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Review

Optimizing community effectiveness of antimalarial drugs in malaria-endemic areas of Africa: Issues, challenges, and proposed actions

A. Chika and S. O. Bello

Department of Pharmacology, College of Health Sciences, Usmanu Danfodiyo University, Sokoto, Nigeria.

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Malaria remains a disease of public health concern, which is associated with high mortality and morbidity, particularly in sub-Saharan Africa. This picture is mainly due to low effectiveness of antimalarials at the community level, a scenario caused by different factors related to the availability, quality, and efficacy of antimalarials as well as the degree of the patients' and providers' adherence to evidence-based recommendations about malaria treatment. This review presents an overview of the problem of low community effectiveness of antimalarials in sub-Saharan Africa, with a focus on the various causes as well as potential strategies to combat the problem.

Key words: Antimalarials, sub-Saharan Africa, disease, high mortality and morbidity.

INTRODUCTION

Despite considerable progress in the fight against malaria, the disease remains a global public health problem associated with high morbidity and mortality. According to a recent report of WHO (2014), 90% of all malaria deaths in 2013 (about 528,000 fatalities) occur in the sub-Saharan Africa. Children constitute the worst affected group, with 430,000 deaths (WHO, 2014).

The widespread resistance of *Plasmodium falciparum* to chloroquine and sulfadoxine-pyrimethamine (SP) prompted WHO to recommend artemisinin combination therapy WHO (2001) with the aim of delaying the emergence of resistant parasites. The recommended artemisinin-based combinations include artesunate + SP,

artemether + lumefantrine (AL), artesunate + mefloquine, artesunate + amodiaquine (ASAQ), and dihydroartemisinin + piperazine WHO (2015). The global acceptance of artemisinin-based combination therapies (ACTs) as first-line antimalarial therapy has contributed immensely to the recent global sharp decline not only in malaria deaths (Eisele et al., 2012; Tambo et al., 2012; WHO, 2014), but also in malaria cases (Gosling et al., 2011). These developments occurred partly, because of a reduction in mosquito transmission of malaria infection due to suppression of the development of *P. falciparum* gametocytes by the drugs (Gosling et al., 2011). Non-ACT antimalarials recommended by WHO

*Corresponding author. E-mail: chika.aminu@gmail.com.

include SP for intermittent preventive treatment of malaria in pregnancy (IPTp) in pregnant women and infants as well as parenteral artemisinin monotherapy and quinine for severe malaria WHO (2015).

In the next few years, the most advanced malaria vaccine (RTS,S/AS01) will be available in the market (Penny et al., 2015). However, although useful, the vaccine is only moderately effective (Penny et al., 2015), and therefore, optimizing drug treatment of malaria will remain pivotal to malaria control in the foreseeable future.

It is well known that efficacy of antimalarial drugs in the ideal situation of clinical trials is much higher than their effectiveness under the real-life situation, otherwise known as community effectiveness (Krause and Sauerborn, 2000). For any drug, including antimalarial, to be effective, it has to be of good quality, prescribed in compliance with evidence-based instructions after a correct diagnosis, and taken at an appropriate dosage, for an adequate duration (Krause and Sauerborn, 2000). Accordingly, community effectiveness is determined by drug efficacy, availability, and quality, as well as physicians' adherence and patients' adherence.

The aim of this review is to provide an updated narrative review of systematic reviews on the extent of the problem of suboptimal antimalarial community effectiveness in sub-Saharan Africa (SSA) with emphasis on the causes and possible solutions. Selected recent primary studies will also be cited to illustrate certain points. The results and methodological qualities of the included reviews are summarized in Table 1.

COMMUNITY EFFECTIVENESS OF ANTIMALARIAL DRUGS IN SSA

Community effectiveness of antimalarial agents can be assessed using two measures, namely systems effectiveness (Research, 2011) and effective coverage (Tanahashi, 1978; Shengelia et al., 2005). Systems effectiveness of antimalarials assesses the proportion of the community that gets cured of malaria fever after receiving drugs from formal healthcare centres (Galactionova et al., 2015). On the other hand, effective coverage, which is much wider, assesses the overall proportion of the community who are cured of malaria fever. This measure incorporates cure from self-treatment or medicines obtained from informal healthcare providers in addition to systems effectiveness (Galactionova et al., 2015).

Although artemisin derivatives, the most frequently prescribed antimalarials, are still very effective in SSA; community effectiveness of malaria therapy is currently very low. A recent mathematical modeling based on available data (Galactionova et al., 2015) revealed a high average rate of access to malaria therapy by patients with fever (up to 60%) in the sub-Saharan African region. On the other hand, effective coverage was found to be

low (about 40% on the average) in the region, ranging from 8% in Somalia to 72% in Botswana. A similar pattern was observed in systems effectiveness, which varies from 0.1% in Chad to about 68% in Botswana (Galactionova et al., 2015). The details of the data for other countries are presented in Table 2.

CHALLENGES TO ACHIEVEMENT OF OPTIMAL COMMUNITY EFFECTIVENESS OF ANTIMALARIAL DRUGS IN SSA

1. Delay in adoption of evidence-based international policies on management of malaria. For example, by the end of 2013, intermittent preventive treatment of malaria in infants was adopted by only one country in SSA (Burkina Faso) (WHO, 2014). Similarly, although WHO recommended seasonal malaria chemoprevention to 16 countries in the region, only six (Chad, Congo, Mali, Niger, Senegal, and Togo) have complied so far (WHO, 2014).

2. Poor compliance of the healthcare practitioners with first-line treatment policy: Compliance among healthcare providers represents the worst affected component of community effectiveness, with a median of 28% (Galactionova et al., 2015). This attitude has been shown to lead to antimalarial treatment failure. Countries with a low rate of compliance among healthcare givers have been observed to show a wide difference between access and effective coverage. A good example of this situation is the particular case of Nigeria, a nation with a very high access to antimalarial treatment (84%), but low effective coverage (41%), which is mainly attributable to low compliance (12%) with first-line treatment policy among its health practitioners. On the other hand, few countries, including Uganda, Botswana and Sao Tome and Principe, have high rates of both access to treatment and compliance with their respective first line treatment policies, resulting in high effective coverage (Galactionova et al., 2015). The details are shown in Table 2.

Numerous recent studies in sub-Saharan Africa have reported instances of non-compliance with the recommended national malaria treatment policy. For example, contrary to WHO recommendation, about 40% of individuals suspected to have malaria are not confirmed using laboratory test (WHO, 2014). Accordingly, individuals are still presumptively treated with antimalarials (Ezenduka et al., 2014; Isiguzo et al., 2014; Taberner et al., 2014). Additionally, prescription of ACTs to febrile patients who tested negative for malaria parasites remains common (Hamer et al., 2007; Ndyomugenyi et al., 2007). These two practices may lead to over treatment with ACTs and a possible increase in the risk of emergence of resistance.

In addition, recent reports in SSA have documented

Table 1. Characteristics, limitations and conclusions of the included systematic reviews.

Study characteristic	-	Limitations of the study	Conclusions of the study
Author(s)	Bello et al. (2010)		
Study type	Meta-analysis		
Search period, years	2004-2009		
Number of Articles (included/excluded)	15/46		
Design(s) of included studies	Randomized control trial	A high degree of heterogeneity exists between the included studies. Number of eligible clinical trials was limited and most of the studies were conducted in Western and Eastern regions of Africa.	Artemether-lumfantrine was more effective than artesunate amodiaquine.
Total sample size (included studies/excluded studies)	4265/Not reported		
Geographic area(s)	Africa		
Service/intervention	Comparison of the efficacy of Artesunate-amodiaquine vs. artemether-lumefantrine		
Outcome measures	Day 28 parasitaemia		
Quality of the review (AMSTER/R-AMSTER scores)	8 (72.7%)/29 (65.9%)		
Author(s)	Taberner et al. (2014)		
Study type	Systematic review	No report was found from the majority (61%) of malaria-endemic countries. Few of the reports employed random sampling techniques. Most reports failed to use rigorous chemical analytic methods and experimental procedures.	About 30% of the antimalarial samples tested within the period under study were of poor quality.
Search period, years	1946-2013		
Number of Articles (included/excluded)	251/404		
Design(s) of included studies	<i>In vitro</i> and <i>in vivo</i> studies		
Total sample size (included studies/excluded studies)	9348/Not reported		
Geographic area(s)	Africa, Asia, Middle East, Europe, South America		
Service/intervention	Assay of antimalarial quality	-	-
Outcome measures	Chemical analysis, packaging analysis		
Quality of the review (AMSTER/R-AMSTER scores)	7 (63.6%)/29 (65.9%)		
Author(s)	Banek et al. (2014)		
Study type	Systematic review		
Search period, years	1991-2013		
Number of Articles (included/excluded)	37/51		
Design(s) of included studies	Randomized control trial, Cross sectional study, prospective observational study	A high degree of heterogeneity was found between the studies, thus precluding the use of metaanalysis. The studies varied widely in the methods they used to measure adherence and in their definition of adherence. Most of the studies (28) were not randomized clinical trials. The overall quality of RCTs and cross sectional studies was good, but the methodological quality of the prospective observational studies was weak.	The degree of adherence to ACT varied considerably between different study populations. Across the studies, there was no consistent association between adherence to ACT and demographic characteristics of the patients.
Total sample size (included studies/excluded studies)	17,119/Not reported		
Geographic area(s)	Africa, Asia		
Service/intervention	Evaluation of patient adherence to ACTs		
Outcome measures	Level of patient adherence, determinants of patient adherence to ACTs		
Quality of the review (AMSTER/R-AMSTER scores)	7 (63.6%)/30 (68.2%)		

Table 1. Contd.

Author(s)	Rao et al. (2013)		
Study type	Systematic review		
Search period, years	Not reported		
Number of Articles (included/excluded)	43/NR (10 randomized)		
Design(s) of included studies	Randomized control trial, Cross sectional study, prospective observational study	Most of the included studies (76.7%) were not randomised clinical trials and there was limited information about the participants.	The impact of improving staff training on the success of malaria treatment was below expectation. Greater involvement of informal sector and community health workers showed more promise.
Total sample size (included studies/excluded studies)	Not reported		
Geographic area(s)	Africa		
Service/intervention	Staff training, use of informal sector, use of mobile phones, involvement of community health workers to improve case management of malaria		
Outcome measures	quality of malaria treatment		
Quality of the review (AMSTER/R-AMSTER scores)	1(9.1%)/14(31.8%)		
Author(s)	Fuangchan et al. (2014)		
Study type	Systematic review		
Search period, years	Inception date -2013	-	-
Number of Articles (included/excluded)	16/73		
Design(s) of included studies	Randomized control trial, prospective observational study		
Total sample size (included studies/excluded studies)	9247/Not reported		
Geographic area(s)	Africa, Asia, Oceania	Most of the included studies had poor methodological quality. A high degree of heterogeneity was present between the studies. Various definitions methods of assessing adherence were used in the studies. Majority of the included provided did not provide definition for adherence.	All interventions tend to improve adherence. Combination of visual media/verbal information may hold the greatest potential for improving adherence.
Service/intervention	Community education, convenient regimen, supervision of medication, visual media, combined verbal information and visual media, packaging aids to improve adherence to antimalarials		
Outcome measures	Patient adherence to antimalarials		
Quality of the review (AMSTER/R-AMSTER scores)	8(72.7%)/33(75%)		

poor adherence of health staff to appropriate management of malaria in pregnancy (Mbonye et al., 2013; Hill et al., 2014) and non-implementation of the guidelines on IPTp (Harrison et al., 2013). Frequent prescription of artemisinin monotherapy (Builders et al., 2014; Afriyie et al., 2015; Elmannan et al., 2015; Romay-Barja et al., 2015) and lack of adoption of first-line ACT among healthcare providers in SSA have also been reported (Harrison et al., 2012).

