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Rx-to-OTC Switches: Future Opportunities and Challenges



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ABSTRACT

Rx-to-OTC drugs are those medications that were prescription medicines but later transferred to the non-prescription drugs (OTC). Earlier the use of medications over the counter (OTC) was concise only for minor afflictions like cough and cold, aches/pain, hyperacidity, etc. Rx-to-OTC switch process has now expanded the category of over the counter (OTC) drugs to a wide range. About 40% of all OTC drugs used today in the US were once sold as prescription only medicines. When the medication is effective and has a high safety margin, it is possible to 'switch' the same drug to over the counter (OTC) status. The emerging category of OTC drugs stimulates production of more OTC drugs for a number of ailments and supports the growth of pharmaceutical industries. This solves the unemployment problem faced by today's population. On the other hand, Rx-to-OTC switch process leads to misuse and abuse of drugs. In near future, switching would be one of the most used strategies to enter OTC drugs list by new players. This leads to pharmaceutical counterfeiting. According to the World Health Organization, about 10% of medicines sold worldwide are counterfeited in underdeveloped and developing countries. Such drugs of poor quality are detrimental to the health of patients and pose a threat to the global economy. There are number of analytical method reported for counterfeit screening of Rx-to-OTC drugs in order to improve the quality of drugs.

1. INTRODUCTION

Rx-to-OTC switching refers to the transferring of FDA approved prescription medications (Rx) to nonprescription, over the counter (OTC) status [1, 3]. According to definition of US Food and Drug Administration, Rx-to-OTC switch is the marketing of over the counter drug product that was once a prescription (Rx) drug for the same sign and symptoms, with same strength, dose, duration of use, dosage form, population and route of administration [2]. Some examples include nicotine replacement therapies (like gum, patch, and lozenge), ibuprofen 200 mg, Benadryl (diphenhydramine), Claritin (loratadine), Nexium (esomeprazole), and Flonase (fluticasone) [3]. The first drug which was switched to OTC status were brompheniramine and chlorpheniramine that were approved on September 9, 1976 for OTC use. Since then, medications ranging from sleep aids to intranasal steroids have been made available over the counter [4].

In Rx-to-OTC switch class, NSAIDs are most commonly used drugs. NSAIDs drugs which have been switched from Rx to OTC status include diclofenac, ibuprofen, naproxen, ketoprofen, fenoprofen and mefenamic acid. Among these ibuprofen, ketoprofen, naproxen and diclofenac are available as both OTC and prescription medications. The other NSAIDs OTC drugs are aspirin, acetaminophen, etc. These drugs are used for pain such as osteoarthritis, intermittent musculoskeletal pain, backache, migraine, fever, menstrual pain, posttraumatic pain and many minor unpleasant conditions [5-7].

Currently, there are several drugs in the Rx category which could be revitalised through OTC switches. The expanded category of OTC drugs includes cuts, wounds and burns, muscle pains and sprains, smoking cessation, diarrhoea, heartburn, yeast infection, allergies, overactive bladder, sleeplessness and constipation [1, 8]. Some recent prescription to OTC (switch) products based on USFDA report from 2004-2019 (CDER) has been shown in Table No. 1.

In order to switch the drug from prescription to over the counter (OTC) status, drug must possess a broad safety margin, efficacy, and easy to understand labelling and language to ensure proper use. Consumers must also be able to self-diagnose and self-medicate a condition, and to understand warnings [1, 3]. In addition, the safety and efficacy data should be submitted to NDA together with post marketing data and additional clinical trials for Rx to OTC switch drug candidates [1].

Table No. 1: Recent prescription to OTC products based on USFDA report from 2004-2019 [9]

OTC Product	Active ingredient	Purpose	Switch Year
Mucinex DM ER Tablet	Dextromethorphan & guaifenesin	Expectorant/cough suppressant	2004
Mucinex D ER Tablet	Guaifenesin & Pseudoephedrine	Expectorant/Decongestant	2004
Lamisil Derm Gel	Terbinafine	Topical Antifungal	2006
Plan B	Levonorgestrel	Emergency Contraceptive	2006
MiraLax	PEG 3350	Laxative	2006
Zaditor	Ketotifen Fumarate	Antihistamine Eye Drop	2006
Alaway	Ketotifen	Antihistamine Eye Drop	2006
Alli	Orlistat	Weight Loss Aid	2007
Zyrtec-D	Cetirizine/Pseudoephedrine	Antihistamine and Nasal Decongestant	2007
Prevacid 24 HR	Lansoprazole	Acid reducer/PPI	2009
Zegerid OTC	Omeprazole & Sodium Bicarbonate	Acid reducer/PPI	2009
Allegra D 12 hr	Fexofenadine HCL & pseudoephedrine	Antihistamine	2011
Allegra	Fexofenadine	Antihistamine	2011
Oxytrol for Women	Oxybutynin	Overactive bladder	2013
Nasacort Allergy 24HR (nasal spray)	Triamcinolone acetonide	Allergic rhinitis	2013
Nexium 24 HR	Esomeprazole magnesium	Frequent heartburn	2014
Flonase Allergy Relief	Fluticasone propionate	Allergic rhinitis	2014
Rhinocort Allergy Spray	Budesonide	Allergic rhinitis	2015
Flonase® Sensimist Allergy Relief	Fluticasone furoate	Allergic rhinitis	2016
Differin Gel®, 0.1%	Adapalene	Anti-Acne	2016
Xyzal Allergy 24HR tablets	Levocetirizine dihydrochloride)	Allergic rhinitis and perennial allergic rhinitis	2017

