



EXTEMPORANEOUS PREPARATIONS OF PEDIATRIC ORAL FORMULATIONS: STABILITY STUDIES CONDUCTED IN SPIRONOLACTONE SUSPENSIONS, POWDERS AND CAPSULES IN SAUDI HOSPITAL PHARMACIES

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ABSTRACT

The lack of appropriate pediatric formulations is a worldwide problem. Pharmaceutical companies manufacture special preparations for paediatric patients mainly if the products are likely to be marketable and will generate profit for the manufacturer. The range of doses used may be wide for paediatric patients, because of the developmental changes that occur during a child lifetime. Suitable dosage forms formulated in much different strength by including harmless excipients would be needed to medicate children of different ages. Therefore, extemporaneously prepared products are still required to ensure that accurate doses and suitable dosage forms. The present study aimed to investigate physical and chemical stabilities, content uniformities and microbiological stability of extemporaneously prepared spironolactone oral suspensions to be used in newborns and infants, prepared extemporaneously in Saudi hospitals from spironolactone tablets. The stability of spironolactone in suspensions prepared extemporaneously by four Saudi hospitals at Aseer region and those prepared in the pharmaceutical laboratory were studied. Also Spironolactone oral powders and capsules were prepared by mixing crushed and carefully ground spironolactone tablets and the geometric amounts of either lactose or microcrystalline cellulose to achieve a final spironolactone concentration of 1.0 mg/unit. The resulting powder was divided into portions in powder papers or capsule shells. At intervals up to thirty five days. The suspensions were visually inspected for color and odor change precipitation, sedimentation and rheological properties. Also the suspensions were tested for changes in pH, as well as for microbial growth. The powders and capsules were assayed at interval up to 6months. Samples were assayed for spironolactone content by a reproducible and validated stability-indicating Spectrophotometric method. During the first 14 days of storage, mean spironolactone concentrations in all suspensions were >90% of the initial concentrations. After 30 days only one suspension remained stable, with >90% of the initial spironolactone concentration. Suspensions pH remained unchanged throughout the period of test and there were no changes in physical appearance. Also counts of bacteria and fungi remained within acceptable limits within 35 days. Only one spironolactone suspensions (1 mg/ml) was found to fulfill the expiry date (one month) stated in the labels. The content uniformities of spironolactone powders and capsules complied with the test specifications. The content of spironolactone theoretical content 1.0 mg was 0.92 ± 0.03 mg in powders. Oral powders and capsules filled with the powder of crushed tables were stable for up to 6months and were faster to prepare and upon comparing the quality, do represent an alternative to oral liquids.

1. INTRODUCTION

Despite efforts to improve the availability of suitable licensed and manufactured medicine products for children, extemporaneously prepared products are still needed to ensure that accurate and effective doses and dosage forms are available to achieve optimal drug therapy for children.

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There are many reasons for the lack of commercially available paediatric formulations. The overall size of the paediatric market is much smaller than for adults, especially for common diseases such as hypertension. There are no appropriate and comprehensive published standards for the process of extemporaneous preparation (1, 2). To ensure product quality, harmonization of extemporaneous formulations and quality-control procedures are needed and collected data should be published as standards and

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uniformly implemented in all countries, and these should lead to the creation of a monograph in a pharmacopoeia (1,2,3,4). Spironolactone is a specific pharmacologic antagonist of aldosterone, acting primarily through competitive binding of receptors at the aldosterone-dependent sodium-potassium exchange site in the distal convoluted renal tubule. It may also reverse aldosterone-induced cardiac fibrosis and improves morbidity and survival of patients with congestive heart failure (5). Furthermore, it is used in neonates, infants and children with congestive heart failure secondary to congenital heart disease (6). The drug is commercially available as film-coated tablets of 25, 50 and 100 mg. but not in liquid or suspension dosage form. Spironolactone is practically insoluble in water and soluble in alcohol. It is less stable in alkaline conditions with maximum stability at pH 4.5. Extemporaneously prepared spironolactone oral liquids, appear to be stable for at least 30 days and usually have a final pH in the range 3.5 - 6.5 (7). To improve stability, or even drug solubility, most of the described spironolactone formulations contain complex vehicle mixtures, including propyleneglycol, glycerine, alcohol and artificial sweeteners, such as saccharin. However, the use of these excipients in the concentrations described is not desirable in infants (8, 9).