The reported high rate of presumptive treatment

of malaria by physicians in Africa is mainly attributed to lack of trust in the results of laboratory tests (Chandler et al., 2008; Rowe et al., 2009; Kyabayinze et al., 2010). Another factor contributing to poor adherence to guidelines by healthcare providers is insufficient knowledge. For example, Agbo et al. (2012) have reported poor knowledge of treatment guidelines among health staff at primary healthcare centres in Nigeria. Poor knowledge of healthcare providers about IPTp (Diala et al., 2013; Rabiou et al., 2015) and

appropriate treatment of malaria in pregnancy (Rabiou et al., 2015) has also been documented.

3. Poor quality of antimalarial drugs in SSA: A recent review of 251 antimalarial quality reports from some malaria-endemic countries (Taberner et al., 2014) has found out that about 30.1% of the antimalarials sampled were of poor quality, of which 39% were fake. However, the total picture of the problem is far from clear, due to unavailability of data from the majority of the

Table 1. Contd.

Author(s)	Hill et al. (2014)		
Study type	Systematic review and meta-analysis		
Search period, years	2006-2014		
Number of Articles (included/excluded)	37/92		
Design(s) of included studies	Randomized control trial, cross sectional study, longitudinal study	Only one of the included studies was a randomized control trial. There was a high degree of heterogeneity between the studies.	Up to 5 to 40% of women with malaria during pregnancy reported using either traditional healers or self-medication. The included studies consistently showed poor adherence to WHO malaria treatment guidelines and reliance on presumptive treatment among health care providers, especially in first trimester of pregnancy. Barriers to Women's access to standard malaria management were self-treatment habits, lack of knowledge about drug safety and high costs. Determinants of Women's access include education, previous history of antenatal care and miscarriage. Barriers to standard case management practices among health care providers include pressure from patients and concern over cost, availability, safety or side effects of the drug. Determinants of standard practice among providers were the type of health facility (public versus private) and training.
Total sample size (included studies/excluded studies)	16,395/Not reported		
Geographic area(s)	Africa, Asia, Middle East, South America		
Service/intervention	Evaluation of women's access and provider adherence to standard management of malaria in pregnancy		
Outcome measures	Prescription pattern of antimalarial drugs in pregnancy, determinants of standard management of malaria in pregnancy	-	-
Quality of the review (AMSTER/R-AMSTER scores)	9(81.8%)/35(79.5%)		
Author(s)	Yakasai et al. (2015)		
Study type	Systematic review, and meta-analysis		
Search period, years	Inception date-2015		
Number of Articles (included/excluded)	25/42		
Design(s) of included studies	Randomized control trial, Cross sectional study, prospective observational study	Of the included studies, only six were randomized control trials. There was a high degree of heterogeneity between the studies. Factors contributory to the observed heterogeneity were not exhaustibly discussed.	Patient adherence was significantly lower for ACTs procured from private informal sector than for ACTs purchased from public sector. Significant determinants of ACT adherence were high income, education, number of tablets administered, belief in the efficacy of traditional remedy for malaria. The level of adherence to ACT s was not affected by variations in ACT formulations and dosage regimens.
Total sample size (included studies/excluded studies)	8654/Not reported		
Geographic area(s)	Africa, Asia		
Service/intervention	Evaluation of patient adherence to ACTs		
Outcome measures	Level of patient adherence, determinants of patient adherence to ACTs		
Quality of the review (AMSTER/R-AMSTER scores)	7(63.6%)/31(70.5%)		
Author(s)	Karunamoorthi (2014)		
Study type	Systematic review		
Search period, years	1600s-2013		
Number of Articles (included/excluded)	117/159		
Design(s) of included studies	Cross sectional, case control, cohort	A high degree of heterogeneity between the studies (in study designs and target populations) precluded meta-analysis.	About one third of antimalarial drugs in sub-Saharan Africa were fake. Majority of counterfeit antimalarial drug are made in East Asian region, with the major target being the resource- limited developing countries. Inexpensive technologies for detecting fake antimalarial agents hold a great potential for fighting this menace.

Table 1. Contd.

Total sample size (included studies/excluded studies)	Not reported
Geographic area(s)	Africa, Asia, Europe, South America
Service/intervention	Evaluation of extent and impact of the problem of fake and substandard antimalarial drugs.
Outcome measures	Prevalence of fake and substandard antimalarials, clinical, public health and socioeconomic impact of fake antimalarials
Quality of the review (AMSTER/R-AMSTER scores)	6(54.5%)/28(63.6%)

affected nations (60%) as well as the poor methodological quality of most of the studies (Taberner et al., 2014). In SSA, it has been estimated that up to 17% of AL purchased at informal health sectors are of poor quality. On the other hand, the estimated prevalence of fake SP is even much higher, at 33% (Taberner et al., 2014). Most of the fake antimalarials originated in South-east Asia (Newton et al., 2011; Karunamoorthi, 2014). Renschler et al. (2015) estimated that in 2013 over 122,000 under-five children died in SSA from poor quality antimalarials.

The lucrative nature and the perceived low risk (with lenient punishment) associated with the business of making and marketing fake drugs, ineffective law enforcement and drug regulatory agencies as well as corruption are the major factors associated with the continuing existence of the problem in the sub-Saharan African region (Karunamoorthi, 2014; Taberner et al., 2014).

4. Suboptimal effectiveness and resistance to antimalarials: In 2009, the first cases of artemisinin-resistant *P. falciparum* infection were observed in Cambodia (Frenk, 2010) the same region where chloroquine and SP resistance originated before it spread to Africa and other parts of the world. The resistance has been linked to a mutation in the kelch13 gene (gene ID PF3D7_1343700) (Ariey et al., 2014; Mok et al.,

2015; Straimer et al., 2015). Since then, the resistant mutants have spread to other East Asian nations (WHO, 2014), but it is yet to be documented in SSA. However, there are reports of reduced effectiveness of specific ACTs in some parts of African region (Bonnet et al., 2009; Zwang et al., 2009; Group, 2011). The report of a severe case of malaria not responding to artemisinin derivatives observed in a Vietnamese man who returned from Angola is a quite disturbing development (Van Hong et al., 2014).

A meta-analysis by our team suggested that the efficacy of ACTs varies from one country to another (Bello et al., 2010). For example, studies from East African nations, where resistance to amodiaquine is common, suggest the superiority of AL (Table 3). On the other hand, reports from some West African nations (where amodiaquine resistance is low) indicated that ASAQ is non-inferior to AL (Happi et al., 2006; Ndiaye et al., 2009; Faye et al., 2010). Such variation in response to a particular ACT has been reported even from the same country (Bonnet et al., 2009). One disadvantage of the use of ASAQ is the selection of mutants that are resistant to both chloroquine and amodiaquine (Frank et al., 2011; Menard et al., 2012; Van Tyne et al., 2013). It is well-known that amodiaquine undergoes cross-resistance with chloroquine (Happi et al., 2006) and resistance to amodiaquine, just like that of chloroquine, has been associated with mutations

in the *pfprt* and *pfmdr* genes (Djimé et al., 2001; Sidhu et al., 2002). On the other hand, there is evidence suggesting that the use of AL instead of ASAQ (Alifrangis et al., 2009; Mwai et al., 2009) or even the use of concurrent multiple first-line antimalarial therapies (e.g., AL and ASAQ) as practised in some West African countries (Salissou et al., 2014) may confer an advantage in reversing chloroquine resistance.

Due to their reduced host immunity with consequent elevation and recurrence of parasitaemia, malnourished, especially underweight, young children, are found to be less responsive to ACTs and may require a higher dose of artemether (White, 2002; Verret et al., 2011).

5. Poor patients' adherence to antimalarial therapy: According to a recent systematic review and meta-analysis, adherence to ACTs was significantly lower among patients who procured the drugs from patent medicine stores as compared to their counterparts who purchased the medicines from public health centres (Yakasai et al., 2015). The authors suggested that the finding might be due to the fact that patients received less qualitative instructions from patent medicine vendors. Patient adherence to ACTs also varied between different populations (Banek et al., 2014).

Self-medication with antimalarials is also common (Mussa and Gedif, 2013). In sub-Saharan

Table 2. Data on various components of antimalarial community effectiveness for countries in sub-Saharan Africa affected by malaria (Galactinova et al., 2015).

Country	Access to any provider (%)	Access to a formal care provider (%)	Effective coverage (%)	Provider Compliance with first line antimalarial treatment (%)	Patient Adherence (%)	Systems effectiveness (%)
Eastern Africa						
Burundi	65	99.9	42.4	69.6	74.5	21.8
Comoros	63	91.8	39.2	51.5	71	14.7
Djibouti	75.6	97.5	48.6	22	97.5	15.2
Eritrea	44	85.8	25.2	62.9	63.8	9
Ethiopia	25.8	94	16.4	58.9	70.7	7
Kenya	61.8	78.6	37.8	43.9	77.2	12
Madagascar	41.4	79.2	22.4	13	71.3	2.1
Malawi	57.7	84.8	37.7	90.9	73	21.6
Mozambique	59.2	99.5	38.7	63.2	72.1	19
Rwanda	48.4	88.2	41.5	95.7	89.5	31.8
Somalia	13	94	7.8	59	64.6	3
Tanzania	77.3	73.3	46.9	55.9	72.3	15.5
Uganda	84	95.3	67.1	68.6	93.9	47
Zambia	68.8	91.4	52.7	81	83.4	34.7
Zimbabwe	42.9	85.8	27	49.1	75.3	9.9
Middle Africa						
Angola	56.9	98	49.5	77.1	97.6	40.4
Cameroon	54.5	50.4	29.9	26.1	86.8	4.8
CAR	33.9	93.3	18.9	9	69.1	1.3
Chad	50.1	17.4	20.7	3	72.4	0.1
Congo	61.4	74.2	44.1	57	88.3	18.7
CDR	58	78	30.2	4	64.3	0.7
Equatorial Guinea	49	50.4	24	6.7	88.3	1.2
Gabon	67.4	74.8	40.8	35.3	93.1	12.8
Sao Tome and Principe	71.1	97.5	68.8	99.2	97.5	65
Northern Africa						
South Sudan	16	94	9.2	33	61	1.1
Sudan	39.1	72	20.7	8	96.8	3.2
Southern Africa						
Botswana	75.1	97.5	72	99.2	97.5	68.1
Namibia	58.6	95.3	39.6	31	97.1	16
Western Africa						
Benin	63.4	58.2	34.5	32	72.4	5.7
Burkina Faso	60.1	90.5	35.9	24.7	83.9	8.7
Cote d'Ivoire	54.6	62.4	29.2	17.1	80.8	3.5
Gambia	60.8	78.1	40.8	64	79.7	18.2
Ghana	67.5	75.2	43	35	90.7	13.8
Guinea	52.8	66.3	28.4	21.3	72.8	3.7
Guinea-Bissau	52	78.6	29.5	31.6	71.8	6.2
Liberia	76.3	72.6	47.4	69.7	70.3	18.1
Mali	49.9	89.1	29.2	22	78.5	5.8
Mauritania	45	85.8	24.5	6.7	74.7	1.4

Table 2. Contd.

Niger	61.7	47.8	33.1	65.3	64.9	7.1
Nigeria	83.8	41.2	40.9	11.9	83.9	2.6
Senegal	50.4	85.8	34	42.7	89.1	14.2
Sierra Leone	62	83.6	39.3	31	89.3	12.4
Togo	34	76.7	19.8	28	78	4.2

Table 3. Meta-analysis of randomized control trials comparing efficacy of artemether lumefantrine with artesunate+ amodiaquine by country of study (Bello et al., 2010).