2. OVER THE COUNTER (OTC) DRUGS

OTC drugs are over the counter drugs that are legally sold to the general public without a prescription from Registered Medical Practitioner or healthcare professionals [10]. These medicines come under the Consumer Healthcare segment of Pharmaceutical companies and considered as non-prescription drugs [8]. An approximate 350,000 OTC drugs are available that can be purchased without any prescription from pharmacies grocery stores and convenience stores, etc. These include analgesics, cold and cough medications, antacids, antihistamines, sedatives and so on. Among these medications cough syrups, sleeping aids and appetite-depressants are commonly abused. They can be used to relieve a variety of daily health problems due to their easy availability; safety and efficacy [11]. Consumers prefer OTC products because they save time and money to see a doctor at their clinic or hospital. Other possible reason which leads a consumer towards OTC products are his previous experiences with the product and also his economic status [12]. OTC drugs are the most purchased drugs in countries like India, USA, UK and many other parts of the world because they are easily available and significant in action [13]. Many medications have been switched from prescription only drugs to over the counter (OTC) status over the decades [14]. This permits more patient right regarding their health condition, contributes to greater appreciation of pharmacists' knowledge and puts less pressure on publicly funded healthcare systems [15].

The present study has been designed to investigate Rx-to-OTC switches' benefits & risks, future opportunities and challenges. It also explains about various analytical methods for detection of pharmaceutical counterfeiting that occurs due to Rx-to-OTC switching.

The main categories of medicines sold in India as OTC drugs are [16].

- Vitamins and minerals
- Gastrointestinal
- Cough and cold medications
- Analgesics
- Dermatological preparations.

Nowadays even Anti-obesity drugs and Anti-stress candies are switching from Rx-to-OTC medicines in India.

Possible benefits of switching prescription only medicines to over the counter status are:

- Easy, rapid access to effective medicines.
- Wide availability of the required medications.
- Lower cost of the healthcare system due to decreased number of visits to doctors.
- Increased markets for pharmaceutical companies.
- Allowing individuals to self-diagnose and self-treat their minor ailments.
- Improved health through self-care medication
- Decreased costs to third-party payers [16, 17]

3. OPPORTUNITIES

Increasing consumer awareness, growth of self-medication and government efforts to curtail public spending on prescription products for minor self-treatable ailments are the reasons behind switching of prescription drugs to OTC status [1]. The availability of Rx-to-OTC medications generates an important value in annual savings for public healthcare system [10]. Rx-to-OTC switch process increases the consumer assessment to safe and effective drugs. This creates a growing demand among the people for non-prescription drugs. People's lives are becoming more complicated and stressful in today's world. Acute and chronic diseases are also increasing day by day, hence the pharmaceutical companies [8]. Thus, the pharmaceutical company manufacture more pharmaceutical products to meet the requirements of people [18]. Increasing access to OTC drugs offers new self-care opportunities to consumers [19].

The other factors for OTC drug market expansion are emergence of a defense strategy against generic competitors, proliferation and growth of an OTC product category and increasing consumer access to new OTC products. Some of the driving factors for Rx-to-OTC switch process are listed in Figure No. 1.

