow	Lemon	Palatable	Smooth
F-II	99.8 ± 0.2	Yellow	Lemon	Palatable	Smooth
F-III	99.9 ± 0.1	Yellow	Lemon	Palatable	Smooth
F-IV	98.0	Yellow	Lemon	Palatable	Granular
F-V	99.25 ± 0.12	Yellow	Lemon	Palatable	Granular
F-VI	98.0	Yellow	Lemon	Palatable	Granular
F-VII	98.7± 0.55	Yellow	Lemon	Palatable	Granular
F-VIII	99.0 ± 0.3	Yellow	Lemon	Palatable	Granular
F-IX	98.2 ± 0.22	Yellow	Lemon	Palatable	Granular

Table 5 shows Evaluation data for pH and flow properties of Cephalexin formulations

Formulations	pH	Flow properties				
		Flow rate (g/sec)	Angle of repose (^{0})	Bulk density (g/ml)	Tap density (g/ml)	Porosity (%)
F-I	6.0	16.75± 0.01	10.73± 0.11	0.625	0.8± 0.01	21.87± 0.01
F-II	6.0	12.5± 0.02	10.65± 0.12	0.66± 0.01	0.80	16.66
F-III	6.0	12.5± 0.12	11.20± 0.01	0.625± 0.04	0.833± 0.01	25.0± 0.11
F-IV	6.0	10.25± 0.01	5.79± 0.05	0.47± 0.02	0.625± 0.11	23.80± 0.01
F-V	6.0	16.5± 0.02	8.91± 0.05	0.47± 0.11	0.58± 0.11	19.04± 0.02
F-VI	6.0	15.0± 0.02	5.33± 0.03	0.5± 0.12	0.625± 0.01	20.0± 0.04
F-VII	6.0	28.0± 0.01	9.66± 0.02	0.47± 0.01	0.66± 0.03	28.5± 0.02
F-VIII	6.0	23.15± 0.01	10.50± 0.01	0.512± 0.03	0.66± 0.02	23.07± 0.03
F-IX	6.0	44.5± 0.02	13.35± 0.01	0.526± 0.03	0.66± 0.01	21.05± 0.01

Table 6 shows Evaluation data for viscosity, redispersibility, sedimentation behavior and *in vitro* drug release of Cephalexin formulations

Formulations	Viscosity (cps)	Sedimentation Behavior	Redispersibility	*In vitro* drug release (T90%) (mins)
F-I	396.36± 0.01	Not adequate	Not redispersible	10± 0.01
F-II	1066.66± 0.11	Good	Redispersible	10± 0.11
F-III	735± 0.01	Good	Redispersible	35± 0.14
F-IV	4480± 0.03	Not adequate	Not redispersible	30± 0.11
F-V	408.0	Good	Redispersible	50± 0.45
F-VI	666± 0.02	Good	Redispersible	30± 0.11
F-VII	2728.5± 0.01	Not adequate	Not redispersible	54± 0.23
F-VIII	326.66± 0.04	Good	Redispersible	45± 0.11
F-IX	1087.14± 0.01	Good	Redispersible	87± 0.1

REFERENCES

1. Ofner III CM, SChnaare RL, Schwartz JB, Oral aqueous suspensionsIn: Pharmaceutical Dosage forms: Disperse Systems, 2nd ed. Vol. 2, Marcel Dekker, New York.
2. Punit PS, Rajashree CM, Formulation and Evaluation of Taste Masked Oral Reconstitutable Suspension of Primaquine Phosphate. AAPS PharmSciTech, 2008; 9(3):1025-1030.
3. Sneader, Walter, Cephalosporin analogues. Drug discovery: a history. New York: Wiley, 2005.
4. Aronoff GR, Berns JS, Brier ME, Drug Prescribing in Renal Failure: Dosing Guidelines for Adults, 4th ed. Philadelphia, PA: American College of Physicians, 1999.

5. Donowitz GR, Mandell GL, Beta-Lactam Antibiotics. N Engl J Med, 1988; 318(7):419-26.
6. Donowitz GR, Mandell GL, Beta-Lactam Antibiotics. N Engl J Med, 1988; 318(8):490-500.
7. Saxon A, Beall GN, Rohr AS, Immediate Hypersensitivity Reactions to Beta-Lactam Antibiotics, Ann Intern Med, 1987; 107(2):204-15.
8. Smith GH, Oral Cephalosporins in Perspective, DICP, 1990; 24(1):45-51.
9. IP Committee, Indian Pharmacopoeia. Delhi: Controller of publication, 1996.
10. USP Convention, USP 24 NF 19. Asian edition: Rockville: USP, 2000.
11. Physicians' Desk Reference, 57th Ed. Montvale New Jersey: Medical Economics, 2003.
12. Elkheshen SA, Badawi SS, AA Badawi, Optimization of a Reconstitutable Suspension of Rifampicin Using 2^4 Factorial Design. Drug Development and Industrial Pharmacy, 1996; 22(7):623-630.
13. JP Hou, JW Poole, Kinetics and Mechanism of degradation of ampicillin in solution. Journal of Journal Pharmaceutical Sciences, 1969;58:447-457.

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