World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 5.088

NOVEL CONCEPT IN VAGINAL DRUG DELIVERY SYSTEM: AN OVERVIEW

Abhishek Soni*[1], Dr. Shivali Singla[2], Dr. Sachin Goyal[2]

[1]Ph.D Scholar, Department of Pharmaceutics, School of Pharmacy, Abhilashi University, Chail Chowk, Mandi (H.P).
[2]School of Pharmacy, Abhilashi University, Chail Chowk, Mandi (H.P).

***Corresponding Author: Abhishek Soni**
Ph.D Scholar, Department of Pharmaceutics, School of Pharmacy, Abhilashi University, Chail Chowk, Mandi (H.P).

Article Received on 12/06/2018 **Article Revised on 02/07/2018** **Article Accepted on 23/07/2018**

ABSTRACT

Some drugs are poorly absorbed after the oral administration. Over the last twenty years, extensive efforts have been made towards the administration of poorly absorbed drugs through different delivery systems and routes but the presence of a mucus laden cervix (vagina) in women provides an opportunity as a conjoint site for such drug delivery. The vaginal route has been rediscovered as a potential route for systemic delivery of various therapeutically important drugs avoid first pass metabolism. However, fruitful delivery of drugs through the vagina remains a challenge because of poor absorption of some drugs across vaginal epithelium. The various factors like Vaginal Secretions, Vaginal pH, Microflora, Cyclic changes are affecting the rate of drug absorption after vaginal administration. The future of vaginal drug delivery lies in the bioadhesive tablets, liposomes, niosomes and microparticles, which although relatively new and show great promise in providing truly controlled delivery of drugs. In the current study, further attention has been made on various polymers which are used in hydrogel which provide bioadhesive property to the vaginal formulations, so that the formulation remains vaginal tissues for proper time. The main objective of the present review is to summarize various vaginal drug delivery systems with an special emphasis an vaginal anatomy and physiology, vaginal drug delivery system, factors affecting the vaginal drug absorption, Vaginal drug formulation, including the Novel concepts in vaginal drug delivery systems.

KEYWORDS: Vagina, Drug delivery, Novel, Bioadhesive.

1. INTRODUCTION

In this era of pharmaceutical research, the field leading is the development of novel drug delivery system for drug molecules which already exist so that their efficacy is maximised with better patient compliance and reduced adverse effects. With the advancement in technology of drug delivery there has been a wider choice of sites for drug administration. Vagina, as a site for drug delivery, has certain advantages due to which it has been exploited in order to achieve desirable therapeutic effects. The above said advantages are presence of dense network of blood vessels which makes it excellent route of drug delivery for both systemic and local effects. Others include its ability to by-pass first pass metabolism, ease of administration, low enzymatic activity, high permeability for low molecular weight drugs and this route provides for self medication continuously for weeks or months at a time with a single application resulting in better pharmacokinetic profiles. The first formulation which was designed for vagina was to treat local bacterial, fungal infections and inflammations. With the development of novel products for female health, comprising therapeutic substances such as peptides, proteins, antigen there is need for designing high performance intravaginal drug delivery systems. This route provides a better alternative to the parenteral route for drugs like bromocriptine, propanolol, oxytocin, calcitonin, LHRH agonists, human growth hormone, insulin and steroids used in hormone replacement therapy or for contraception. The vagina serves as an excellent route for the delivery of hormonal contraceptives because of lack of drug interactions as observed in the gastrointestinal tract.[1] The main advantages of vaginal drug delivery over conventional drug delivery are the ability to by-pass first pass metabolism, ease of administration and high permeability for low molecular weight drugs. However, several drawbacks, including cultural sensitivity, personal hygiene, gender specificity, local irritation and influence of sexual intercourse, need to be addressed during the design of a vaginal formulation. Further, considerable variability in the rate and extent of absorption of vaginally administered drugs is observed bychanges in the thickness of the vaginal epithelium.[2]