2. MATERIALS AND METHODS

2.1 Collection and testing of suspensions

Five major national hospitals in Assir area, South Kingdom of Saudi Arabia were requested to prepare spironolactone suspensions according to physician's order. 500 ml of each sample was supplied in amber bottles and labeled "shake well and refrigerate. Stable for 30 days". The suspensions were then stored at 4°C. On days 0, 7, 14, 21, 28, and 35 the bottles were brought to room temperature and stability of the liquids were assessed by stability studies

2.2 Microbiological stability studies

Immediately after receipt of suspensions (day 0) microbial testing was performed according to the (USP 31/NF 26.. (United States Pharmacopoeia 2008) employing the multiple tube method. Microbial limit testing for detecting levels of contamination with bacteria

and fungi, the presence of the pathogenic bacteria *E. coli* and *Salmonella sp.* will also be tested.

2.3 UV-Spectrophotometer assay

A UV-Spectrophotometric method was developed for the estimation of spironolactone. A dual-beam shimadzu UV-visible spectrophotometer 1601 was used. Freshly prepared 50 % v/v methanol in distilled water was used as solvent. Sample of Spironolactone was purchased from local market.

2.4 Application of proposed procedure for the determination of spironolactone in tablet dosage form

Twenty tablets were taken, and accurately weighed. The tablets were crushed to a fine powder. The powder sample equivalent to 50 mg of spironolactone was transferred to a 100 ml volumetric flask and about 80 ml of 50 % v/v methanol in distilled water was added and sonicated to dissolve. The volume was made up to the mark with 50 % v/v methanol in distilled water. This solution was filtered through whatman filter paper 42. 10 ml of this solution was diluted to 100 ml with 50 % v/v methanol in distilled water. The solutions were analyzed by UV-spectrophotometer. 50 % v/v methanol in distilled water was used as blank.

2.5 PH measurements of Suspensions

The bottles were then thoroughly shaken (30 inversions), and the pH of the samples were determined on each of the above-mentioned days with a pH meter (Metrohm 744 pH meter, Metrohm Co., Switzerland).

2.6 The sedimentation rate

The sedimentation of suspended spironolactone tablet panicles was studied by placing 10 ml of spironolactone suspension from the same batch (Manually shaken for one minute) directly into each of five borosilicate glass tubes with polypropylene screw caps (13 mm in diameter x 100 mm in length) and visually observing the settling process. The sedimentation time that the first visible precipitation was noted on the bottom of the tube and precipitate (height in mm) level after one minute, five minutes, 10 minutes, one hour and six hours were determined.

2.7 Preparation of oral powders and capsules

Spirolactone oral powders and capsules were prepared by mixing five crushed and carefully ground 25mg spironolactone tablets and the geometric amounts of either lactose or microcrystalline cellulose to achieve a final spironolactone concentration of 1.0 mg/unit. Spirolactone tablets were crushed in a mortar with a pestle. Crushed spironolactone tablets and spironolactone drug powder were examined in the scanning electron microscope. The particle size of spironolactone drug powder and crushed Aldactone 25 mg tablet was characterized visually in a scanning electron microscope to obtain information about the properties of the powder mixture and suspension. The resulting powder was divided into portions in powder papers or capsule shells. To prepare oral powders, the powder mixture was individually weighed into portions of 50 mg, 100 mg, 300 mg or 500 mg. The powders were packed in waxed powder papers. While preparing capsules, hard gelatin capsules of sizes 1 (0.50 ml), 3 (0.30 ml) and 4 (0.21ml) were filled with the resulting powder using a hand operated capsule filler.