Driving factors for Rx-to-OTC switch process

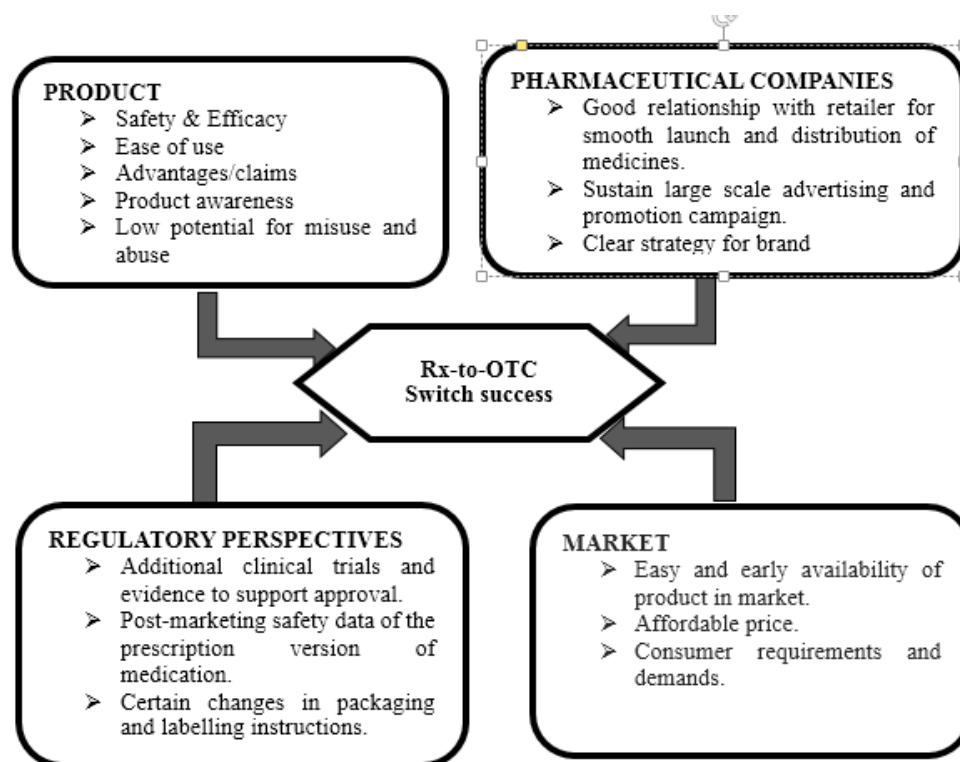


Figure No. 1: Kline & Co. (Source)

Rx-to-OTC switch process gives opportunities to pharmaceutical manufacturers to prolong the life cycle of their drug product. The switching also helps company to defense with generic competitor entering market when patent for prescription drug expires. Patents of drugs can be extended by switching it to OTC status. These may include drugs like drugs for pediatric, extended drug release formulations, etc. Thus Rx-to-OTC process is the way to manage the drug's life cycle and represent a way to infuse growth into the pharmaceutical company. A new switched drug will results in high rates of rapid sales growth [2] and increased production by pharmaceutical companies. This helps to expand the market strategies of company [8].

One of the fields that is least affected by recession is the pharmaceutical market which can provide people with sufficient employment. OPPI 46th annual report explains that pharmaceutical industry in India is growing at around 16% annually. According to the data collected in 2013, about 4 million people were directly employed by Indian pharmaceutical industry. Switching thus helps to solves unemployment problem faced by today's world [8]. About 96% of consumers believe OTC medicines can be used for minor medical ailments.

The availability of Rx-to-OTC switch drug candidates in market helps individuals and families fulfill their routine healthcare requirements [10].

Most of the consumers depend on OTC medications for first line defense for healthcare activities. Consumers, for example, rely on OTC cough medicines as a first response to relieve cough symptoms for themselves and their children [10]. The switching of allergy medicines to OTC status has become convenient and affordable options. As a result, the number of people using OTC drugs has increased from 66% in 2009 to 75% in 2015 [20].

Similarly, switching of nicotine replacement therapies to OTC triggered their purchase and use and caused rise of 150-200 percent in the first year after the switch. Increased access made it possible for tens of thousands of smokers to use these products to help quit smoking and live longer, healthier lives [21]. NRT provides users with “clean” nicotine to reduce craving and withdrawal [22]. The US Food and Drug Administration (USFDA) first approved 2mg Nicorette in 1984. In 1996, the FDA approved nicotine gum (Nicorette chewing gum) and nicotine patches (Nicoderm CQ and Nicotrol transdermal patch) for over the counter sales [2, 22]. In an OTC Nicotine-Replacement-Therapy (NRT) study, it was found that the OTC availability of NRT increased access and use of safe and effective treatment without substantial misuse or abuse [3].

Category of OTC drugs has been increased with growing medicines development. The availability of information regarding the drugs’ safety, effectiveness and ease of use enable the movement of prescription only medicines to non-prescription. Indications like cholesterol management, menorrhagia, incontinence, obesity, etc that were known to be treatable only under supervision of healthcare practitioners can now be transferred to OTC drugs based on consumer literacy and awareness [1]. There are some of the drugs which have potential to switch from Rx sectors. These include triptan for migraines, oral contraceptives, albuterol, epi-pen, and naloxone. The indications for which the prescription drugs can be switched to OTC status in future are shown in Figure No. 2.