2. Anatomy and Physiology of The Vagina[3,4]

In the pharmaceutical literature, human vagina is often described as slightly Sshaped fibro muscular collapsible tubes between 6 and 10 cm long extending from the

cervix of the uterus. The vaginal wall consists of three layers: the epithelial layer, the muscular coat and the tunica adventia. During the menstrual cycle, the thickness of the vaginal epithelial cell layer changes by approximately 200–300 Am. The surface of the vagina is composed of numerous folds, which are often called rugae. The rugae provide dispensability, support and an increased surface area of the vaginal wall. The vagina has an excellent elasticity because of the presence of smooth elastic fibers in the muscular coat. Loose connective tissue of tunica advent further increases the elasticity of this organ. The network of blood vessels that supply blood to the vagina include a plexus of arteries extending from the internal iliac artery, uterine, middle rectal and internal prudential arteries. In fact, arteries, blood vessels and lymphatic vessels are abundant in the walls of the vagina. Drugs absorbed from the vagina does not undergo first-pass metabolism because blood leaving the vagina enters the peripheral circulation via a rich venous plexus, which empties primarily into the internal iliac veins. There is some drainage to the haemorrhoidal veins as well. The lower part of the vagina receives its nerve supply from the prudential nerve and from the inferior hypogastria and uterovaginal plexuses. Although the vagina does not possess any gland, it secretes a large amount of fluid. Cervical secretion and transudation from the blood vessels with desquamated vaginal cells and leucocytes mainly constitute the vaginal fluid. Secretions from the endometrium and fallopian tubes also contribute to the vaginal fluid. Like the thickness of the vaginal epithelium, the amount and composition of the vaginal fluid also change throughout the menstrual cycle. Women of reproductive age produce fluid at a rate of 3–4 g/4 h, while the discharge produced by postmenopausal women is reduced by 50% compared to that produced fluid may contain enzymes, enzyme inhibitors, proteins, carbohydrates, amino acids, alcohols, hydroxyl ketones and aromatic compounds. Sexual arousal may affect the volume and composition of vaginal fluids and that can alter the drug release pattern from the vaginal delivery system. Lactic acid produced from glycogen by the Lactobacillus acidophilus present in the vagina acts as a buffer to maintain the vaginal pH between 3.8 and 4.2.During menstruation, the pH of vaginal fluid increases and frequent acts of coitus may also cause an increase in the vaginal pH because both ejaculate and vaginal transudate are alkaline. The presence of cervical mucus and the amount of vaginal transudate may also alter vaginal ph. The vaginal epithelium has a high activity of enzymes that could potentially affect short- and long-term stability of intravaginal delivery systems and devices.

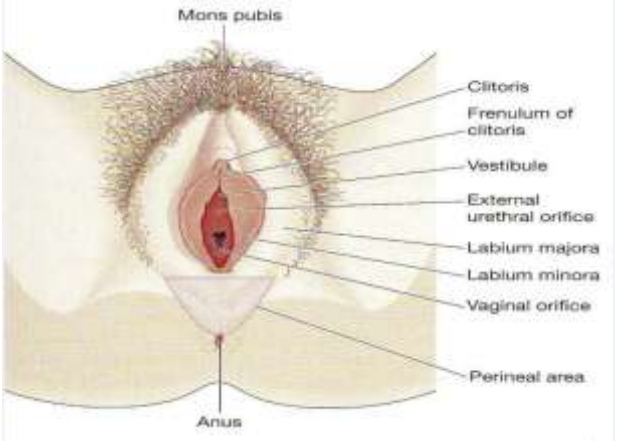

Figure 1: The external genitalia of the female

3. Vaginal drug delivery system

Vaginal drug delivery systems are traditionally used to deliver contraceptive and drugs to treat the vaginal infections. However, vaginal drug delivery is not limited to these drugs as a the vagina has promise as a site to topically deliver drugs which will be absorbed systemically because of the dense network of blood vessels in the vaginal wall.[1] A formulation given by this route as pessaries, vaginal tablets, inserts, cream, powders, douches, gel, etc. The first truly controlled drug delivery systems for use in the vagina were developed in 1970, when the first vaginal ring was used for delivery of medroxy progesterone acetate for contraception. Still, tablets, creams and counter (OTC) vaginal medications while vaginal rings are the most common long-term drug delivery systems currently used. In recent years vaginal Bioadhesive preparations have been developed as a new type of controlled release form for the treatment of both topical and systemic diseases.[5] The greatest advantage of such dosage forms is the possibility of maintaining them in the vagina for an extended period of time including day hours and night, thereby enabling lower dosing frequencies. The concept of controlled-release drug delivery has also been successfully applied to the intra-vaginal administration of a systemic prostaglandin derivative for abortion indication. Intra-vaginal controlled-release drug delivery system is an effective means of continuing delivery of therapeutically active agents such as a contraceptive steroids and prostaglandins.