3. RESULTS

3.1 Stability studies results

3.1.2 The spectrophotometric assay results of spironolactone

Following the spectrophotometric conditions described above in the method. Spirolactone was well separated (Fig-1, 2). Maximum absorbance for spironolactone was found to be at 238 nm. The results for intraday and intraday experiments with a good correlation were obtained and evaluated statistically as demonstrated in (Table 1) and (Table 2). No interfering peaks were found in the chromatogram due to excipients, or other formulation additives or any apparent spironolactone decomposition products. A UV-spectrophotometric method developed for the estimation of spironolactone in tablet dosage form was found to be simple, accurate, precise

and reproducible. Method is based on the estimation of spironolactone in 50 % v/v methanol in distilled water at 238 nm. Beer's law was obeyed in the concentration range of 2-24 μ g/ml. The value of standard deviation was satisfactory and the recovery studies were close to 100%. (Table- 3). Contain summary of the spectrophotometric assay results of the drug in four suspensions (obtained from four major different Saudi hospitals), in addition to results of recoveries after storage at 8°C for five weeks. After 21days, three suspensions (A, B & D) remained stable. With more than 90% of the initial Spirolactone concentrations. After 30 days, two suspensions- (A &D) remained stable. With more than 90% of the initial spironolactone concentrations. The results of the study also, revealed that pH of the suspensions play a major role on the stability of spironolactone. Since the from the result that suspensions B and C have optimum pH for stability of spironolactone appears to be approximately 4.5

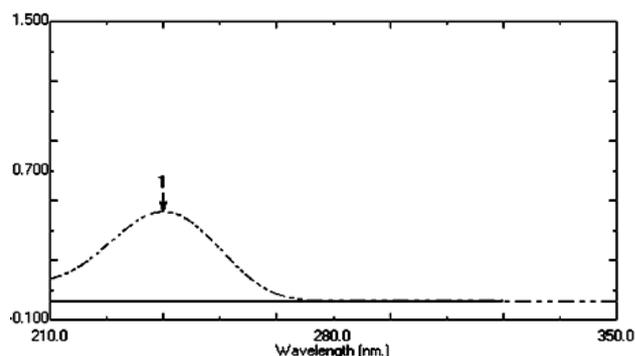


Fig 1: Spectrum picks peak report

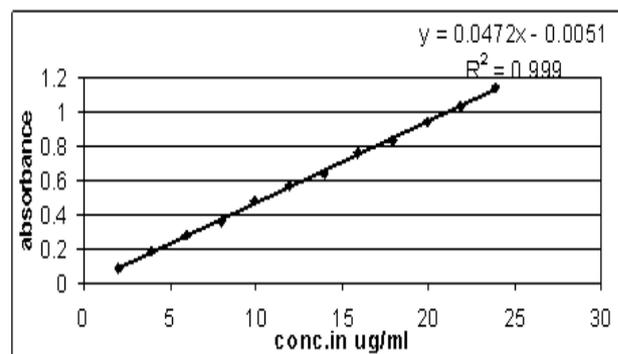
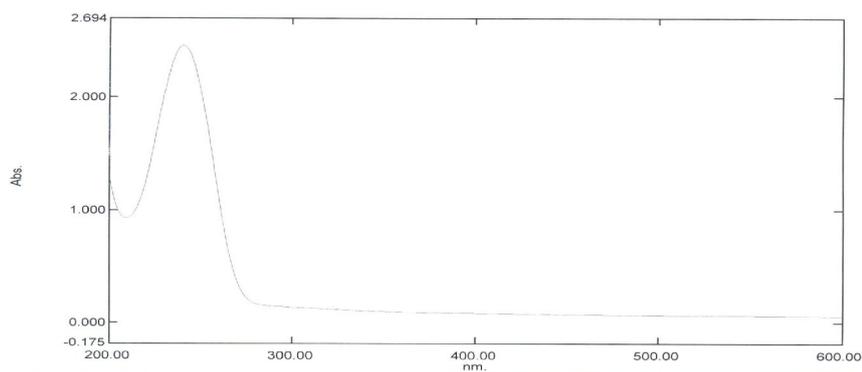