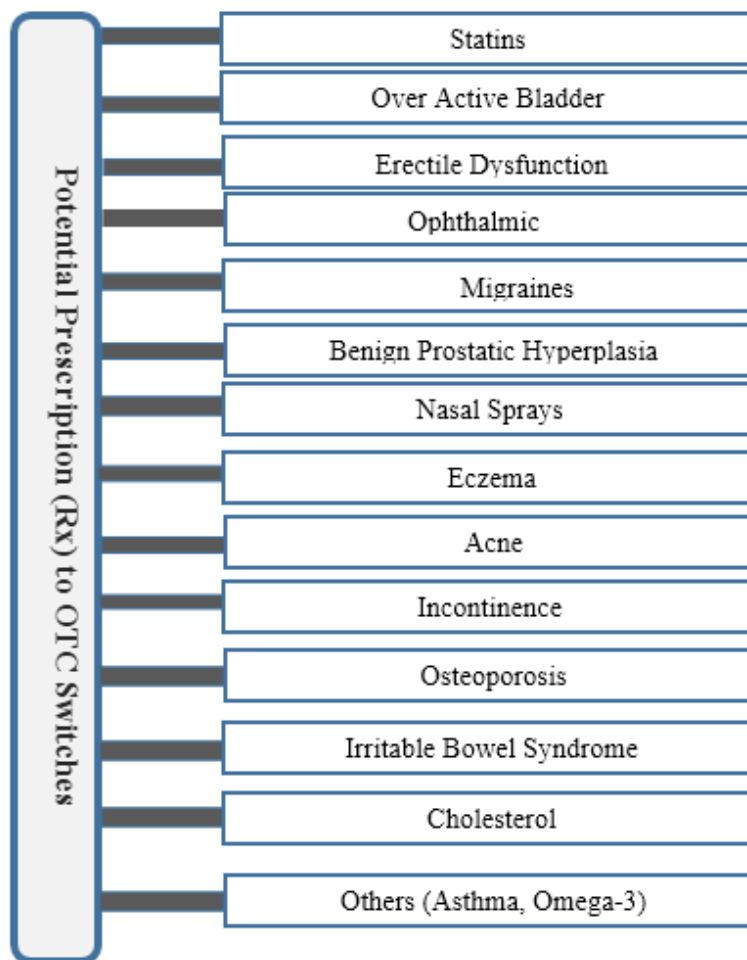


Figure No. 2: Barclays Global Healthcare Conference 2015 (Source)

Kyrillos Guirguis (2010) conducted a retrospective study in order to know the prevalence of non-prescription medicines among elderly patients with chronic disease and the type of pharmacist interventions needed by patients to improve the use of OTC products. In the course of the study, pharmacist visited 51 elderly patients and found that 80.4% of patients used OTC drugs and 21.6% used counterfeit medicines products. About 18.7% patients did not use the correct dose of OTC drugs and 18.8% were unaware of dosing regimens. About one-third of patients required to know about the way to manage their ailments through the use of OTC drugs. Moreover, they also needed the pharmacist interventions [23].

4. INDIAN OTC MARKET

According to data collected in 2012 India ranks 11th in terms of OTC market worldwide and the OTC drugs sector is growing at the rate of 23 percent. Around 70000 brands are used as OTC drugs. The most used brands are Revival, Crocin, Smyle, Glycodin, etc [24]. Pharmaceutical industry in India is on the threshold of becoming a major global market by 2020 [8, 25].

Some of India's top OTC brands are Dabur Honitus lozenges, cough syrups, Vicks VapoRub, Zandu balm, Iodex, Moov, cough drops and lozenges, etc [8]. Pharmaceutical industry in India is one of the country's most important economic factors, exporting \$15 billion products annually, and some of its factories are world-class. India is the second-largest exporter of OTC and prescription drugs to the United States [10].

5. CHALLENGES

The switching of Rx-to-OTC process has positive growth indications in the field of Indian pharmaceutical market but in the current scenario, it faces significant transition challenges.

The possible challenges faced in present due Rx-to-OTC switching are:

- Incorrect self-diagnosis.
- Delay in diagnosis and treatment of serious illnesses.
- Increased risks of drug-drug interactions.
- Weakens the relationship between patients, physicians and pharmacists.
- Increased healthcare cost.
- Potential for misuse and abuse of drugs.
- Increased resistance to antimicrobial agents due to inappropriate use.
- Failure to follow label instructions and warnings.
- Effects on pediatric patients.