3.1 Factors considered with reference to vaginal drug delivery system

- **Vaginal Secretions:** Though there are no goblet cells in vagina and hence it does not release mucin even then vaginal epithelium is considered as a mucosal surface, Vaginal discharge consists of a mixture of several components including transudates through the epithelium, cervical mucus, exfoliating epithelial cells, leukocytes, endometrial and tubal fluids. The cervical mucus contains inorganic and organic salts, mucin, proteins, carbohydrates, urea and fatty acids (lactic and acetic acids). The volume, viscosity and pH of vaginal fluid may have impact

on vaginal drug absorption. The absorption of poorly water-soluble is increased when the fluid volume is higher.[6] Whereas presence of overly viscous cervical mucus may present a barrier to drug absorption and increased fluid volume may remove the drug from vaginal cavity and subsequently reduce absorption.

- **Vaginal pH:** The vaginal pH of healthy women of reproductive age is acidic (pH 5 4–5); which is maintained by lactobacillus convert glycogen from epithelial cells to lactic acid. The changes in pH occur by factors such as age, stages of menstrual cycle, infections and sexual arousal. Menstrual, cervical and uterine secretions and semen act as alkalizing agents and increase the pH.[7] The vaginal Ph should be controlled for successful vaginal delivery of drugs.
- **Microflora:** The factors which influence the ecology of the vagina are glycogen content of epithelial cells, glucose, pH, hormonal levels, and trauma during sexual intercourse, birth-control method, age, antimicrobial treatment and delivery. The most prevalent organism in the vaginal environment together with many other facultative and obligate aerobes and anaerobes is lactobacillus. The human genital tract has lower enzymatic which results in less degradation of protein and peptide drugs in the vagina than the gastrointestinal tract.
- **Cyclic changes:** The changes in hormone levels (especially estrogens) during the menstrual cycle lead to alterations in the thickness of the epithelial cell layer, width of intercellular channels, pH and secretions.[8] The variations in enzyme activity (endopeptidases and aminopeptidases) with hormonal changes creates problem in achieving consistent drug delivery.
- **Physicochemical Factors:** Lipophilicity, Ionization, Molecular weight, Surface charge and Chemical nature can influence the vaginal drug absorption. In consideration to permeability the lipophilic steroids like progesterone and estrone having better permeability than the hydrophilic one like hydrocortisone and testosterone.

3.2 Advantages of Vaginal Drug Delivery Systems[9]

This route is the most preferred and targeted goal of new drugs and dosage forms, vaginal administration can be used as an alternative route in certain cases of therapeutic importance:

- This is a better delivery system in case of nausea and vomiting.
- Stomach and intestinal irritation can be avoided.
- Hepatic first pass elimination can be avoided.
- As there is no contact with digestive fluid so enzymatic degradation of drugs is avoided.
- Drug delivery can be stopped by removing the dosage form e.g. Vaginal rings.
- Rapid drug absorption and quick onset of action is achieved.
- When compared to parenteral medication in terms of patient on long term therapy, this system is convenient.
- The vaginal bioavailability of smaller drug molecules is good and in case of larger drug molecule it is improved by means of absorption enhancer.
- Self-medication is possible.
- It permits continuous and prolonged residence of the dosage form at the site of application.
- It overcomes the inconvenience caused by pain, tissue damage and probable infection by other parenteral routes.
- The self-insertion and removal of the dosage form is possible.

3.3 Limitations of Vaginal Drug Delivery Systems[10]

- Local irritation of some drugs.
- Influence of sexual intercourses.
- Gender specificity.
- Personal hygiene.
- Sometimes leakage of drugs from vagina and wetting of under garments.
- The amount of vaginal fluid of an adult woman was reported to be in the range of 2–3 g (gram)/24 h (hour) and this amount is decreasing with increasing age which can affect the vaginal absorption of drugs.
- The pH of the vaginal fluid is also a factor which affects the drug absorption as the unionized forms will be preferable absorbed.