Figure 2: Calibration curve

Spectrum Peak Pick Report

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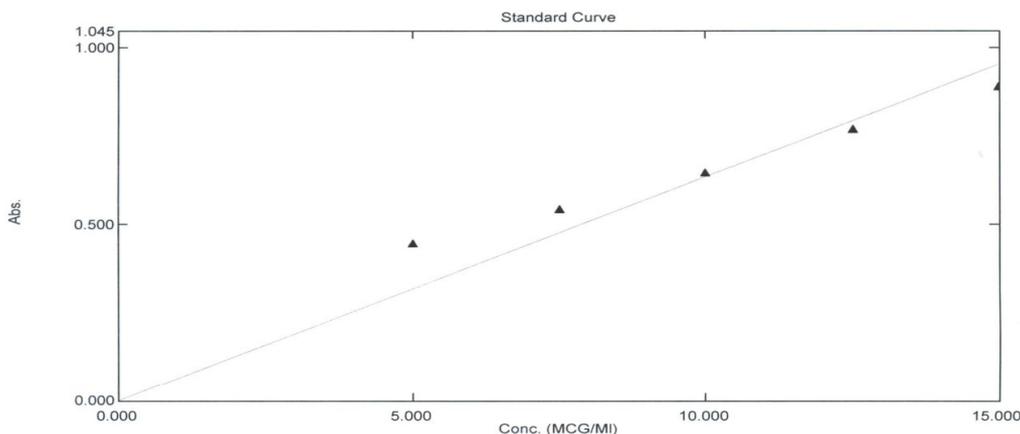
Data Set: SPECTRUM 50 MCG SPIRONOLACTONE - RawData



Standard Table Report

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$y = 0.06340x + 0.00000$
Correlation Coefficient $r^2 = 0.99738$

Sample ID	Type	Ex	Conc	WL240.5	Wgt.Factor	Comments
1	standard 1	Std-Repeat	5.000	0.446	1.000	
2	standard 1-2	Std-Repeat	5.000	0.446	1.000	
3	standard 1-3	Std-Repeat	5.000	0.446	1.000	
4	standard 1-Av	Average	5.000	0.446	1.000	Avg of preceding 3 Samples
5	standard 2	Std-Repeat	7.500	0.541	1.000	
6	standard 2-2	Std-Repeat	7.500	0.541	1.000	
7	standard 2-3	Std-Repeat	7.500	0.541	1.000	
8	standard 2-Av	Average	7.500	0.541	1.000	Avg of preceding 3 Samples
9	standard 3	Std-Repeat	10.000	0.646	1.000	
10	standard 3-2	Std-Repeat	10.000	0.647	1.000	
11	standard 3-3	Std-Repeat	10.000	0.647	1.000	
12	standard 3-Av	Average	10.000	0.647	1.000	Avg of preceding 3 Samples
13	standard 4	Std-Repeat	12.500	0.767	1.000	
14	standard 4-2	Std-Repeat	12.500	0.767	1.000	
15	standard 4-3	Std-Repeat	12.500	0.767	1.000	
16	standard 4-Av	Average	12.500	0.767	1.000	Avg of preceding 3 Samples
17	standard 5	Std-Repeat	15.000	0.886	1.000	
18	standard 5-2	Std-Repeat	15.000	0.888	1.000	

Table 1: Recovery study of spironolactone

S. No	Drug	Initial Conc. (mg/ml)	Reference Std. added (mg/ml)	Conc. after Addition (mg/ml)	Recovery Percentage	Percentage Mean Recovery
1	Aldactone	7.96	4.12	12.16	101.94	100.55 ± 1.27
		7.96	6.18	14.13	99.83	
		7.96	8.14	16.09	99.87	