Country of study	Statistics					
	Risk ratio	Lower limit	Upper limit	Z-value	P-value	Comment
Angola (1 trial)	1.910	0.362	10.082	0.762	0.446	No significant difference
Benin (1 trial)	1.920	1.013	3.640	1.999	0.046	AL better than ASAQ
Burundi (1 trial)	6.620	0.827	52.980	1.781	0.075	No significant difference
Congo (1 trial)	2.460	1.371	4.414	3.018	0.003	AL better than ASAQ
Ghana (3 trials)	0.600	0.424	0.849	-2.889	0.004	ASAQ better than AL
Nigeria (2 trials)	2.130	1.067	4.250	2.145	0.032	AL better than ASAQ
Senegal (1 trial)	0.580	0.099	3.407	-0.603	0.546	No significant difference
Tanzania (3 trials)	3.260	1.451	7.325	2.861	0.004	AL better than ASAQ
Uganda (2 trials)	1.310	1.112	1.543	3.233	0.001	AL better than ASAQ
Total (15 trials)	1.285	1.124	1.470	3.665	0.000	AL better than ASAQ

Africa, medicine vendors play a role in the delivery of 15 to 85% of child healthcare products. Many of these distributors do not possess an updated licence (Palafox et al., 2014). The availability of a particular antimalarial in these shops is mainly driven by the patients demand and preference rather than the dictation of the national guidelines (Palafox et al., 2014).

Subsidy of antimalarials was first advocated by Gelband et al. (2004). The Affordable Medicines Facility for malaria (AMFm), an initiative aimed at subsidizing the first-line ACTs, was created in 2008 with support from Global Fund (Gelband and Laxminarayan, 2015). However, although ACTs are subsidized or even given free in public health centres in SSA, access to the drugs is limited by frequent stockouts (Palafox et al., 2014). As a consequence, in African countries, non-ACT drugs remain more widely available and less expensive than ACT or artemisinin monotherapy (Rao et al., 2013; Palafox et al., 2014; Lussiana, 2015; Palafox et al., 2015). Accordingly, many patients, being poor and buying drugs from their pockets tend to buy the less expensive non-ACTs.

6. Poor access to antimalarials: It has been documented that up to 15 million pregnant women did not receive malaria prophylaxis in 2013 (WHO, 2014). Multiple studies have identified barriers to optimal utilization of IPTp, including out-of-pocket payments (due to lack of health insurance), lost time, stockouts, the absence of a clear policy and poor knowledge of the providers (Hill et

al., 2013).

STRATEGIES FOR IMPROVING COMMUNITY EFFECTIVENESS OF ANTIMALARIAL DRUGS

Any strategy that can improve the quality or access to recommended antimalarials and increase provider adherence to malaria treatment guidelines, as well as patient adherence to the treatment, can lead to improvement of community effectiveness of the drugs.

Adoption and implementation of policies that will reduce the costs of genuine drugs (e.g., extension of the subsidy of recommended antimalarials to private health sector) will go a long way to making antimalarial counterfeiting business not attractive (Karunamoorthi, 2014). Another strategy that can help in reducing the menace is creation and enforcement of laws designed to severely punish the culprits as well as honor informants who assist in the successful conviction of those found guilty of the crime (WHO, 2005). A recent systematic review has indicated the superior effectiveness of using a multifaceted approach to tackling drug counterfeiting compared to individual interventions (El-Jardali et al., 2015). The problem of substandard and varying batch-to-batch pharmaceutical products maybe reduced through efficient internal and external quality control.

Provider adherence to antimalarial treatment guidelines, including increased implementation of IPTp, has been

shown to improve following enhanced training of healthcare personnel (Mbacham et al., 2014; Mbonye et al., 2014). Also, the common practice of malaria overtreatment with ACTs may be reduced by subsidizing rapid diagnostic tests (Lussiana, 2015).

Similarly, improvement in patient adherence to anti-malarial treatment has been documented with strategies such as community education and a combination of visual media/verbal information (Fuangchan et al., 2014).

Availability of artemisinin-derived products can be optimized by expanding the subsidy to the private sector and increasing the yield of artemisinin from plant origin and supporting the semi-synthetic production of artemisinin (Fuangchan et al., 2014).

Optimal therapy of malaria can also be achieved by variation of the doses of the constituents of ACT. For instance, there is evidence that the use of an optimized fixed dose combination of ASAQ is associated with success in therapy (Sirima et al., 2009; Group, 2015), while loose non-fixed dose formulation is associated with recrudescence at day 28 of therapy (Group, 2015). Systematic reviews revealed the effect of changes in dosing on the efficacy of AL (Dose et al., 2015) and dihydroartemisinin-piperazine (Group, 2013).

The continuing search for an effective alternative to artemisinin derivatives is highly needed due to the imminent threat of the spread of artemisinin resistance from South East Asia to other malaria-endemic nations, especially in SSA. Being a non-lucrative business, development of new drugs for parasitic infections (diseases of underdeveloped nations) is not attractive to pharmaceutical companies (Pink et al., 2005). Drug repositioning-exploration of registered drugs for new indications is a potentially cost-effective strategy for discovery of new interventions against such diseases. Using molecular docking against *P. falciparum* targets, our research team has applied such approach to search for new treatments for malaria with some promising results (Yunusa et al., 2015).

LIMITATIONS TO THE STUDY

There is a large amount of data on the subject area of community effectiveness of antimalarial drugs in sub-Saharan Africa. Therefore, an updated review of systematic reviews on the subject area was conducted citing selected recent primary studies to illustrate some points. A qualitative narrative approach was chosen rather than a quantitative approach to synthesizing the data due to a high degree of heterogeneity of the studies as well as the duplication of many primary studies included in the reviews. One limitation of this approach of reviewing secondary literature was that the quality of the evidence presented in the review depends on the quality of the systematic reviews. Generally, the methodological quality of the reviews was fair and comparable to that found in other reviews of systematic reviews (Burda et

al., 2011).

CONCLUSION

Community effectiveness of antimalarial drugs remains low in sub-Saharan Africa. Although various factors have been documented to contribute to this picture, provider, and patient non adherence to first line treatment is the major factor that plays a key role in the development of the problem. Accordingly, community education and enhanced training of healthcare providers are pivotal in combating the problem.

Abbreviations

ACT, Artemisin-based combination therapy; **AL**, artemether-lumefantrine; **ASAQ**, artesunate + amodiaquine; **IPTp**, intermittent preventive treatment of malaria in pregnancy; **SP**, sulfadoxine-pyrimethamine; **SSA**, sub-Saharan Africa.

Conflict of Interests

The authors have not declared any conflict of interests.

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Full Length Research Paper

Supercritical fluid and pharmaceutical applications. Part I: Process classification

Valquíria Miwa Hanai Yoshida^{1,3*}, Victor Manuel Cardoso Figueiredo Balcão^{1,4}, Marta Maria Duarte Carvalho Vila¹, José Martins Oliveira Júnior², Norberto Aranha², Maria Palmira Daflon Gremião³ and Marco Vinícius Chaud¹

¹LaBNUS – Biomaterials and Nanotechnology Laboratory, University of Sorocaba, Sorocaba/SP, Brazil.

²LaFINAU – Laboratory of Applied Nuclear Physics, University of Sorocaba, Sorocaba/SP, Brazil.

³Pharmaceutical Sciences School of São Paulo State University – UNESP, Araraquara/SP, Brazil.

⁴CEB – Centre of Biological Engineering, University of Minho, Braga, Portugal.

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The supercritical fluid technology has been target of many pharmaceuticals investigations in particles production for almost 35 years. This is due to the great advantages it offers over others technologies currently used for the same purpose. A brief history is presented, as well the classification of supercritical technology based on the role that the supercritical fluid (carbon dioxide) performs in the process.

Key words: Supercritical fluid technology, supercritical carbon dioxide, pharmaceuticals.

INTRODUCTION

Caignard de la Tour (1822) discovered the critical phenomena by observation of natural mineralization. The supercritical fluid technology (SCF) is based on the discovery of this phenomenon. Although the SCF is known since late nineteenth century, the basic concept of rapid expansion of supercritical solutions (RESS) was first described by Hannay and Hogarth (1879), in a study of the solubility of metal chlorides in supercritical ethanol to understand natural mineralization, observed by Caignard de la Tour (1822), in this study the authors reported the great power of SCF solvation. However, was Worthy (1981) whom steered the study of SCF to optimize micromeritic of organic materials difficult to form powders.

For more than one hundred years the broad assortment

of techniques, limitation of the equipment and specific conditions to achieve the supercritical state made an accelerated advancement scientific research difficult (Berche et al., 2009). The concept of SCF technology as said by Jung and Perrut (2001) was better understood and developed after the pioneering work of Krukoni (1984) and, especially, by the disclosure of the Battelle Institute's research (Smith, 1985; Petersen et al., 1986; Matson et al., 1987a, b), they described and modeled flow pattern and nucleation process at supercritical conditions. Since then, many methods using this technology have been published and patented.

A supercritical solvent is one that at a certain temperature and pressure, does not condense or evaporate, it exists as a fluid (Yasuji et al., 2008). This

*Corresponding author. E-mail: valquiria.yoshida@prof.uniso.br. Tel: +55 (15) 21017049. Fax: +55 (15) 21017000.

happens when a substance is high above its critical temperature and pressure, and passes it to a condition called "supercritical fluid state". Under these conditions, the densities of the liquid and vapor are identical, and for this reason the meniscus, on the interface between the two phases, disappears (Moribe et al., 2008).

In SCF conditions, substances exhibit physical properties that are intermediate between gases and liquids of the start material. Thus, the density of a SCF can be altered by the variation of the pressure applied on the fluid. When the fluid is compressed at high temperatures it can have a density varying between those displayed by gases up to typical values of liquids. Likewise, a SCF maintained at a relatively high density has the ability to dissolve a variety of materials, exactly as conventional liquids do, but with the power of gases penetration (Chan and Kwok, 2011).

The use of environmentally more acceptable intermediaries, such as carbon dioxide (CO₂) and water, is an advantage of SCF technology. The SCF most used in pharmaceutical applications is the CO₂, due to its low cost and also because of its supercritical milder condition, which enables the processing of pharmaceuticals and other thermolabile raw materials (DeSimone, 2002).

Increased bioavailability of poorly-soluble molecules, development of modified release systems of drugs, and drug delivery via oral, pulmonary or transdermal - which are less invasive than the parenteral route - are the main objectives of the pharmaceutical industry. These objectives can be achieved by SCF technology which demonstrates dramatic change in the solid morphology after processing, that is, medium-size and particle size distribution, particle shape and porosity, and, consequently, surface area and dissolution rate are often quite different from those of the starting material (Perrut, 2003).

The supercritical CO₂ (SC-CO₂) is easily obtained in critical temperature (T_c) of 304K and critical pressure (p_c) of 7.38 MPa (Yasuji et al., 2008) but there are other substances such as nitrogen, ethanol and water, which also have interesting solvent properties in its supercritical state. However, for reasons of cost, danger of explosion, flammability, toxicity and adverse physical properties (conditions for T_c and p_c too high), these substances are less used commercially (Maul, 1999).

Currently, the SCF technology is an alternative for application in drug release technology, in addition to meeting the principles of green chemistry, who's most accepted definition (Anastas and Warner, 1998) is "the design, development and implementation of chemical processes and products to reduce or eliminate hazardous substances to human health and the environment". This definition has been expanded by Poliakoff et al. (2002) in 12 principles.