3.4 Drug delivery systems for vaginal administration

Traditionally, solutions, suppositories, gels, foams and tablets have been used as vaginal formulations. More recently, vaginal ring has been introduced for hormone replacement and contraceptive therapy. In general, based on the drug delivery system or formulations used, drug absorption, distribution and residence time in the vagina may vary. In fact, early work in this field the drug distribution and coverage of vaginal tissue varies considerably with the nature of the delivery system; solution, suspension and foam showing greater superiority over tablet dosage form. Ideally, a vaginal drug delivery system that is intended for local effect should distribute uniformly throughout the vaginal cavity. Ideally, the choice of vaginal drug administration depends on the applicability of the intended effect; whether a local or topical effect is required, For a local effect to occur, semi-solid or fast dissolving solid system will be required. For a topical effect, generally, a bioadhesive dosage form or intravaginal ring system would be more preferable. However, by far, it had been difficult to quantitatively measure the distribution of a drug after an intravaginal administration and also it is

uncertain if the administered formulation coated the whole organ In this regard, an interesting helpful.

Vaginal delivery may be designed for the administration of drugs by using an applicator or specifically designed systems for intravaginal administration. Further, vaginal formulations may be designed to produce local effect such as spermicidal or antibacterial effects or to produce a systemic effect by continuous release of drugs such as contraceptives. Intra-Vaginal Drug Delivery System is classified as.[11]

- Vaginal Tablet
- Vaginal Powder
- Vaginal Capsule
- Vaginal Ointment
- Vaginal gel and creams
- Suppositories or Pessaries
- Vaginal rings

3.4.1 Vaginal Tablets[12]

The Vaginal tablets are same in composition as conventional oral tablets but it has the advantage of ease of manufacture and insertion. The lactose based progesterone tablet can be used to deliver drug up to 24 hours and also can treat a variety of progesterone deficiency conditions such as menstrual irregularities, functional bleeding, luteal phase defects, and infertility.

Figure 2: Vaginal Tablet.

3.4.2 Vaginal Powder[8]

Vaginal powder is prepared by dissolving hydroxypropyl cellulose in water with heat. The mixture is slightly cooled and the bisphosphonate is added. The mixture is lyophilized.

Figure 3: Vaginal Powder.

3.4.3 Vaginal Capsule[8]

Vaginal capsule is prepared by filling the prepared powder into capsules. While the invention has been described in terms of various preferred embodiments, the skilled artisan will appreciate that various modifications, substitutions, omissions and additions may be made without departing from the spirit thereof. Accordingly, it is intended that the scope of the present invention be limited solely by the scope of the following claims.

Figure 4: Vaginal Capsule

3.4.4 Vaginal Ointments[13]

Vaginal ointment consists of oil and an aqueous phase. Vaginal ointment mainly comprises drug such as alendronate, clodronate, tiludronate, pamidronate, etidronate, ibandronate, neridronate, residronate, zoledronate or olpadronate dissolved in the aqueous phase and the oil phase added and both phases are properly mixed.

Figure 5: Vaginal Ointment

3.4.5 Vaginal Creams and Gels[14]

Vaginal Creams and gels are mainly used for topical delivery of contraceptives and anti-bacterial drugs. Metronidazole and clindamycin are the most commonly used vaginal cream for the treatment of bacterial vaginosis. The main underlying principle behind vaginal creams and gels is that of emulsion or hydrogel based drug delivery. These hydrogels, when placed in an aqueous environment, swell and retain large volumes of water in their swollen structure and results in drug release in a controlled fashion. A swelling controlled release hydro gel delivery system for intravaginal

administration of an antifungal drug, Miconazole has been reported. A gel micro emulsion based formulation of a spermicidal with anti- HIV effect, a vinyl phosphate derivative of zidovudine, has been developed. Drugs for cervical ripening and induction of labor are also available as a vaginal gel form. Oxytocin, dinoprostone and misoprostol are commonly used drugs for cervical ripening and induction of labor.

Figure 6: Vaginal Gel.

Figure 7: Vaginal Cream.

3.4.6 Vaginal Suppositories and Pessaries[15]

This vaginal formulation also known as Pessaries are designed to melt in the vaginal cavity and release the drug for several hours. These are now most commonly used to administer drugs for cervical ripening prior to childbirth and local delivery of drugs. Other drugs that are administered as suppository include dehydroepiandrosterone sulphate for ripening effect on the uterine cervix, Miconazole for vaginal candiasis and progesterone for hormone replacement therapy. The medicated pessaries have recently been used for delivery of prostaglandin E2 (PGE2) for ripening of the cervix and induction of labor.