- Leads to pharmaceuticals counterfeiting.
- Effects on pregnant and breastfeeding women [16,17]

5.1. Incorrect self-diagnosis

Patients can use over the counter drugs based on their previous experience, although the condition is different from the earlier one. An incorrect diagnosis by patient leads to the use of over the counter (OTC) drugs that may not be effective in treating actual condition of diseases [16]. For example, women are likely to diagnose vaginal fungal infection condition and use antifungal drugs without prescription if the condition is previously diagnosed by healthcare professional. Therefore, in this case, many women who have never been diagnosed with fungal vaginitis use antifungal drugs. Thus it causes adverse drug effects and various health problems [26].

5.2. Delay in diagnosis and treatment of serious illnesses

The availability of over the counter (OTC) drugs makes people to use them for a particular diseased condition which may be susceptible. Patients may use nonprescription drugs for long period of time based on their assumption and personal experience. This cause delays in diagnosis of actual condition of illness and hence delays in treatment [18].

5.3. Increased risks of drug-drug interactions

NSAIDS are most commonly used as OTC drugs. The pharmacologically induced adverse reactions caused by NSAIDs are gastrointestinal bleeding and cardiovascular risk. NSAIDs are mostly responsible for non-dose dependent reactions, such as acute liver failure. About 40% percent of Americans believe that OTC products are safe [27]. As a result, very few inform their doctor about use of these products, which places the patients at risk because of interactions or potentiated pharmacological effect. In many cases, doctors do not inquire into a patient's use of OTC or counterfeit medicines products and patients are not likely to inform doctors of their OTC/CM use [28]. The risk perception of certain OTC medications is impacted by route of administration, the drug's indication and the active substance. This is because most of people do not read the instructions on packaging of OTC products properly [29].

Sometimes the self-medication of OTC drugs and prescription drugs together becomes harmful and has high abuse potential. Some OTC drugs when taken with alcohol cause drowsiness, dizziness, euphoria, nervousness, blurred vision, ringing in ears, etc. It also causes confusion, muscle twitching, irregular heartbeat, tremors, convulsions, etc at a higher dose [30].

5.4. Potential for misuse and abuse of drugs

OTC drug abuse has been commonly described as the systematic overuse of non-prescription medicines [31]. The ineffective control of OTC drugs licit supply cause increase in abuse of OTC drugs. The abuse of these medications is a severe and increasing problem for public health worldwide. Large doses of OTC drugs can be harmful [11]. OTC abuse is a critical and global health problem that imposes major burdens on many healthcare systems [32, 33]. These OTC drugs abuse is mainly observed in children and adolescents [33]. Teenagers more often use OTC drugs for indications like headache or menstrual pain, allergies, common cold and fever [19]. Shone et al focused on the harmful use of paracetamol among teenagers and young adults in the United States. Analgesics OTC drugs are popular mainly among school going girls for headache and menstrual pain [34].

The excess use of OTC drugs result in physical dependence, psychological dependence or both [35]. One of the main areas of OTC drugs are cough-cold preparations [36]. OTC drugs which have been heavily abused are cough–cold preparations due to their easy availability, cost effectiveness and inducing feeling desired by the abusers [37]. Approximately 1 million (1.7%) and 3.1 million (5.3%) people aged between 12 and 25 years misused OTC cough and cold medicines to get high in 2005 and 2006 [38]. Many deaths occurred due to toxic effects induced by ingestion of high amounts of cough–cold preparations [39]. Authors also reported cases in which a number of deaths occurred due to the ingestion of cough syrups containing dextromethorphan [40]. Pharmacists face everyday problematic situations while dealing with clients who abuse or misuse OTC drugs [41]. Many consumers do not know that repeated routine use and high doses of paracetamol may cause damage to liver and ibuprofen can result to gastrointestinal damage, bleeding and ulcers [32, 42].

5.5. Effects on pediatric patients

The common OTC medications for pediatric include cough syrups, decongestants, antihistamines, nasal drops or sprays, pain and fever relievers and antibiotics. The use of OTC drugs for children under 3 years of age without consultation of the medical practitioner causes reactions and overdosing. This occurs when parents do not understand the label or fail to measure the medicine correctly [12]. It leads to serious health problem because pediatric patients require different doses per kilogram of body weight than adults due to difference in their pharmacokinetics, as well as pharmacodynamic factors [12]. In most of cases, parents tend to try out the same medication purchased as OTC drugs without knowing the present condition of child health. This activity is practiced because of the lack of time due to present day professional life and busy schedule and poor economic conditions. This practice seems definitely dangerous and has to be avoided. Some parents even try antibiotics as OTC products based on their previous experience with the products and as well as symptoms without having any knowledge on disease, symptoms, dosing, drug profile. Such practices have to be checked and controlled at the earliest to avoid any accident [43, 44]. Inappropriate use of OTC drugs in pediatric patients may cause side effects like drowsiness, light headaches, increase in heartbeat, Reye's disease, constipation, diarrhea, etc especially with anti-cold, antipyretic and anti-bacterial products [10, 12].