The traditional methods for developing drug delivery systems, either in micro or nanoscale, using technologies such as co-precipitation, coacervation and solvent evaporation polymerization, use large amounts of organic

solvents and/or surfactants which, in general, are harmful to the environment (Kawashima et al., 1989; Yoshida et al., 2015). The aforementioned methods used to produce particles which commonly exhibited low rates of drug entrapment and difficulties in scaling, and most often require further treatment to remove solvent(s) and/or impurities from the particles. Although the pharmaceutical industry shows interest in innovative technologies involving production of micro and nanoparticles, the solvent disposal strongly limits the industrial production and generates increased costs (Jung and Perrut, 2001). Hence, the subject of several studies has been about the development of other technologies that minimize the problems related to pollution, toxicity and ease of production scale-up (De Zordi et al., 2012).

PROCESSES IN SCF TECHNOLOGY

The SCF technology can be classified into three broad categories according to the use of the SCF in the process: (i) as solvent, (ii) as antisolvent, and (iii) processes that do not depend on the solvent power of CO₂.

SCF used as solvent

Supercritical carbon dioxide (SC-CO₂) density is extremely sensitive to minor changes in temperature and pressure near the critical point. The density of the SC-CO₂ is closer to that of organic liquids but the solubility of solids can be 3-10 orders of magnitude higher (Motonobu et al., 2008).

The solvent strength of a SC-CO₂ can be expressed by the solubility parameter which is the square root of the cohesive energy density and is defined rigorously from first principles. A plot of the solubility parameter for carbon dioxide versus pressure would resemble that a plot of density versus pressure. This confirms that the solvation strength of a supercritical fluid is directly related to the fluid density. Thus the solubility of a solid can be manipulated by making slight changes in temperatures and pressures. Another attractive feature of SC-CO₂ is that the properties lie between that of gases and liquids. A SC-CO₂ has densities similar to that of liquids, while the viscosities and diffusivities are closer to that of gases. Thus, a SC-CO₂ can diffuse faster in a solid matrix than a liquid, yet possess a solvent strength to extract the solute from the solid matrix.

Rapid expansion of supercritical solutions (RESS)

The RESS process has been extensively investigated and involves two steps, solubilization followed by particles formation (Figure 1a). The fallout of particulate material is obtained by dissolution of the material in the

SCF to form a solution, and then this mixture is expanded and suddenly depressurized. This decompression causes a rapid increase in supersaturation, leading to rapid nucleation and generation of sub-micrometer sized particles (≤ 100 nm) (Reverchon et al., 2000). Changing the process variables, particularly the temperature and pressure of the expansion and the diameter of the nozzle, it is possible to control the average diameter of particles and their size distribution. The advantage of the RESS process is to present valuable commercial-scale applications when the solubility of material or product on SCF (preferably CO_2) is not too small ($\geq 10^{-3}$ kg/kg or mole fraction $> 10^{-4}$). The application of RESS process is limited to the nonpolar compounds or of low polarity (Perrut and Clavier, 2003; Reverchon et al., 2007).

The most commonly used inputs for the development of particulate systems are not sufficiently soluble in SC- CO_2 to make the efficient production process. Thus, it is often necessary to modify the RESS process, as for example, using an organic cosolvent (Sauceau et al., 2004; Chattopadhyay et al., 2007) or a cosolvent solid (Thakur and Gupta, 2006).

Rapid expansion of a supercritical solution into a liquid solvent (RESOLV)

Sun and Rollins (1998); Sun et al., (2000) and Meziani et al. (2005) made a simple but significant modification in the RESS process, using a liquid on the receiving end of the rapid expansion (Figure 1b). This modification was developed for the production of nanoscale particles. It has been shown that the RESOLV is, potentially, a good platform for the nanonization of water-insoluble drugs (Meziani et al., 2005; Sun et al., 2005, 2006). Although both, RESS and RESOLV, appear to involve a process of particle agglomeration, one could argue that the particle growth and aggregation observed in RESOLV should not be necessarily considered as a part of the technique, because they are on a longer time scale after the initial formation of nanoparticles. On the other hand, the growth of particles and aggregation in RESS happens in jet expansion, which differentiates it from the RESOLV process (Sun et al., 2005).

Particularly, the RESOLV process makes use of a liquid to suppress the growth of particle in the jet expansion, making it possible to keep the particles in nanoscale. However, being the nanoparticles produced in suspension, these can lead to clustering and form aggregates. A critical issue in the particles nanonization of drugs through the RESOLV is to initially protect the formed particles of agglomeration using stabilizing agents (Sun et al., 2005).

Rapid expansion from supercritical to aqueous solution (RESAS)

Young et al. (2000, 2003) proposed the RESAS system

(Figure 1c) to overcome the problem in the difficulty of collecting the particles that occurs in the RESS process. From theoretical calculations, the RESS process could form particles as small as 20 to 50 nm. The inability of the RESS process in approaching the theoretical limit is probably related to the growth of particles during collisions in the free jet expansion (Debenedetti, 1994).

To provide stabilization against particle growth resulting from collisions in the jet of expanding, Young et al. (2003) used an aqueous solution containing phospholipid vesicles mixed with non-ionic surfactant to obtain sub-micrometer particles with high drug loading rate.

Rapid expansion of supercritical solution with solid cosolvents (RESS-SC)

The RESS-SC process is divided into three parts, pre-extraction, extraction, and expansion (Figure 1d). In pre-extraction phase, CO_2 is pressurized until the desired pressure. In extraction phase two cylindrical vessels are used as extraction column, one for the solid cosolvent, and one for the drug. Both vessels are kept at a constant extraction temperature and pressure is monitored in this phase. In the expansion phase temperature is controlled to be less than 5°C . A filter of glass wool is used at the end of the expansion chamber output to retain the particles produced in the process (Thakur and Gupta, 2006).

In the RESS-SC process the choice of the solid cosolvent is very important, due to its need in offering interaction to improve polar solute solubility in CO_2 . The solid cosolvent must have the following properties: (i) high vapor pressure enough for easy removal by sublimation; (ii) solid output conditions of nozzles (typically -5 at 25°C); (iii) appreciable solubility in SC- CO_2 ; (iv) non-reactive solute with desired or SC- CO_2 ; (v) non-flammable and non-toxic properties; and (vi) low cost. Menthol is a compound that meets all the requirements of solid cosolvent. Its melting point is 34 to 36°C , with high vapor pressure, good solubility in SC- CO_2 and is widely used in pharmaceutical and food industries (Thakur and Gupta, 2006).

Thakur and Gupta (2006) proposed that the solid cosolvent not only enhances the solubility of polar compounds in SC- CO_2 , but also avoids particle growth by hindering agglomeration. In their work, low solubility and growth by coagulation are addressed by utilizing a cosolvent that is solid at the nozzle exit conditions.

SCF used as antisolvent

Application of SCF as antisolvent is an alternative to the technique of recrystallization to processes insoluble solids in the SCF. This method exploits the ability of gases to dissolve in organic liquids, decreasing the "solvent power" of the solvent for solution components,

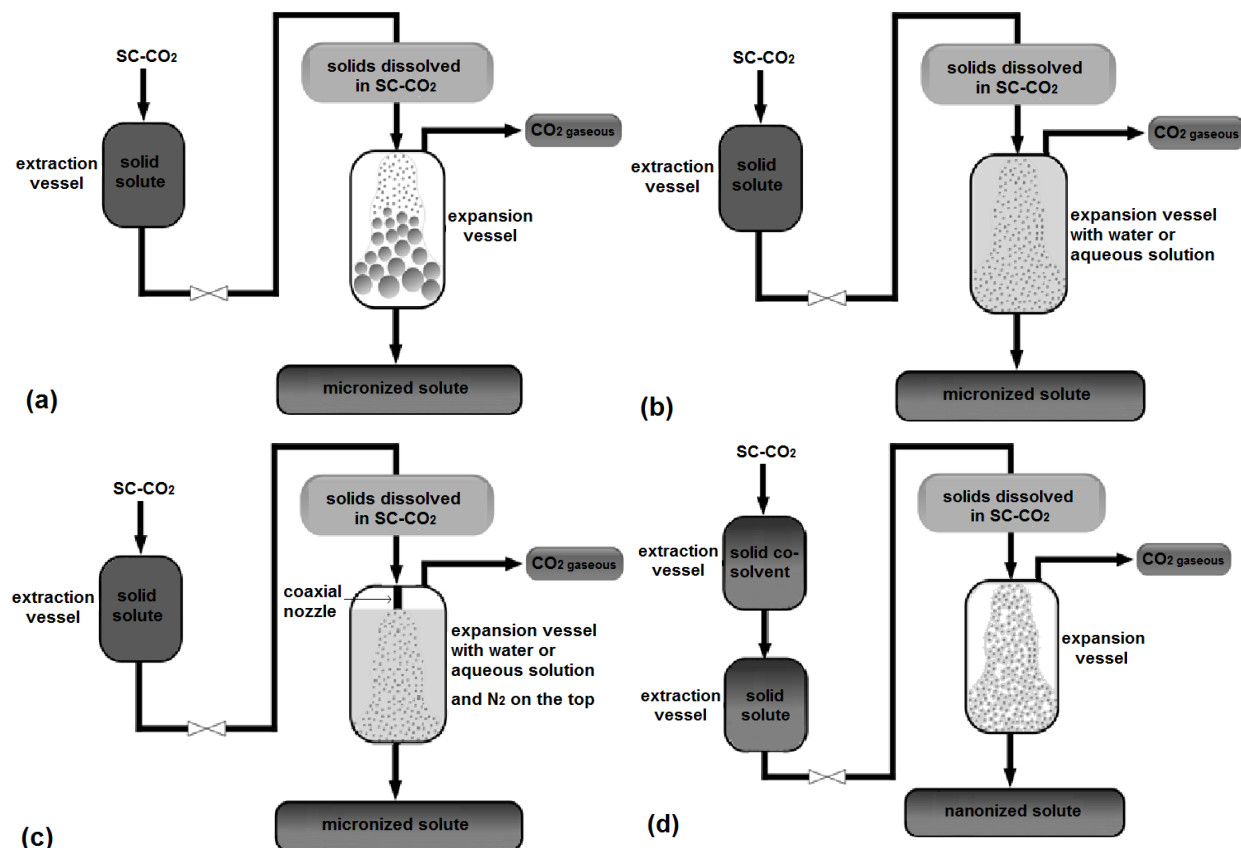


Figure 1. Schematic diagrams of the processes (a) RESS, (b) RESOLV, (c) RESAS, and (d) RESS-SC.

which causes precipitation solutes (Jung and Perrut, 2001; Knez and Weidner, 2003; Perrut et al., 2007). Processes using gas antisolvent differ in how the contact is obtained between the solution and the antisolvent (Jung and Perrut, 2001; Knez and Weidner, 2003).

Supercritical anti-solvent (SAS)

The process named SAS is based on the decrease of the solvent power from a polar organic solvent, in which the substrate(s) of interest (pharmaceutical active ingredient and/or polymer) is/(are) dissolved. The dissolution of the SCF in the solution greatly expands its volume, acting as an antisolvent, which causes the formation of crystallized solutes and precipitation of the substrate of interest. In this way, the SCF is used to extract the solvent of this solution (Jung and Perrut, 2001; De Zordi et al., 2012) (Figure 2a).

The SAS process is easily escalated and has been largely studied due to its potential of micro- and nanoparticles production, with control of the particles size and morphology (Perrut and Clavier, 2003; Shariati and Peters, 2003; Reverchon and Adami, 2006). The procedure is usually carried out at temperatures ranging

between 308 K and 333 K, being useful when thermolabile compounds need to be micronized (Reverchon et al., 2010).