Table 2: Validation parameters for UV Spectrophotometric method

PARAMETER	OBSERVATION
Specificity	No interference was found with excipients
Linearity (Correlation coefficient r^2)	0.999
Accuracy (% Recovery)	100.55
Precision RSD	
Repeatability (n= 6)	0.72
Intra-day (n=3)	0.77
Inter-day (days=3)	1.14

Table 3: Stability of extemporaneously prepared spironolactone suspensions after storage at 8C°

Code	Label Concentration	Actual Concentration	% conc remainig after					PH
			7 DAYS	14 DAYS	21 DAYS	28 DAYS	35 DAYS	
A	1 mg/ml	101.5±0.02	0.97±0.02	96.4±1.6	91.2±1.6	90.3±1.8	85.5±1.7	4.21
B	1 mg/ml	0.95.9±0.03	0.94±0.03	93.1±1.1	90.2±1.7	79.9±1.0	80.4±0.6	5.58
C	1 mg/ml	0.92.8±0.01	0.90±0.01	88.3±1.6	84.1±1.5	80.0±1.1	69.2±1.3	6.30
D	1 mg/ml	0.92±0.01	0.91.6±0.01	91.6±1.4	90.8±1.5	90.0±0.6	86±0.6	3.99

3.1.3 Sedimentation rate of spironolactone suspensions

In the sedimentation experiments, the mean time for sediments to first appear on the test tube bottom was 7, 15, 8, 8 and 10 minutes for suspensions A, B, C&. D respectively (Table-4). All of the preparations were pourable (A, B.C and D) while only one formula (C) was relatively viscous. Spironolactone suspensions that were made from hypromellose concentrations of 0.5%, 1.0% and 1.5% were more flocculated and easier to redisperse than the other suspensions. Suspensions made from nifedipine drug powder were more difficult to redisperse than the suspensions made from crushed tablets, but the concentrations after mixing were close to each other. As a result, hypromellose 1.0% was selected as a vehicle for suspensions with both drug powders and crushed tablets.

Table 4: Sedimentation rate of the extemporaneously prepared suspensions

Code	Time Precipitate min appear	Level of Precipitate	
		30 min	6 hrs
A	7	2.0	20
B	15	2.5	12
C	8	3.0	09
D	8	2.7	14
E	10	1.9	12

3.1.4 Particle size characteristics of spironolactone drug powders and crushed tablets

Spironolactone drug powder was relatively uniform in particle size whereas crushing of spironolactone tablets produced particles less than 100 µm that differed in size and shape. The particle size, which was less than 100 µm, was about the same particle size of the excipients and thus prevented stratification between large and small particles (Figures 3 and 4).

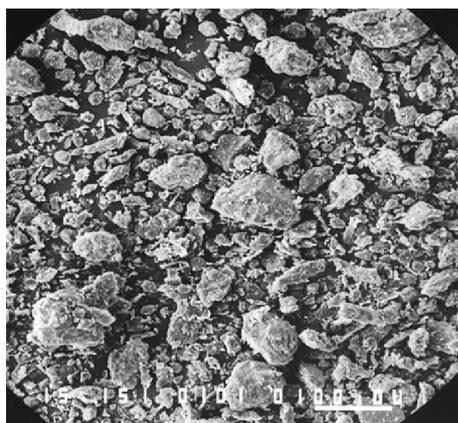


Fig 3: Spironolactone tablet crushed with a mortar and pestle and examined in a scanning electron microscope Scale bar is 100 μm

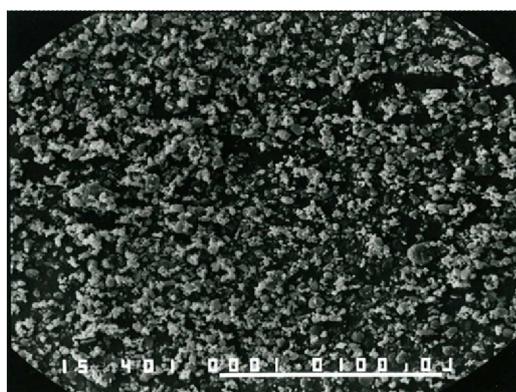


Fig 4: Spironolactone drug powder as viewed in a scanning electron microscope Scale bar is 100 μm .