5.6. Effects on pregnant and breastfeeding women

OTC drugs when given to pregnant women may cross placenta and may exerts teratogenic effects. Similarly, OTC drugs pass into breast milk and attain a high concentration in mother plasma from where it may passes to baby and cause different health problem [45, 46]. Inappropriate and long term use of OTC drugs may cause perinatal mortality, neonatal hemorrhage, reduced birth weight, prolonged gestation and labour [47, 48]. Studies have reported that in many pregnant women aspirin may increase the risk of gastroschisis. When used in third trimester, acetaminophen was associated with the premature closing of the fetal ducts. Therefore, pregnant women can consult a medical practitioner before taking any OTC medicines [10].

5.7. PHARMACEUTICALS COUNTERFEITING

As the switch of Rx-to-OTC process has expanded OTC category from minor afflictions like cold, cough and pain to a wide range, it causes increasing demand for Rx-to-OTC switch drug candidates [2]. Increased demand stimulates the production of OTC drugs by pharmaceutical companies. As a result, these drugs are easily available online, in market and retail shops. Easy availability of OTC drugs encourages their use by people. Moreover, pharmaceutical companies may offer much needed medications as counterfeit versions at low cost in order to enhance patient affordability of their medications. Pharmaceutical companies also provide cheaply available generics for stakeholders meant for substitute of expensive one. Thus, increasing demand for Rx-to-OTC switch drugs may increase a chance of pharmaceutical counterfeiting [49].

Pharmaceutical counterfeiting has serious implications for patients, healthcare providers, drug supplier and manufacturers and governments. Counterfeit medicines are growing worldwide threat that endangers patient lives. The growing demand for Rx-to-OTC switch drug candidates therefore seeks a higher level of quality control, must adhere to the strictest safety criteria and must offer the maximum guarantees of its purity [50].

Antihistamines and decongestants drugs such as diphenhydramine, doxylamine, phenylephrine, pseudoephedrine, and dextromethorphan hydrobromide are mostly abused drugs and require methods for their detection and quantitation. Cold medicines and antihistamines products are psychotropic drugs and are often abused due to their OTC status. Accidental overdose, especially in children, can lead to death [51].

Pharmaceutical counterfeiting should be treated as unlawful. So it is prudent to be careful and watchful. It requires appropriate analytical methods to detect the drugs counterfeiting [52]. A number of analytical methods for screening of Rx-to-OTC drugs have been reported. These methods include thin layer chromatography (TLC) to more advanced techniques such as near infrared spectroscopy (NIR), gas chromatography (GC), high performance liquid chromatography (HPLC), mass spectroscopy (MS), hyphenated techniques such as GC-MS, LC-MS and RAMAN spectroscopy has been approached for pharmaceutical counterfeit screening [49].

Ahmed DA et al. developed four consistent and accurate spectrophotometric methods for concurrent estimation of pseudoephedrine hydrochloride and ibuprofen which are widely

used as OTC drugs. The four methods used were dual wavelength method (DW), ratio difference method (RD), constant multiplication coupled with spectrum subtraction method (CM-SS) and constant center coupled with spectrum subtraction method (CC-SS) [53].

5.7.1. METHODS OF DETECTION

5.7.1.1. Simple method

Thin layer chromatography (TLC) and colorimetry are the two most simple and common methods used to determine the quality of drug. These methods are cheap, specific and rapid. It is also possible to detect counterfeit drugs by measuring bulk properties of drugs such as density, viscosity, refractive index and optical rotation. Even low cost, mislabeling and improper packaging can also help detect falsified medicines [49].

5.7.1.2. Chromatography Method

Different methods of chromatography used to detect counterfeit drugs includes thin layer chromatography (TLC), high performance liquid chromatography (HPLC), gas chromatography (GC), etc. TLC method has been utilized for identity testing of drugs while HPLC has been used for impurity profiling, adulterants detection and for identification of any residues if present. HPLC technique is fast and sensitive. It is the most common instrumental techniques used to evaluate pharmaceutical product contents quantitatively. The main advantage of HPLC is that it can be paired with many detector such as UV detector, photodiode array (PDA), fluorescence, MS detectors and electrochemical detector [52]. Gas chromatography (GC) has been used for headspace analysis. For detection of trace components in bulk products, capillary electrophoresis has been employed [49].

Active ingredients in many OTC preparations have been detected and measured using thin layer chromatography (TLC) and high performance liquid chromatography (HPLC). Sagathiya et al. used reverse phase high performance liquid chromatography (RP-HPLC) and high performance thin layer chromatographic (HPTLC) techniques in order to determine dextromethorphan hydrobromide and guaifenesin in pharmaceutical cough–cold preparation [54].