SAS process, with minor changes, is also known as the ASES or PCA. In these techniques, a SCF acts as antisolvent for polymer solutions, such as in the GAS process, but the contact mechanism is different than the one used in the GAS process. The polymer is dissolved in a liquid solvent and the solution is sprayed into a chamber, where an antisolvent already exists, causing rapid contact between the two means. This generates greater reason of solution supersaturation, resulting in rapid growth and nucleation, and consequently, causing smaller particles. A special advantage of this technique is its adaptability to continuous operation, which is important for large-scale production.

Gas anti-solvent (GAS)

The GAS recrystallization process or GASR (Gas Anti-Solvent Recrystallization) was patented by Krukoniš et al. (1994) and was recognized as a solid material recrystallization method from systems composed of solute, suitable liquid solvent, and gaseous component in

soluble solvent, which presence makes the solvent approaches or reaches a supersaturated state, precipitating the solute. The recrystallized material properties can be controlled by the parameters adopted in the process, among them, pressure, temperature, time, and gas injection flow.

The GAS process was originally designed for recrystallizing solid compounds that are soluble in SCF, having its principle based on the solution supersaturation, gas supercritical solution and antisolvent contact-induced. The role of the antisolvent is to reduce the solubility of compounds dissolved in solution and promote breakthrough, nucleation and crystal growth (Sacha et al., 2006).

In the GAS process, after the introduction of the antisolvent gas, the boundaries of the fluid-solid and liquid-liquid phases are shifted, respectively, for higher temperature or higher pressures. As a result, the system was initially a homogeneous phase region that turns into a two-phase region, where it suffers separation, leading to the particles formation. A significant difference between the GAS and RESS processes is that the RESS process works with a binary system of polymer and SCF, while in the GAS process have a ternary system of polymer, organic solvent, and antisolvent gas (Yeo and Kiran, 2005).

The solubility is directly related to the solvent power of a particular solvent for the crystallization compound, which may affect the breakthrough degree and nucleation rate when the antisolvent is added to the solution. The solute solubility in a solvent is determined by the parameters of the solute and solvent physicochemical properties, such as, dipole moment, dielectric constant and solubility coefficient (Park et al., 2006).

Aerosol solvent extraction system (ASES)

Müller and Fischer (1989) patented the ASES process which uses the supercritical gases properties of organic solvent extraction. The CO_{2(t)} is introduced in a cooled condenser and is pumped through a heated high pressure column, the column temperature can be adjusted with another heater and is controlled by a thermostatic cartridge, and pressure in the middle column is regulated by a magnetic valve controlled by a gauge pressure. Under these conditions the CO₂ is expanded in subcritical conditions into the separation container, where it evaporates and is transferred to the condenser, and then is liquefied again (Bleich et al., 1993) (Figure 2b).

During the time of spraying it is possible to work with CO₂ directly in a current or static phase. To produce the drug and polymer microparticles, the drug and polymer are dissolved or dispersed in an organic solvent and sprayed through an atomizing nozzle as fine droplets inside the column with SC-CO₂. The organic solvent is soluble in SC-CO₂, and is extracted, leading to the

microparticles formation. The SCF dissolution in atomized liquid droplets is accompanied by a large expansion in volume and, consequently, a reduction in the liquid solvent power causing supersaturation and formation of microparticles, submicroparticles, and uniform liposomes (Bleich et al., 1993; Yu et al., 2008).

Many variants of the ASES technique were proposed in order to control the particles morphology and size by using special nozzles. The preparation of thin particles for pulmonary administration opens a future for new types of materials engineering. Nanoparticles (50 to 500 nm), microparticles (500 to 5000 nm) or hollow nanoballoons (5 to 50 µm), enabled a significant increase in the bioavailability of poorly water soluble drugs or microspheres preparation with drugs for sustained release (Perrut, 2000; Perrut and Clavier, 2003).

Supercritical solvent impregnation (SSI)

In the SSI process the drug is transported by a SCF and adsorbed onto a porous carrier. The polymers can be impregnated through the dissolution of the drug in SCF and, consequently, resulting in the mixture of the fluid with particles of polymers (Figure 2c). The interest in polymeric material by impregnation SCF stems from the opportunity to use high diffusivity, low surface tension and ease in solvent recovery for preparation of new polymeric materials (Kikic and Vecchione, 2003).

Supercritical anti-solvent with drug excipient mixing (SAS-DEM)

In the SAS-DEM process the drug particles are precipitated in SC-CO₂ within a vessel containing, in addition to the SC-CO₂, particles of excipient (lactose and/or microcrystalline cellulose) in suspended state (in dichloromethane), with or without a surfactant (polaxamer407 or sodium dodecyl sulfate), and under agitation (Sanganwar et al., 2010; Sathigari et al., 2011) (Figure 2d). The SAS-DEM process was effective in overcoming drug-drug particle aggregation (Sanganwar et al., 2010), but the product further undergo aggregation which can be minimized by the addition of surfactant (Sathigari et al., 2011).

Supercritical anti-solvent with enhanced mass transfer (SAS-EM)

The SAS-EM process was proposed (2001) and patented (2003) by Chattopadhyay and Gupta and can be used to fabricate micro- and nanoparticles possessing very narrow size distribution due to the increased mass transfer system (Chattopadhyay and Gupta, 2002).

In the SAS-EM apparatus, an ultrasound field is

generated by the nozzle surface and also provides a velocity component in the normal direction to the buccal surface which significantly increases the turbulence and mixing potential within the supercritical phase (Figure 2e), resulting in a high mass transfer between the solution and the antisolvent. The combined effect of the rapid mixing rate between antisolvent and solution, reduce the solution droplets size due to atomization, providing approximately particles 10 times smaller than those obtained from conventional SAS process (Chattopadhyay and Gupta, 2001, 2003).

Solution enhanced dispersion with supercritical fluid (SEDS)

In SEDS the SCF is used as an antisolvent agent for polymer solutions and dispersing agent. The SEDS process is similar to the semi-continue SAS process, which consists of spraying a solution in condensate gas in a pressurized vessel. However, the design of the nozzle of both proceedings is different. The SEDS nozzle features a coaxial design with a length of mixture, in order to improve the mass transfer and get a simultaneous release of the solution and the antisolvent (York and Hanna, 1996).

The SEDS process is distinguished by three main features: (i) solution and SCF are co-introduced in a jet with high speed, (ii) SCF turbulent flow accelerates mixture and particles formation processes, (iii) solvent composition and SCF material in the jet stream, the precipitation is fixed from the mixture start point, providing conditions for particles formation in uniform and continue procedure (York and Hanna, 1996).

The SEDS process also involves the application of organic solution in SC-CO₂ to precipitate the solute. In this process the CO₂ is liquefied through cooling system and then pumped into the precipitation vessel through the piston pump and heat exchanger of the outdoor coaxial nozzle tubule. Vessel pressure is regulated and when the flow rate, temperature and pressure of SC-CO₂ in the vessel of precipitation reaches the desired values, the drug solution is released into the vessel of precipitation through the inner tubule of the coaxial nozzle (Palakodaty and York, 1999; Edward et al., 2001; Taberero et al., 2012).

In this process, it is important to consider the different theoretical and experimental aspects, such as phases equilibrium, nucleation kinetics, hydrodynamics and mass transfer (Reverchon et al., 2010). It is essential to study the phase behavior of solids-solvent-antisolvent system, in order to determine the conditions under which this mixture lies in a single phase (supercritical phase) or vapor-liquid binary region. In this context, the critical mixing point may be defined as the pressure and temperature conditions at which the vapor-liquid mixture melts in a single supercritical phase (Franceschi et al., 2008).

Atomization of supercritical antisolvent induced suspensions (ASAIS)

In the ASAIS process the SCF is used as antisolvent and dispersion agent. Rodrigues et al. (2011) developed this process, which is a small volume of SAS process characterized by inline dissolution from antisolvent before the liquid atomization for the solvent extraction step. The antisolvent (CO₂) is mixed with a solute solution contained in a small volume mixer, immediately before the hole in the nipple, under such conditions to cause precipitation of the solutes.

The suspension generated is then treated by spray-dried for the separation of solvent. In comparison with other similar techniques of producing particle, this approach allows a more effective control of antisolvent process and reduces the volume of the high-pressure precipitator in several orders of magnitude. The particles of theophylline produced by ASAIS are the polymorph previously obtained by conventional SAS. However, the normal crystalline form (non-polymorphic) is obtained under non-antisolvent conditions (Rodrigues et al., 2011).

Precipitation with a compressed fluid anti-solvents (PCA)

In the PCA process the SCF is used as antisolvent and dispersion agent, being an alternative way for micronization in a single-stage process. Operation is either batchwise or semi-continuous with promising scale-up perspectives and particle sizes ranging from submicron to few microns. The drug is first dissolved in organic solvent and then the solution is sprayed inside, or mixed with, the SC-CO₂ which causes the drug precipitation due to the solvent dissolve in CO₂ (Figure 2f). The operating temperature and pressure are selected so the SCF is totally miscible with the organic solvent (Snaveley et al., 2002).

In order to control the acute phase transition kinetics and produce uniform particle size distribution throughout PCA processing, two conditions must be met. First, there must be uniform conditions within the nucleation medium (that is, can not exist supersaturation gradients). The uniform conditions in the nucleation medium can be performed by a perfect blend of fluid, resulting in a homogeneous level of supersaturation and nucleation rate. Secondly, each formed critical stage should experience the same amount of time for the particles growth. Variations in the particle's permanence time result in a fine particle size distribution, due to different particle growth times after primary nucleation. Mixing settings, used to optimize the gas mixture, allows control over the supersaturation's level and uniformity, providing control of the average residence time and distribution of the particles size (Jarmer et al., 2003).

The design of the nozzle's key feature is the combination of a swirl flow and a chamber micro mix to

optimize the mixture between the solvent and compressed antisolvent gas. PCA nozzles designed to optimize the gas mixture are essentially different from conventional spray nozzles, and enable the production of particles in nano scale PLLA size distribution with a sharper than previously possible (Jarmer et al., 2003) (Figure 2).

Supercritical fluid extraction of emulsions (SFEE)

In the SFEE process the SCF is used as antisolvent and dispersion agent, producing suspension of drug nanoparticles. SFEE technology combines the advantages of using emulsion, which controls the size of the particles and the surface properties, with the continuous extraction process for SCF (Chattopadhyay et al., 2006).

Since the main control parameters are the physical properties of the emulsion, instead of drug characteristics, the development of the formula that will sustain the stable emulsion and ensure the particles' suspension must be preformulated with caution (Yasuji et al., 2008).

Processes that do not depend on the carbon dioxidesolvent power

This category comprises all operations that do not depend on the solvent potency of CO₂, but instead takes advantage of the great volume expansion and cooling effect produced when the CO₂ is depressurized, in operating condition, to the ambient pressure.

The combination of SC-CO₂ technology with other technologies (such as, for example, coacervation and emulsion), as well with equipment for special methods (spray drying, specialised beaks, and freeze drying) could solve the problems for the production of functional particles while having control of involved physicochemical variables (Yasuji et al., 2008).

Particles from gas saturated solutions (PGSS)

In the PGSS process SCF employs the function of co-solute (Nunes and Duarte, 2011), a melted substance is delivered with a pressurized gas in a static mixer (that is, the CO₂ is dissolved in organic solutions or melted compounds) and is expanded through a nozzle of ambient pressure, forming particles from saturated gas solutions (Brunner, 2010).