Figure 8: Vaginal Suppositories.

3.4.7 Vaginal rings[16,17]

Vaginal rings are circular ring type drug delivery devices designed to release the drug in a controlled fashion after insertion into the vagina. Advantages of vaginal rings are that it is user controlled, does not interfere with cation, does not require a daily intake of pills and allows continuous delivery of low dose steroids. They are approximately 5.5 cm diameter with a circular cross section diameter of 4–9 mm and the ring is inserted in the vagina. In simple vaginal rings, drug is homogeneously dispersed within a polymeric ring. Drug at the surface of the ring is released faster than drug in the inner layer of the ring. Sometimes, drugs in the outermost layer provide an initial burst release. To obtain a constant release of drug from vaginal ring, sandwich or reservoir type rings has been developed. Sandwich type devices consist of a narrow drug containing layer located below the surface of the ring and positioned between a non-medicated central core and a no medicated outer band. In reservoir type rings, drugs are dispersed in a centralized core, which is then encapsulated by a drug free layer of polymer. In a single ring, it is possible to have several cores of different drugs and thereby allowing administration of several drugs from the same device. The rate of drug release can be modified by changing the core diameter or thickness of the no medicated coating. The material for making vaginal ring is usually polymeric in nature. Much of the vaginal ring literature relates to commonly used polymer, poly (dimethylsiloxane) or silicone devices, although other elastomeric polymers such as ethylene vinyl acetate and styrene butadiene block copolymer have been tested in recent years Ethylene vinyl acetate polymers are classified by the content of vinyl acetate. The addition of vinyl acetate units in the polyethylene provides the following advantages: increased flexibility, improved optical properties, greater adhesion, and increased impact and puncture resistance. Further, the clinical acceptability of rings made of ethylene vinyl acetate is very high In evaluating the tolerability of ethylene vinyl acetate no medicated vaginal ring of diameter 54 mm, the acceptability percent among the subjects involved in

the study was 91%. The ring was to remain inserted for 21 consecutive days after insertion, permitting temporary removal during coition. Most of the women judged the ring easier to insert and remove. No adverse effects were experienced among the test group during the study period. Vaginal rings are used for contraceptive and hormone replacement therapy. For most contraceptive applications, the rings are placed in the vagina for 21 days followed by a week of ring free period. Nuva Ring is the only combined contraceptive vaginal ring available in the US market. Nuva Ring is a flexible, transparent, contraceptive vaginal ring containing two active components, etonogestrel and ethinyl estradiol. The ring releases 120 mg/day of etonogestrel and 15 mg/day of ethinyl estradiol over a 3-week period of use. Clinical trials show that Nuva Ring is an effective contraceptive ring with good cycle control and user acceptability Femring R and EstringR are estrogen releasing rings used for estrogen therapy. Femring R, which is made up of silicone elastomer, contains acetate derived of estradiol, which is placed in the vagina once every trimester. Estradiol acetate is hydrolyzed to estradiol after being released from the delivery device. Estring R is made of silicone polymers and when inserted in the vagina releases 7.5 mg of estradiol per day.

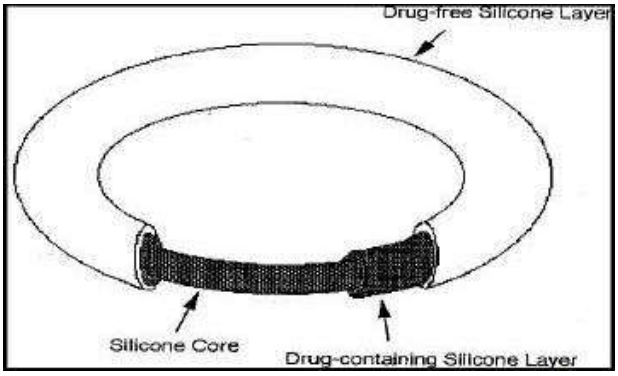

Figure 9: Vaginal Suppositories.