3.1.4 Content uniformity of spironolactone powders and capsules

The content uniformities of spironolactone powders, capsules and suspensions complied with the test specifications. The mean \pm SD content of spironolactone theoretical content 1.0 mg was 0.92 ± 0.03 mg in powders and 1.06 ± 0.05 mg and 1.09 ± 0.05 mg in spironolactone suspensions made from crushed tablets and drug powders with 1.0% hypromellose, respectively. The largest deviations from the mean content were 4.6% for powders, and 8.5% and 9.2% for suspensions. No remarkable differences were noted between hypromellose concentrations 0.5%, 1.0% and 1.5% or between spironolactone drug powders and crushed tablets. Comparison between the different amounts of lactose monohydrate and

microcrystalline cellulose as excipients in oral powders and capsules indicated that content uniformity remained acceptable although content was reduced down to about 85–90% of the theoretical value. In powders weighing 100 mg and 50 mg, the content was below 80% of the theoretical value both with lactose and microcrystalline cellulose (figure 5). The spironolactone content was over 80% of the theoretical value in small capsules where the amount of the excipients were quite similar. It was noticed that about 8% of the spironolactone amount of 1.0 mg was lost during the preparation and storage of powder papers. About 75% of that was found from the emptied powder papers. Minor amounts were found in the mortar and pestle and the other equipment used.

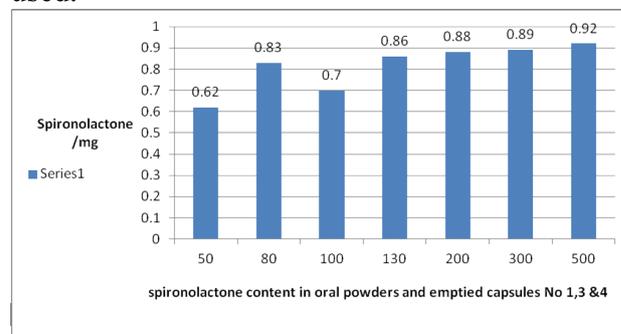


Fig 5: spironolactone content in oral powders and emptied capsules (No.1, 3 & 4)

4. DISCUSSION

4.1. Spironolactone and excipients

It is extensively used in medicine, though until recently it was considered only as potassium-sparing diuretic and antihypertensive drug. It may also reverse aldosterone-induced cardiac fibrosis and improves morbidity and survival of patients with congestive heart failure. Furthermore it is used in neonates, infants and children with congestive heart failure secondary to congenital heart disease. An Spironolactone formulation obtained from crushed solid dosage form may not be bioequivalent with the same dosage form swallowed whole. To administer spironolactone orally to infants, one of the following methods may be used: Crushing the tablets and administering it with food or beverages, Preparation of extemporaneous suspensions, powders or capsules from crushed tablets or drug powder. Splitting of tablets may lead to significant fluctuations in the administered dose. Thus, extemporaneous