The PGSS process offers promising prospects of industrial development where the SC-CO₂ is used as a reducing viscosity agent (solute) (Fages et al., 2004) because it is known that an increase in viscosity and an unequal coating material distribution leads to a non-uniform mixing of carrier material and coating material,

resulting in inefficient coating and particles with wide size distribution (Chattopadhyay et al., 2006). The advantages of techniques based especially in SAS and PGSS are the production of spherical nano or microparticles with smooth surfaces and with narrow size distribution (Sheth et al., 2012).

Concentrated powder form (CPF)

The products obtained with the RESS, SAS, and PGSS drying process typically comprise only solid compounds. In 1997, the so-called CPF process was proposed by Weidner et al. (1997; 2001) allowing the generation of dry, free-flowing powders, and containing a very high liquids content. The liquid to be turned into powder comes in contact with a pressurized gas and is expanded through a nozzle. A thin spray of dispersed liquid droplets is formed. A solid support material is blown into the spray through an inert gas. The expanding gas causes a high turbulence area in the case of liquid droplets and solid support material, which are intensely mixed (Weidner, 2009).

The support material is agglomerated by liquid droplets. If the spray tower is high enough, the agglomerated are formed before reaching the bottom or the wall. The clusters can contain up to 90% (w/w) (in some cases, more than liquid % (w/w)). They are continuously removed from the bottom of the spray tower (Weidner, 2009).

The CPF process was applied to more than 100 liquids and approximately 60 different solids vehicles (Grüner et al., 2003). The properties of clusters rely heavily on the support and liquid material properties. The supporting materials ability to take certain amount of fluid depends on its chemical composition and physical properties. The net uptake of transporting materials has been investigated in detail by theoretical and experimental view point (Lankes et al., 2001).

A procedure for selecting suitable support material has been developed by Otto et al. (2001). The density of support material is an adequate quantity parameter to correlate the experiments on the liquid absorption. Highly dispersed silica with a 50 kg.m⁻³ density can connect to more than 90% of the liquid, while the silica, with 200 kg.m⁻³ density, can connect to 60% in mass (Otto et al., 2001).

Other product properties correlated with the process parameters are: (i) Joule–Thomson effect in spray tower; (ii) inert gases are applied without oxygenation in the spray tower, and (iii) selected products (unsaturated fats) versus stability (Grüner-Richter, 2007). In addition to these data, there is lack of knowledge about the processes in the static mixer, drops formation, spray sintering process on spray tower, and behavior of product properties during long-term storage (stress) (Weidner, 2009).

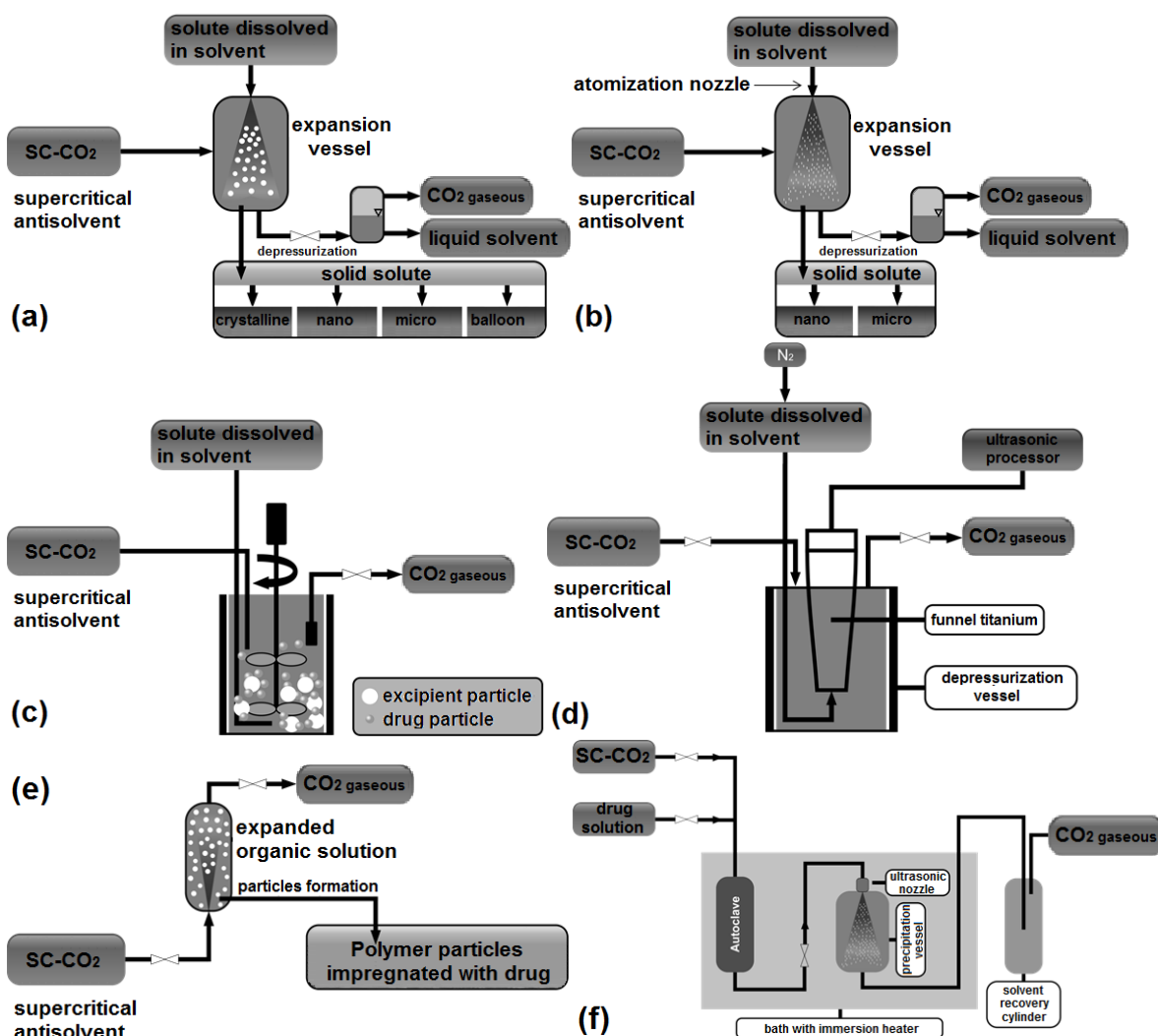


Figure 2. Schematic diagrams of some antisolvent processes (a) SAS, (b) ASES, (c) SSI, (d) SAS-DEM, (e) SAS-EM, and (f) PCA.

Continuous powder coating spraying process (CPCSP)

The CPCSP is another process derived from PGSS and was proposed by Weidner et al. (1999), as an alternative technique for the manufacture of powder coatings (Weidner et al., 2001; Petermann et al., 2003).

The continuously operated process is applicable to low-melting, fast-reacting, and conventional powder coating systems and allows coatings production with improved properties. The process uses the dense gases solubility which has solute-solute in molten coating polymers at pressures up to 220 bar. In separated tanks, the single components of a powder coating mixture are melted and are dosed to a static mixer by means of high-pressure pumps. In the mixer, the melts are homogenized and simultaneously the CO₂ compressed is dissolved. In the sequence of the process this solution is depressurized

over a nozzle into a spray tower. In that way, the melt is atomized into fine droplets and cooled by the expanding gas. The drops solidify and form fine solid particles. The operating parameters on the plant modify particle size, particle size distribution, and powders morphology (Weidner et al., 2001; Petermann et al., 2003).

Supercritical enhanced atomization (SEA)

The SEA technique essentially explored the CO₂ atomization enhancement in a spray drying process and is based on the SCF ability to improve break-up of liquid jets into fine droplets when simultaneously depressurized with liquid solutions (Padrela et al., 2010; Rodrigues et al., 2012). The SCF-assisted atomization is particularly intense, mostly due to the SCFs exhibit high densities and low viscosities, causing a strong increase in the

liquid's momentum and interfacial shear forces (Rodrigues et al., 2012). The atomization of liquid jets assisted by a gas is a classical fluid mechanics process although the use of SCF for this purpose is relatively recent.

Supercritical fluid-assisted atomization (SAA)

The SAA was described by several researchers (Sievers et al., 1998; Sellers et al., 2001; Reverchon et al., 2004) as a process where the SC-CO₂ and a drug solution (in water or organic solvent) are heated separately, mixed into the saturator and then sprayed into the vessel in close conditions to atmospheric pressure at a stream of heated nitrogen to assist liquid droplets evaporation. On SAA apparatus a bottling thermostat contactor is used to obtain a dissolution nearly the equilibrium of SC-CO₂ in liquid solution (Reverchon et al., 2004).

A two-step atomization is achieved: the primary droplets on output injector are still divided into secondary droplets due to expansion SC-CO₂ from the inside of the primary. This process was used to improve the micronization of drugs through SCF, since with the SAS process for extraction some drugs presented unsatisfactory results (Sievers et al., 1998; Reverchon et al., 2004).

Carbon dioxide assisted nebulization with a bubble dryer (CAN-BD)

CAN-BD process originated from the SAA process and was patented by Sievers et al. (2003). This process has been shown to have wide applicability for small molecule, as well as for macromolecule (including therapeutic proteins) by obtaining dry powders with good stability and activity. In addition the dry powders are thin enough to be inhaled and reach the lungs (Cape et al., 2008). In this process, the drug dissolved in water or alcohol (or both) is mixed intimately with almost-critical or supercritical CO₂ for pumping both fluids through a low volume tube in 'T' to generate micro-bubbles and micro-droplets, which are then uncompressed by a low-temperature drying chamber, where aerosol plume is dried in a few seconds. The CO₂ and solution are mixed in the 'T' at room temperature while the micro-bubbles and micro-droplets formed are quickly dried at lower temperatures (25 to 80°C) than are used in the traditional spraying drying processes. The particles residence time inside the drying glass chamber, laboratory-scale of 750 mL, is less than 3 s (Sievers et al., 2001, 2003).

The best advantage of this process is that there is less thermally labile drug decomposition. Secondly, no high pressure vessels are required to proceedings CAN-BD, except for the syringe pump, the 1/16 inch OD stainless steel tube, the 'T' of low volume and flow limiter, which allow the fluid mixture to a moderate pressure (that is,

between 80 and 100 bar), and the micro-bubbles and micro-droplets expansion at atmospheric pressure.

Thirdly, these particles are generally formed in a suitable size distribution for the release in the pulmonary alveoli (Sievers et al., 2003, 2007).

PGSS drying

In a different approach named PGSS drying, which the SCF exerts the co-solute and propellant function, the particles need not be dried through a stream of heated N₂ as in CAN-BD and SAA processes. Instead, the solvent is removed from the spray tower along with the gas, and a free flowing powder precipitates at low temperatures (30 to 60°C) in an inert oxygen-free atmosphere which is particularly important when processing oxidation-sensitive substances (Weinreich et al., 2002; Nunes and Duarte, 2011). Such as in the PGSS process, the liquid solution to drought is intensely mixed with SC-CO₂ using a static mixer at desired temperature and pressure. The mixture is expanded in a nozzle into a spray tower, in which its conditions are adjusted in a method that the solvent is removed together with the gas. Super heating the mixture under pressure promoted adjusts in the spray tower temperature. The post-expansion temperature must at least be higher than the dew point in the gas and solvent binary system. In that case, solvent and gas form a homogeneous phase being removed from the spray tower and fine droplets are formed, due to expansion of CO₂ because atmospheric conditions. In addition, evaporation of residual solvent takes place due to the pre-selected temperature conditions in the spray tower (Weidner, 2009). If mixture as a liquid solvent is used, the equilibrium phase data of multicomponent system are required to determine the appropriate conditions to attain the precipitation (Meterc et al., 2007; 2008).