4. Novel Concepts In Vaginal Drug Delivery

Several aesthetic and functional qualities must be incorporated into VDFs. NVDDS need to be designed with desirable distribution, bioadhesion, retention and release characteristics. The conventional VDFs, such as suppositories, gels, creams and foamscan meet some but not all of these requirements. These features can be achieved by the use of Bioadhesive and other novel delivery systems.

4.1 Bioadhesive delivery systems[18]

The Vaginal Dosage forms currently in use are tablets, creams, gels and suppositories which come with the disadvantages of low retention to the vaginal epithelium, leakage and messiness and hence causing inconvenience to the patient. To compensate for these problems, bio adhesive drug delivery systems are taken into account. In bio adhesive drug delivery system, bio adhesive molecules capable of delivering the active compound for an extended period at a predictable rate are incorporated into a formulation. The vagina is a most suitable site for bio adhesive formulations as the product absorbs moisture, becomes a gel and releases medication in a time-controlled manner. Bioadhesive polymers that have been used for vaginal formulation include hydroxypropylcellulose, polycarbophil and polyacrylic acid.

4.2 Solid Polymeric Carriers[19]

These are the specifically designed non-messy intravaginal drug delivery systems that can be used to generate a variety of controlled delivery profiles over periods ranging from several days to several months.

These are of Two Types

4.2.1 Solid Hydrogels[20] The gelation and retention of in situ-gelling vaginal formulations could be a landmark in improving the therapeutic efficacy of drugs. The phase changes polymers polyoxypropylene and polyoxyethylene are used to form thermo reversible gels when incorporated into aqueous solution. Phase change polymers like poloxamer exhibit sol–gel transition in response to body temperature, pH and specific ions, and they prolong the residence time of the dosage form in the vagina. Formulations based on a thermoplastic graft copolymer have been developed to provide the prolonged release of active ingredients like nonoxynol, progestins, estrogens, peptides and proteins in a vaginal environment. Non aqueous solutions of the copolymer in hydrophilic excipients undergo in situ gelation in a short period of time after application. These in situ gelling liquid formulations can provide the necessary vaginal and cervical coverage as a result of their fluidity before gelation, and retention owing to the formation of a mucoadhesive gel.

4.2.2 Elastomeric Intravaginal Rings (IVR)[21] The vaginal ring is an innovative platform for the convenient delivery of hormonal agents. The vaginal ring is a torous or circular shaped device which is made up of silicone elastomers which owing to its elastomeric properties exert a slight tension on vaginal walls.

4.3 Vaginal Immunisation[22]

Most of the conventional vaccines are administered via the oral or parenteral route resulting in systemic rather than mucosal immunity. Scientists have developed the successful immunization with DNA vaccines administered via various mucosal routes. Mucosal sites, mainly the vaginal route, represent the primary site of entry of pathogens into the human body. In addition the, mucosal immunization causes mucosal as well as systemic immunity. In this concern, several vaginal vaccine formulations are ongoing research against a variety of pathogens, including the human immunodeficiency virus (HIV). A recent study reports the development of a novel HIV-CCR5 receptor vaccine for the control of mucosal simian (SIV) and human forms of the virus. The vaccine, which targets both the virus and its CCR5 receptor, was administered in female

rhesus monkeys either by the vaginal route or by targeting the proximity of the draining iliac lymph nodes. This immunization strategy through the vagina was found to significantly inhibit SIV/HIV infection in the animal model and shows promise for a novel approach in the prevention of HIV transmission.

5. CONCLUSTION

The vagina remains to be an underutilized route of drug delivery. Although the human vagina is used as a route for local action in the cervicovaginal region, its adoption for systemic delivery of macromolecules still needs to be accomplished. Various therapeutically important drugs such as insulin, calcitonin and sex hormones have been attempting to deliver via the vaginal route but there is not much success in the development of safe and viable vaginal formulations for these macromolecule drugs. The ongoing trend of research work is on Nanoparticles, microparticles drug, liposomal, niosomes formulation, delivery systems in vaginal route. Recent research efforts have perused applications other than contraception and vaginal infections to use these delivery systems to treat cancer, polycystic ovary syndrome and to deliver various protein and peptide drugs. The potential exists for a much wider use of vaginal delivery systems than currently existing systems. Hopefully novel bioadhesive systems in regards to microparticulate and nonparticulate systems will be developed in an advanced manner to meet these opportunities.

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