suspensions, powders or capsules are the choice to produce Spironolactone drug products to infants. The selection of the appropriate excipients for extemporaneous preparation is the responsibility of the pharmacist. Adverse toxic effects have been reported in paediatric patients due to the use of inappropriate excipients. Properties of the excipients may have also an influence on the uniformity of content and on loss of drug substance during its dispensing. Instead of the preparation of an extemporaneous product, tablet segments are sometimes used. According to our studies, better content uniformity is, however, achieved by extemporaneous preparation of oral solid or liquid dosage forms. Crushing of tablets is a critical point in the powder mass preparation. The grinding time and technique can influence the resulting homogeneity of the powder mixture by affecting the electrostatic properties of the powder. It also has to be noted that particles may become segregated if they need to be stored before dispensing the doses. Thus, an awareness of this problem and professional skills are key factors in preparing extemporaneous medicines of good quality. The ingredients in our spironolactone oral powder and capsule studies were selected because of their flow properties and particle size distribution. Both lactose and microcrystalline cellulose are widely used and safe excipients in solid oral pharmaceutical formulations. The ingredient used in the suspension study, hypromellose, also known as hydroxypropylmethylcellulose, is nonreactive and pH-neutral, and thus assumed to be suitable for neonatal use. While it was appreciated that pure hypromellose as a suspending agent would not to produce an ideal suspension but it was believed that the suspension would be accurate and safe to use also for neonates who have several restrictions on what excipients can be used. Lactose is broken down after hydrolysis by intestinal lactase and absorbed (10). Unabsorbed lactose is converted to lactic acid, carbon dioxide and hydrogen gas by the intestinal flora, and this can acidify the bowel, increase the osmotic load and irritate the colon. The safety of lactose during the neonatal phase is still being debated, as preterm infants have diminished levels of the enzyme lactase (11). Lactase activity increases progressively in the

fetal intestine through the third trimester and approaches its maximum expression at term. Very few preterm neonates born at 28 weeks' gestation and approximately 40% of infants born at 34 weeks' gestation have significant intestinal lactase activity. Lactose is also contraindicated in infants with galactosemia, a rare congenital disorder that results in accumulation of galactose-1-phosphate, resulting in developmental delay, hepatic failure and cataracts (10). No microbiological contamination was observed in any samples and all suspensions pass microbial limit test. The results of the study also revealed that pH of the suspensions play a major role on the stability of spironolactone. And optimum pH for stability of spironolactone appears to be approximately 4.5, accordingly only two suspensions (A&D) which fulfill this requirement remained stable for four weeks. This finding agrees with the studies which reported stability of extemporaneously compounded oral suspensions of cherry syrup (pH 4.5) (12). In contrast those suspensions having pH of more than 5.0 were only stable for up to 3 weeks.

4.2 Content uniformity

Spironolactone suspension, formulated with hypromellose 1.0% solution, remained sufficiently homogenous to permit the removal of the accurate dose after shaking. Our impression was that suspensions made from crushed tablet were easier to redisperse than suspensions made from drug powder, which may be because of the differences in particle size. The particle size in drug powder was smaller than in crushed tablet. That may result in more closely packed sediment.

4.3 Stability

These formulations provided adequate stability of extemporaneously prepared and light-protected spironolactone powders, capsules and suspensions for use in hospitalized patients. The investigated stability of the spironolactone formulations now means that the spironolactone preparations can be stored. The photo degradation of spironolactone was faster in suspensions made from drug powder than in those made from tablets because of light-protective effect of the excipients present in the tablets. One problem arising in stability testing of powder papers, capsules is that the analytical results tend to be more scattered because they

are distinct dosage units rather than the true aliquots encountered with stability studies on drugs in solution. Thus, the uniformity of content has to be ensured

CONCLUSIONS:

The study recommend the need for the availability of drug in optimal dosage forms for administration to pediatric and elderly patients or those who cannot swallow tablets, which should be stable enough during the administration period specified in the container label. This also recommends the great need to conduct stability studies of the drug in such formulations. In routine work, photodecomposition might occur not only during storage but also during preparation and use of the product. To prevent photo degradation, correct handling and storage procedures of spironolactone preparations needs to be taught to nurses, other health care providers, and parents. The study recommend management flow chart and decision pathway to be created for solving the issues encountered in the production of extemporaneous oral preparations in different steps of preparation process. The study recommends alternative dosage form, which should be stable enough during the administration period specified in the container. Oral powders and capsules filled with the powder of crushed tables were stable for up to 6months and were faster to prepare and upon comparing the quality, do represent an alternative to oral liquids. The study suggests that other suspensions made extemporaneously from tablets might exhibit similar trends, and the results obtained from this work can be extended to other formulations made extemporaneously from tablets

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