Depressurization of an expanded liquid organic solution (DELOS)

DELOS is a single-step process, being employed in direct production of micro- or sub micrometer crystalline particles. This method is based on experienced high temperature, and the fast and very evenly decremented mass of an organic solution, previously expanded with a compressed CO₂, when is depressurized. Through the process DELOS, it is possible to achieve the reduction in size of different types of organic compounds that are difficult to spray through conventional techniques, according to the Ventosa et al. (2001). This process, patented by Ventosa et al. (2002), in which the SCF act as cosolvent being completely miscible, at a given pressure and temperature, with the organic solution of the solute to be crystallized. According to authors, the role of the SCF is to produce a homogenous sub cooling of the solution with the precipitation of solid particles.

Table 1. Pharmaceutical applications of SCF.SCF category, process name, organic solvent use, process type, critical factors in the process, and type of produced particles.

SCF category	Process name	Organic solvent	Process type	Critical factors*	Type of produced particles	References
Solvent	RESS	No	Continue	a, b, c, d	Micro or nanoparticles and compound particles	Krukonic (1984), Türk et al. (2002) [¶]
	RESOLV	No	Continue	a, b, c, d, f	Nanoparticles	Meterc et al. (2008) [¶]
	RESAS	No	Continue	a, b, c	Nanoparticles	Young et al. (2000; 2003) [¶]
	RESS-SC or CSS	No	Discontinue	a, b, c, h, i	Nanoparticles	Thakur and Gupta (2006) [¶]
Anti-solvent	SAS	Yes	Semi-continue	a, e, i, j	Micro ou nanoparticlesandcompoundparticles	Yeo et al. (1993), Reverchon et al. (2003) [¶]
	GAS	Yes	Discontinue	a, e, i, j	Micro or nanoparticles and compound particles	Warwick et al. (2000) [¶]
	ASES	Yes	Semi-continue	a, b, c, e, i, j	Micro or nanoparticles and compound particles	Bleich et al. (1993), Kunastitchai et al. (2006) [¶]
	SSI	Yes	Discontinue	a, b, c, e, h, i	Polymer particles impregnated with drug	Kikic and Vecchione (2003) [¶]
	SAS-DEM	Yes	Semi-continue	a, i, e, j, m	Micro or nanocompound particles	Sanganwar et al. (2010), Sathigari et al. (2011) [¶]
	SAS-EM	Yes	Semi-continue	b, e, f, j	Nanoparticles and compound particles	Chattopadhyay and Gupta (2001; 2002) [¶]
	SEDS	Yes	Semi-continue	a, b, c, e, i, j	Microparticles and compound particles	Yorkand Hanna (1996) [¶]
	ASAIS	Yes	Semi-continue	a, c, e, i, j	Microparticles and compound particles	Rodrigues et al. (2011) [¶]
	PCA	Yes	Continue	b, e, j	Micro or nanoparticles and compound particles	Snavely et al. (2002) [¶]
SFEE	Yes	Continue	a, e, f, i, j	Microparticles and compound particles	Yasuji et al. (2008) [¶]	
Other	PGSS	No	Continue or Discontinue	c, n	Micro or nanoparticles and compound particles	Wendt (2007) [¶]
	CPF	Yes	Continue	b, e, f, j	Dried powders, free flowing and of high liquid content	Petermann et al. (2001), Weinreich et al. (2002) [¶]
	CPCSP	No	Continue or Discontinue	a, b, c, i, j, o	Coated powders	Weidner et al. (2001) [¶]
	CAN-BD	Water and/or alcohol	Continue	a, b, c, e	Nanoparticles and compound particles	Sievers et al. (2003) [¶]
	SAA	Yes	Continue	a, c, e, i, j, n, o	Microparticles and compound particles	Reverchon (2007) [¶]
	SEA	No	Continue	a, c, i, j	Microparticlesandcompoundparticles	Padrela et al. (2010) [¶]
	PGSS <i>drying</i>	Yes	Continue	a, e, f, l, o	Microparticles	Meterc et al. (2007) [¶]
DELOS	Yes	Discontinue	a, b, c, d, e, h, i	Micro or nanoparticles	Ventosa et al. (2001) [¶]	

*FSC factors for particles production: (a) material solubility on FSC, (b) pre-expansion condition, (c) spray device, (d) particulate material aggregation, (e) co-solvent type, (f) choice of plasticizer, (g) diffusion propriety, (h) eutectic propriety, (i) solvent extraction, (j) mass transfer, (l) viscosity, (m) properties of the carrier material and liquid, (n) liquid solution concentration, (o) choice of temperature.

The DELOS process includes three steps: (i) dissolution of the solute to be crystallized in conventional organic solvent, at atmospheric pressure and room temperature to form concentrated solution of solute, which is below the saturation limit. (ii) addition of CO₂ in the organic solution to obtain an volumetric expanded liquid solution at high working temperature and pressure. The solute concentration in this step must remain below

the limit of saturation in the mixture expanded on conventional solvent and CO₂ (iii) rapid reduction of the expanded solution pressure, from the atmospheric pressure through a check valve (Ventosa et al., 2001; 2002). During depressurization process, the CO₂ evaporation from the expanded solution takes place producing a significant volume decrease, in a fast and extremely homogeneous temperature of the solution up

to the final temperature. As a result, a sharp and homogeneous increase of supersaturation ratio over the entire solution takes place and the phenomenon of catastrophic nucleation occurs causing the precipitation of submicron or micron sized crystalline particles with a narrow particle size distribution (Ventosa et al., 2001, 2002).

Table 1 shows the classification of SCF technology, in which is described the process

type of SCF, SCF process critical factors for the production of particles and possible type of particles that can be produced.

CONCLUSION

There are two basic approaches, RESS and SAS techniques, for the production of pharmaceutical micro or nanoparticles by the SCF technology, where the SCF acts as solvent or anti-solvent in the RESS and SAS processes, respectively. Changing the RESS process, particularly modifying the contents of the receiving end vessel, increasing the number of expander vessels in the process or others modifications which increases mass-transfer rate, it is possible to create a new process. However, in many cases, the SAS process is the most suitable because it does not require that the solute is soluble in the SCF as required by the RESS technique. The SAS process received incremented technological innovations generating derivatives processes, especially modifying the atomization efficiency. The SCF technology in the pharmaceuticals application process cannot depend on the SCF solvent power, but other factors, such as the volume expansion or association with other technologies, give rise to new processes. After witnessing a steady growth of this technology over the last 35 years, it is expected in a near future for major investments to happen in facilities related to the production and also the development of other innovative applications, interestingly not only for the pharmaceutical industries but also for the academia.

Conflict of Interests

The authors have not declared any conflict of interests.

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Full Length Research Paper

Did drug availability in Malawian central hospitals improve after the conversion of central medical stores to a trust?

Felix Khuluza*, Precious Kadammanja, Collins Simango and Mirriam Mukhuna

Pharmacy Department, College of Medicine, University of Malawi, Private Bag 360, Blantyre 3, Malawi.

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Malawian public hospitals have reportedly been experiencing a lot of shortages in medicines and medical supplies in recent years. This was at least in part, attributed to the traditional placement of the drug supply system under the Ministry of Health, and therefore a change in the organizational set-up was implemented in 2011. This study aimed at finding out if the availability of medicines in central hospitals in Malawi improved after the change of Central Medical Stores (CMS) to a Trust (CMST). A retrospective cohort study was done to quantify the availability of selected essential medicines before and after the change of CMS from stock cards. A questionnaire was filled by 23 health professionals to assess their views on whether the change of CMST resulted in improved availability of medicines. The study was done at Queen Elizabeth Central Hospital (QECH), Kamuzu Central Hospital (KCH) and Central Medical Store Trust. The targeted study period was before the change of CMS (2010/2011) and after (2013/2014) the change to CMST. The results of the study showed considerable reduction in stock-out days for both KCH and the CMST (from an average of 80 and 16 days to 42 and 9 days, respectively), with CMST results being statistically significant ($p=0.023$). However, in QECH, there was no improvement (from 22 to 24 days). The view of most respondents was that there was no improvement in medicine availability after the change of CMS, which represented a certain contradiction to the results of the quantitative part. This may be attributed to the fact that the questionnaire targeted only participants from QECH and KCH and left out participants from CMST. The study indicated that the radical shift in the management of CMS was followed by an improvement of drug availability in CMST itself, and in one of the two investigated hospitals. The non-improvement in drug availability in hospitals calls for further investigation in the future to understand the reasons for this.

Key words: Central medical stores, Malawi, medicine availability, essential medicine, autonomous supply agency, pharmaceutical logistics, supply chain.

INTRODUCTION

The lack of access to essential medicines in developing countries is one of the most pressing global health issues

*Corresponding author. E-mail: fkhuluza@medcol.mw, fkhuluza@cartafrica.org. Tel: +265 999289874.

and had an effect on the achievement of Millennium Development Goals (MDG). Also, the change of MDG to the Sustainable Development Goals (SDG) would be meaningless if lack of essential medicines in low income countries is not solved (UN Millennium Project, 2005; Ministry of Health-Malawi, 2009). Many low-income countries are still facing acute shortages of essential medicines because of the limited supply of affordable medicines and inadequate logistical systems to deliver them, and a continuing shortage of new products to meet developing country's health needs. As such, efficient medicine logistic and supply management is viewed as the key strategy in reducing costs of drugs and ensuring their availability in the healthcare facilities (WHO June, 2004).

Essential medicines are those medicines that satisfy the priority health care needs of the majority of the population (Baumgarten et al., 2011; Gyimah et al., 2009). They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost-effectiveness ("WHO Model List of Essential Medicines," 2013). Since 1977, the World Health Organization (WHO) has published a model list of essential medicines, and Malawi created its own Essential Medicines List in 1987. Since then, Malawi has revised its list of essential medicines, approximately every five years.

Essential medicines are provided to the people of Malawi free of charge at all public health facilities, and at a heavily subsidized fee in Christian affiliated hospitals. This is due to the fact that majority of Malawians are poor, and the World Bank has consistently ranked Malawi as one of the ten poorest countries in the world in the last ten years (International Fund for Agricultural Development, 2011; Index Mundi, 2015). Because of the extreme poverty in the country, thus 53% of the population is below poverty line (Index Mundi, 2015); it becomes very difficult for majority of households to pay for the health services. Thus, the government of Malawi provided the free essential medical service to the public which includes free medicines.

In trying to provide free medicines and medical supplies, the Malawi government established in 1968 a centralized facility (Central Medical Stores-CMS) to procure medicines and medical supplies for the country's public sector, for the Christian Health Association of Malawi (CHAM) institutions and some private non-profit health institutions (Supply Chain Management Assistance in Malawi, 2011; Department for International Development-DfID UK, 2011). At that time, this was the most common approach to getting medicines at a fair price for the population, and is sometimes referred to as a traditional CMS.

The main objectives of a traditional CMS are warehousing, procurement, and distribution operations of pharmaceuticals which are to be done under full government control (as owners and executors). In contrast,

an autonomous supply agency emerged due to the failures of the traditional CMS, and this differs from the traditional CMS in that the management responsibility for the CMS rests on an autonomous or semi-autonomous board (Govindaraj and Herbst, 2010; Ministry of Health Tanzania, 2008; Watson and McCord 2013; Wright et al, 2013). Until August 2011, the procurement of drugs in Malawi was done by CMS using the 'traditional CMS model' approach. However, there have been widespread documented evidence of stock-outs of drugs in public hospitals, often being attributed to the failure of the traditional CMS approach (Chandani et al., 2012; Chirwa et al, 2013; Lufesi et al., 2007; Wright et al., 2013). Because of the failure of the traditional role, the CMS in Malawi was converted to a Central Medical Stores Trust (CMST) in 2011. This was done to reduce the government control of CMS which was seen as being a cause of inefficiencies. It was hoped that an autonomous CMST would improve drug availability to the public health system of Malawi.