M. K. Chahal et al. analyzed common over the counter (OTC) cough cold preparation containing dextromethorphan hydrobromide, phenylephrine hydrochloride, paracetamol and

chlorpheniramine maleate in tablets and liquids dosage form using TLC. The solvents used in this method were methanol: ammonia in the ratio 100:1.5 (v/v) and B comprising chloroform : methanol in the ratio 90:10 (v/v). These solvents were found to be the most suitable as it showed a high degree of separation of different components of these preparations. Iodine fuming technique was used as visualizing method for examining the TLC chromatograms of these drug samples prior to subsequent instrumental analysis [11].

5.7.1.3 Mass spectrometry Method

Pharmaceutical products are also characterized by mass spectrometric method. In drug profiling, mostly time of flight (TOF) with both electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) sources has been preferred. TOF-secondary ion mass spectrometry (TOF-SIMS) was employed to study the bulk polymeric film. This is also used to characterize pharmaceuticals products by evaluating the entire drug dosage form [49]. HPLC when paired with MS becomes a powerful technique for structural recognition of chemical entities present in pharmaceuticals even at low concentrations. Quadrupole and ion trap mass spectrometers have also been used. HPLC-TOF-MS has proven to be a very powerful means of characterizing incorrect ingredients in falsified tablets with an average mass accuracy of 2.0 ppm [50].

Hyphenated methods like gas chromatography-mass spectrometry (GC-MS), liquid chromatography-mass spectrometry (LC-MS), mass tandem mass spectrometry, inductively-coupled plasma mass spectrometry (ICPMS) and others such techniques have been reported for determination of quality of drugs [49].

A paper by researchers from Glaxo SmithKline mentioned the analysis of betamethasone, dexamethasone and similar compounds by LC-electrospray MS (HPLC/ESI-MS). This technique differentiates between the epimers and specific esterification products in counterfeit medicines. Using a step gradient system with mobile phases containing ammonium acetate and acetonitrile a strong separation with baseline resolution of all isomers was achieved on the column. Thus different such techniques have been used in order to identify the active ingredient present in the drug products [55].

5.7.1.4 ATR FT/IR Spectroscopy Technique

FTIR spectroscopy is used to identify the functional group of chemical substances. The absorption frequencies ranges from 400 to 4000 cm^{-1} . ATR FTIR spectroscopy is a fast and highly sensitive analytical technique for pharmaceutical products authentication. This helps to carry out drug product qualitative and quantitative analysis.

FTIR spectroscopy is used to characterize and identify the presence or absence of active pharmaceuticals ingredients and excipients. This method however requires a skilled person to prepare sample in the form of crushed powders. Here finely crushed powder is mixed with KBr in fixed proportion. Powder must be mixed properly and then compressed into discs before carrying out the analysis process. This method is time consuming and requires a continuously dried source of KBr. A hydraulic press is also required to produce uniform KBr discs. Sometimes sample extraction process is also required which makes the method lengthier. It also suffers from lack of spectral reproducibility [56].

When spectra are recorded in attenuated total reflectance mode, Fourier transform infrared spectroscopy becomes non-destructive method. ATR-FTIR is faster than conventional FTIR and some of the methods approved by pharmacopoeia as sample preparation step are not required. It provides information on spatial distribution of various components on the sample surface under investigation. It offers simple method for sample treatments. The samples like powder or paste, liquid sample can be applied directly to the head of sensor. Before analysis, the tablet samples need only to be crushed. This method is therefore considered as non-destructive method [57].

Lawson G. et al., (2014) reported attenuated total reflection (ATR) FT/IR techniques for analyzing suspect tablet formulations. Tablet samples were obtained and analyzed from different countries like India, Africa, China, Belgium and the United Kingdom. Quantitative data of the standardized API mixtures in the excipients were collected from ATR FT/IR spectra. Initial results showed that API could be identified to about 5.0 % w/w of the tablet. Here paracetamol was used for the detection of counterfeit product as it is popular OTC medication. Furthermore, paracetamol is mostly found in combination with other active ingredients, in the same dosage which provides an opportunity to determine the interaction of these drugs with other active ingredients added [58].

FTIR2 Bruker Alpha spectrometer was used. Before the beginning of analysis and after each fifth sample, the background spectrum within the instrument was recorded. This spectrum was subtracted from the test spectrum obtained, especially from water vapour. Each sample was scanned 20 times over a range of 4000-400 cm^{-1} and measured at a 2.0 cm^{-1} spectral resolution [58].