The organizational change from central medical stores to a trust meant that management responsibility for the CMS now began to rests on an autonomous or semi-autonomous board (Alternative Public Health Supply Chains, 2013). The system which Malawi adopted in the pharmaceutical supply chain is also used in other countries for example, Tanzania, Cameroon, Burkina Faso and Senegal with mixed results (Govindaraj and Herbst, 2010; Gyimah et al., 2009; Tanzania, 2008). The procurement system in Tanzania has improved greatly as compared to the traditional CMS that was used before the change to the semi-autonomous approach of CMS.

So far, no research has been conducted to assess the performance of CMST in Malawi. However, also after the change of CMS to a Trust (CMST), there have been newspaper reports on frequent stock-outs of medicines in the country (Malawi News Agency, 2013a,b; 2014; Masina, 2013; Mphande, 2014; Department for International Development-DfID UK, 2011). Thus, the present study was aimed at assessing whether drug availability improved in the health facilities in Malawi after the change of CMS to a Trust, and assessing the perceptions of health professionals on the performance of CMST. Further, the study investigated whether the media reports on stock-out of medicine (Malawi News Agencies of, August 2013, November 2013 and September 2014) were true or an exaggeration.

METHODOLOGY

Study sites

The study was conducted at the two largest tertiary hospitals in Malawi and the Central Medical Stores Trust which supplies the hospitals, QECH and KCH, which are also teaching hospitals for both undergraduate and postgraduate medical and allied health professional. The study population and area included CMST, QECH and KCH's drug stock records/cards, and health care workers from QECH and KCH.

Study design

A retrospective cohort study, for a period of 1st July 2010-30th June 2011 and 1st July 2013-30th June 2014, was used to describe whether the change of CMS to CMST was followed by an improvement of drug availability, by looking at the stock card of selected essential medicines, and to get the perceptions of health personnel towards the performance of the CMST.

Sampling

A total of 24 essential drugs were selected from the Malawi Essential Medicine List (MEML) 2009 and grouped into antibiotics/antimicrobial drugs (amoxicillin capsule/tablet 250 mg, ceftriaxone PFR-injection 2 g, ciprofloxacin tablet 250 mg, erythromycin tablet 250 mg, gentamicin ampoules 80 mg, and metronidazole tablet 200 mg); analgesics (aspirin tablet 300 mg, carbamazepine tablet 200 mg, paracetamol tablet 500 mg, ketamine vial and pethidine ampoules); antidiabetic drugs (glibenclamide tablet 5 mg, Insulin Lente vials 10 mL, insulin soluble vials 10 ml, and metformin tablet 500 mg); antihypertensive drugs (hydrochlorothiazide tablet 25 mg, furosemide tablet 40 mg, nifedipine tablet 10 mg and propranolol tablet 40 mg); and others (chlorpheniramine tablet 4 mg, cimetidine tablet 200 mg, phenobarbitone tablet 30 mg, promethazine tablet 25 mg and Salbutamol inhaler). All stock cards of a selected list of drugs years before CMST changed (2010/2011) to a trust and after it changed (2013/2014) were included. For self-administered questionnaire, a total of 58 participants were selected from the staff of QECH and KCH using inclusion criterion. The inclusion criterion for this part was all health professionals that have worked for 5 years or more in the Malawian government health service, specifically at the facility (either KCH or QECH). This ensured that the respondents had personal experience on pharmaceutical supply services before the change from CMS to CMST.

Data collection

The study was conducted from January 2014 to May 2015. Stock cards of 24 selected medicines were used to obtain the information on the availability of essential medicines for quantitative part. The period of stock-outs was determined from the stock cards by checking the number of days the medicines were out for the period 1st July 2010-30th June 2011 and 1st July 2013-30th June 2014.

Data analysis

Data was entered into excel and analysed using SPSS version 22, paired sample correlations and statistics was used to measure associations.

Ethical consideration

College of Medicine Research and Ethics Committee (COMREC) approved the study protocol. Further permission was obtained from the medical directors in the hospitals and the responsible authorities at CMST before conducting the study. For the sake of confidentiality, names were not recorded but codes were used for identification of interviewed persons.

RESULTS

The number of days at which a particular drug was out of

stock were calculated from the stock cards of the selected drugs by counting the number of days when the drug was out of stock for the entire period. Table 1 shows the number of days when individual drugs were out of stock before and after the change (Table 1). The overall results showed an improvement of drug availability at both the CMST and KCH after the change from CMS to a Trust. In contrast, for QECH there was no improvement for the time period. Detailed analysis of the different categories of drugs for QECH showed an improvement in availability for analgesics (from 85 stock-out days to 3 days) and anti-diabetics (from 29 stock-out days to 3 days) while there was a decrease in the availability of antimicrobials (from 102 stock-out days to 284) and anti-hypertensives (from 62 stock-out days to 127). Notably, in QECH no stock-outs were recorded for ciprofloxacin and metronidazole before the change, while after the change, the recorded stock-out days were 230 and 42, respectively.

On average, stock-out days in CMST decreased from 80 to 42 days, corresponding to a reduction of 47% and was statistically significant ($p=0.029$). Stock-out days in KCH reduced from 16 to 10 days, corresponding to a reduction of 41% but was not statistically significant ($p\text{-value}=0.173$). In contrast, stock-out days in QECH increased from 22 to 24 days, with an increase of 9% $p\text{-value}$ of 0.733.

Perceptions of health professionals on the performance of CMST

Out of 58 study participants whom were asked to fill a questionnaire, only 23 (representing 40%) filled and returned the questionnaire. There was equal distribution of responses from both hospital (12 from KCH and 11 from QECH). The number of years the health professionals had worked at each health facility ranged from 5 to 30 with most of them having worked for at least 7 years in their respective hospitals.

All 23 respondents knew the functions and mandates of Central Medical Stores Trust. On the change of CMS to a Trust (CMST), 87% knew about the change unlike the 13% who still thought it was fully under government control. 26.1% of respondent believed that there was an improvement in drug supply to the hospitals from CMST, 69.6% saw no improvement and 4.3% was neutral. With reference to different categories of drugs, the majority of the health professionals were of the opinion that the availability of TB drugs, anti-malarial and anti-retroviral drugs (ART drugs) had improved. However, they said that the availability of analgesics, anti-hypertensives and antibiotics has not improved.

DISCUSSION

The results showed a strong decrease in stock-out days for CMST after the change (from an average of 82 days

Table 1. Total number of days when drugs were out of stock.

Drug name	Central Medical Stores Trust		Kamuzu Central Hospital		Queen Elizabeth Central Hospital	
	Before change	After change	Before change	After change	Before change	After change
Antibiotics						
Amoxicillin	45	36	0	0	15	3
Ciprofloxacin	21	36	0	0	0	230
Erythromycin	150	36	0	0	72	0
Ceftriaxone	50	36	52	0	0	9
Gentamycin	102	36	4	0	15	0
Metronidazole	47	36	0	5	0	42
Analgesics and sedatives						
Aspirin	20	5	0	0	2	0
Carbamazepine	150	39	85	9	4	3
Furosemide	40	46	40	0	1	122
Ketamine	75	0	0	0	56	0
Lignocaine	141	10	50	21	99	43
Paracetamol	36	0	0	0	23	0
Pethidine	0	0	0	0	0	0
Phenobarbitone	110	84	0	3	35	29
Antihypertensive						
Hydrochlorothiazide	36	5	0	0	19	0
Nifedipine	40	218	158	101	24	5
Propranolol	183	150	2	50	18	0
Antidiabetics						
Metformin	251	0	50	25	19	0
Insulin Lente	30	55	0	39	0	0
Insulin Soluble	26	47	1	0	10	0
Glibenclamide	80	0	0	0	0	3
Others						
Chlorpheniramine	15	20	0	0	17	0
Cimetidine	314	0	0	0	91	90
Promethazine	35	16	0	0	94	0
Salbutamol Inhaler	70	118	0	0	20	46
Average stock-out days	80.25	42.46	16.33	9.67	22.29	24.25

to an average of 42 days stock out days per drug per year) which was statistically significant. The results are similar to findings by Wiedenmayer (2000) which showed an improvement in drug availability and performance of CMS in Tanzania after changing the management, supply monitoring and documentation of the institution. Using multidisciplinary training and procurement policy changes, the Association of Central Medical Stores for Essential Drugs (French acronym, ACAME) improved the performance of national CMSs in many Francophone African countries (Govindaraj et al., 2010). A study by

Millot (2006) on three countries- Senegal, Cameroon and Burundi also demonstrated improvements in efficiency-related outcomes, especially service quality and inventory availability after strengthening the CMS (Millot, 2006). Improvements service quality and inventory availability was attributed to the autonomous nature of the CMS which resulted in improved management decision-making, increased accountability and transparency (Millot, 2006). It is suggest that the improvement in availability of drugs (shown by reduction in stock-out days) at CMST, Malawi, may at least in part be attributable

to the change of control from solely government control to an autonomous agent-trust. This gives credence to published literature which supports the beneficiary effect of changing the roles of a 'traditional' CMS to improve its performance (Govindaraj and Herbst, 2010; Gyimah et al., 2009; Millot, 2006).

However, the improvement in drug supply at CMST did not translate to massive improvement in drug availability at the two referral/central hospitals. The results from the two central hospitals were mixed. The results from KCH showed an improvement in drug availability (reduction of stock out days from an average of 16.33 to 9.67 days) while for QECH, there was no improvement. Of special interest is that while data from CMST showed an improvement in drug availability especially for the antimicrobial agents, the results of QECH showed the opposite.

The results may be partly attributed to insufficient number of trained personnel as the pharmacist training in Malawi started in 2006, with few intake of graduates. The baseline drug stock-out at QECH was higher than at KCH as such, may have contributed to the disparity in drug availability between the two hospitals. 70% of the interviewed health workers stated that there was no improvement in the operation of CMST. This is in accordance with data from QECH, but not from KCH. The improvement of drug availability in CMST, recorded in our study, cannot be directly noticed by the health workers, who received their medicines through the hospital pharmacies. This may be attributed to the nature of prepared self-administered questionnaire. If the study had used an interview guide and directly interviewed the participants, the findings could have been different. At the same time, using collecting data on drug availability and questionnaire at the same time, will strength this study as the respondents were not influenced by prior results of drug availability, and hence the inconsistency in their response.

Majority of the health professionals stated that, especially, the availability TB drugs, anti-malarial and the ARV's had improved, unlike some other drug categories. However, this improvement may not be attributable to the change from CMS to CMST. In Malawi, there are vertical supply programs for donor funded drugs and ART, anti-TB and antimalarial falls in this category. The categories in which the respondents stated less improvement is solely funded and supplied by government through CMS.

Limitations

Limitation to this study includes cases of missing stock cards at the hospitals and the CMST, and refusal by many health workers to participate (sometimes demanding money for participation). Due to limited funding, district hospitals and health centres could not be included in this study, which would have given a more complete representation.

Conclusion

In conclusion, the study indicated that the radical shift in the management of CMS was followed by an improvement of drug availability in CMST itself, and in one of the two investigated hospitals. However, most interviewed health professionals stated that they did not observe any effect of the change of CMS to CMST on drug availability in their workplaces. Future research need to be conducted to study the frequency and the reasons for drug shortages in the hospital of Malawi.

Conflict of Interests

The authors have not declared any conflict of interests.

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