5.7.1.5 NIR spectroscopy

The absorption frequencies in NIR region ranges from 700-2500 nm wavelength. The combination bands obtained in this region are broad, unresolved and much weaker than the basic modes in mid-IR. The variations between NIR spectra of compounds are mostly very small and chemo-metric methods like principal component analysis, partial least squares (PLS), and PLS–discriminant analyses are needed to differentiate against the analyzed samples. In order to identify pharmaceutical raw materials and finished products, NIR spectroscopy was used. It is also used for the determination of active ingredient content of medications [59].

In 2001, Scafi and Pasquini reported a NIR spectroscopy method for detecting counterfeit medications. The detection was based on comparing a sample NIR spectrum with reference drug spectra using multivariate modeling and classification algorithms, such as principal component analysis (PCA). NIR spectroscopy was performed for spectrum analysis of different drugs which were chosen to study the physicochemical features in commercial products [60].

NIR spectroscopy is a nondestructive technique. It does not require preparation of sample and has a high analytical speed. It is used for both qualitative and quantitative analysis and gives fingerprints of the whole matrix [61]. The main disadvantages are that combination bands are broad, unresolved and much weaker than the basic modes in mid-IR. Therefore, direct bond assignments to specific frequencies are often not feasible [62].

5.7.1.6. Raman spectroscopy

Raman spectroscopy is a method of dispersion. In a Raman experiment, the sample to be analyzed is illuminated with a high-powered laser beam, usually in the range of 50-400 MW diode. It provides appropriate intensity to obtain better spectra as only around 10^{-6} of the

applied light intensity induces inelastic dispersion at wavelengths shifted from the original one.

Raman frequencies refer to vibrational modes of bonds within molecules and are equivalent to mid-IR frequencies if the vibration modes are IR-active. This technique is generally applicable only to those samples that do not show strong fluorescence. Raman spectroscopy is a nondestructive, precise, and high-speed chemical analysis technique that requires no sample preparation. It has been used in recent years for screening of pharmaceutical formulations' quality through packaging of transparent nature of no or few fluorescence [63].

Abbreviations: OTC: Over the counter; Rx: Prescriptions medications; NSAID: Non-steroidal anti-inflammatory drugs; USFDA: US Food and Drug Administration; NRT: Nicotine-Replacement-Therapy; CM: Counterfeit medicines; TLC: Thin layer chromatography; HPLC: High performance liquid chromatography; PDA: Photodiode array; ATR-FTIR: Attenuated total reflection Fourier transform infrared spectroscopy; NIR: Near infrared Spectroscopy; API: Active pharmaceutical ingredients.

6. CONCLUSION

In this paper, Rx-to-OTC switch process along with its possible benefits and challenges were reviewed. This paper also discussed about the driving factors for Rx-to-OTC switch process, its procedure to switch the drugs from prescription only medicines to OTC status and opportunities that can be obtained from Rx-to-OTC switch process. There a number of Rx drugs which can be shifted to OTC category in future. Rx-to-OTC switch process increases the public assessment to OTC drugs at low cost, stimulates the production of drugs by pharmaceutical companies, solves unemployment problem, etc. On the other hand, it causes misuse and abuse of OTC drugs, pharmaceutical counterfeiting, etc. A number of analytical methods are employed to detect pharmaceutical counterfeiting. Among them, chromatographic techniques like TLC, HPLC, HPTLC, etc are mostly used. Spectroscopic methods used for detection of excipients and APIs in counterfeit products are direct ionization MS, ATR FT/IR spectroscopy, Raman spectroscopy, NIR spectroscopy and NMR spectroscopy method. HPLC with PDA or MS detection has been found to be the most effective for identification and quantification of wrong active ingredients and impurities. Moreover, hyphenated methods have proved to be extremely useful for the screening and characterization of genuine and counterfeit drugs. For example, GC-MS, LC-MS, ICP-MS

and Raman spectroscopy have been successfully employed for detecting the pharmaceutical counterfeiting of drugs.

All the analytical methods mentioned in this review have the potential for structural identification and quantitative determination of drug components. All these analytical techniques should be used in quality control or forensic laboratories but majority of them are expensive, sophisticated and require highly trained personnel to operate the system. On the other hand, strict rules and guidelines should be implemented for pharmaceutical companies in order to maintain the quality of drugs. Similarly, the government should implement the rules that only authorized persons should sell pharmaceutical products. Public awareness regarding the misuse and abuse of Rx-to-OTC medicines and labeling and indications mentioned on pharmaceutical products should be given. These activities will save people from using wrong and counterfeit products for minor ailments which may cause serious health hazards to the consumers.

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CONFLICT OF INTEREST

Authors declare that they have no conflicts of interest.

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