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Selection of the polymers used in oral dispersible films via analytical hierarchy process

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ABSTRACT: Many different active ingredients and excipients are used in the production of pharmaceutical products. Selection of the most suitable active ingredients and excipients is one of the most important stages of pharmaceutical production. When choosing the active ingredients and excipients, several factors and alternatives should be considered. In this instance, it is thought that one of the multi-criteria decision-making techniques, an operational research model, the Analytical Hierarchy Process, can assist in identifying the excipients during the pre-formulation stage. Using the Analytical Hierarchy Process, the current study seeks to identify the polymers most suitable for producing oral dispersible film formulations. The problem's criteria and potential solutions were determined before establishing the goal. Then, pairwise comparison matrices were generated, and the generated matrices were sent to the Super Decisions Version 3.2 software to reach a solution/result. The study's findings showed that the forming capacity is the most crucial factor affecting the choice of polymer to be used in the pre-formulation of oral dispersible films. Hydroxypropyl methylcellulose (14.89%) was found to be the best alternative among the polymers, followed by hydroxyethyl cellulose (12.04%) and carboxymethyl cellulose (11.58%). It was revealed that the least preferred polymers were sodium alginate (5.6%) and pectin (6.8%), which are natural polymers. It is clear from the outcomes of the various pre-formulation investigations that polymer selection in oral dispersible film formulations is one of the most critical points. This study provides a new approach to selecting the most appropriate polymers in oral dispersible film formulations.

KEYWORDS: Analytical Hierarchy Process; Pharmaceutical production; Excipient selection; Pre-formulation; Oral dispersible films.

1. INTRODUCTION

The oral route is the most popular method for administering drugs since it is flexible, non-invasive, patient-acceptable, and easy to administer [1]. However, there are significant differences in the oral bioavailability of the drugs due to a number of factors, including the physiological environment of the gastrointestinal tract and the physicochemical properties of the drugs, which affect oral absorption. Additionally, most oral drugs undergo first-pass metabolism, which may occur in the gastrointestinal tract prior to absorption and most likely in the liver following absorption, resulting in a significantly reduced bioavailability [2]. Furthermore, administering solid oral dosages, such as tablets and capsules, to patients who have trouble swallowing can be extremely difficult [3]. This is particularly true for the elderly, children, individuals with Parkinson's disease, and patients who have just undergone anesthesia [4-7]. Therefore, many alternatives to the oral drug administration method have been continually developed for patients who are non-compliant, nauseated, elderly, and paediatric patients employing new and innovative technologies [2]. Adhesive tablets, gels, and patches are products of technical advancement and provide fast onset of action or extended-release that increase patient compliance [8, 9]. Among the bio-adhesive mucosal dosage forms, the use of orally disintegrating films (ODFs), provides not only overcomes the swallowing problem but also ensures good oral bioavailability [10].

ODFs are defined in the Turkish Pharmacopoeia as "Single or multi-layer versions of suitable materials that are placed in the mouth and dispersed very quickly" and in European Pharmacopoeia 9 as "Single or multi-layer layers of suitable materials that can be dispersed quickly when placed in the

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mouth"[11, 12]. According to the Food and Drug Administration (FDA), ODF is defined as "a thin layer or coating that is susceptible to dissolving when it comes into contact with a liquid" [13]. ODFs are mainly composed of polymeric matrices, and when they are placed inside the mouth, they immediately soak the saliva. Throughout the hydration process, which triggers disintegration and/or dissolution, they release the active pharmaceutical agent from the dosage form [14]. Active pharmaceutical ingredients can be incorporated with the excipients, which are non-active components added to the formulation to provide the dose of the active agent at the proper weight, consistency, and volume and to make it easier to administer [15]. Excipients are designed to enhance drug stability and add additional properties to their conventional effects as a support and a carrier [16]. Oral dispersing film formulations have a polymeric matrix structure consisting of several components. The main components in these formulations are polymers, and substances such as flavouring, colouring, and thickener are added to the formulations in addition to the active substance [8]. The typical composition of an ODF formulation is given in Table 1.

Table 1. Components of a general ODF formulation [27].

Ingredients	Percentage (%)
API	1-30
Polymer	40-50
Plasticizer	0-20
Taste Masking, Colouring and Filling agents	0-40

Numerous variables influence the selection of a suitable excipient [17, 18]. Therefore, selecting a proper excipient to be used- is crucial since choosing the wrong excipient could result in a loss of economic resources and time in the research [19]. Stated differently, a multitude of conditions need to be taken into account to create the ideal formulation at the pre-formulation stage. Except for the active pharmaceutical, the most essential factor of a successful ODF formulation is the correct choice of the excipients, particularly the polymer. In this context, it is thought that an operational research model, the Analytical Hierarchy Process (AHP), which is one of the multi-criteria decision-making techniques first developed by Saaty in 1980, can be used in the pre-formulation stage for determining the excipients to be included in drug formulations [20, 21]. AHP divides a complex problem into a hierarchy concerning one or more criteria [22]. One advantage of the AHP is that it can be used to manage situations where people's subjective opinions are a major factor in decision-making [23, 24].

When oral film preparations in both national and international pharmaceutical markets are reviewed, it is seen that there are different pharmacological product groups produced for different purposes, such as analgesic, antiemetic, antidiabetic, antihypertensive, etc. It is not feasible to assert, though, that all active substances are suitable for oral film formulations [25, 26]. ODFs are rapidly dissolving thin films with a surface area of 5 to 20 cm^2 that contain drugs integrated within a polymer matrix [27]. Due to its limited size, this formulation type cannot be preferred for active ingredients that act in high doses or have high molecular weight. In the choice of active ingredients, factors such as solubility, taste, sensitivity to heat, and stability are also considered in addition to the dose or molecular weight [28, 29].

Researching and selecting suitable polymers to obtain oral films is a long process, and extensive research is carried out to ensure the incorporation of different drugs into these films and to overcome some of the production bottlenecks [25, 26]. The strength of the oral film is determined by the amount of polymer used, and a variety of characteristics, including cost, toxicity, dispersibility, purity, and drug loading capacity, should be taken into account when determining which polymer is optimal. Many different types of natural and synthetic polymers are used in pharmaceutical production [30]. Each polymer has different characteristics and is also a determinant of many properties. The polymers indicated in Table 2 are commonly used to prepare ODFs [1, 25, 28, 29].

Table 2. Frequently used polymers in the preparation of oral films [29, 31].

Natural polymers	Synthetic polymers
Pullulan	Hydroxyethyl cellulose (HEC),
Starch	Hydroxypropyl cellulose (HPC),
Sodium alginate	Hydroxypropyl methylcellulose (HPMC),

Pectin	Carboxymethyl cellulose (CMC)
Gelatine	Polyvinyl alcohol (PVA)
Polymerized resin	Polyethylene oxide (PEO)
Chitosan	Polyvinylprolidone (PVP)
	PVA-g-PEG (Kollicoat IR)

When the literature is reviewed, it is seen that different techniques such as solvent casting, hot melt extrusion, semi-solid casting, electrospinning, rolling, solid dispersion, and 3D-printing methods are used in the production of ODFs [32-34]. Also, different patented production techniques can be used [35]. Production managers from companies indicated that they mostly prefer using the solvent casting method because it is inexpensive and doesn't require any specialized equipment for production. Accordingly, Figure 1 illustrates the oral film production process with the solvent casting technique, along with the quality control criteria that need to be taken into account at each stage.

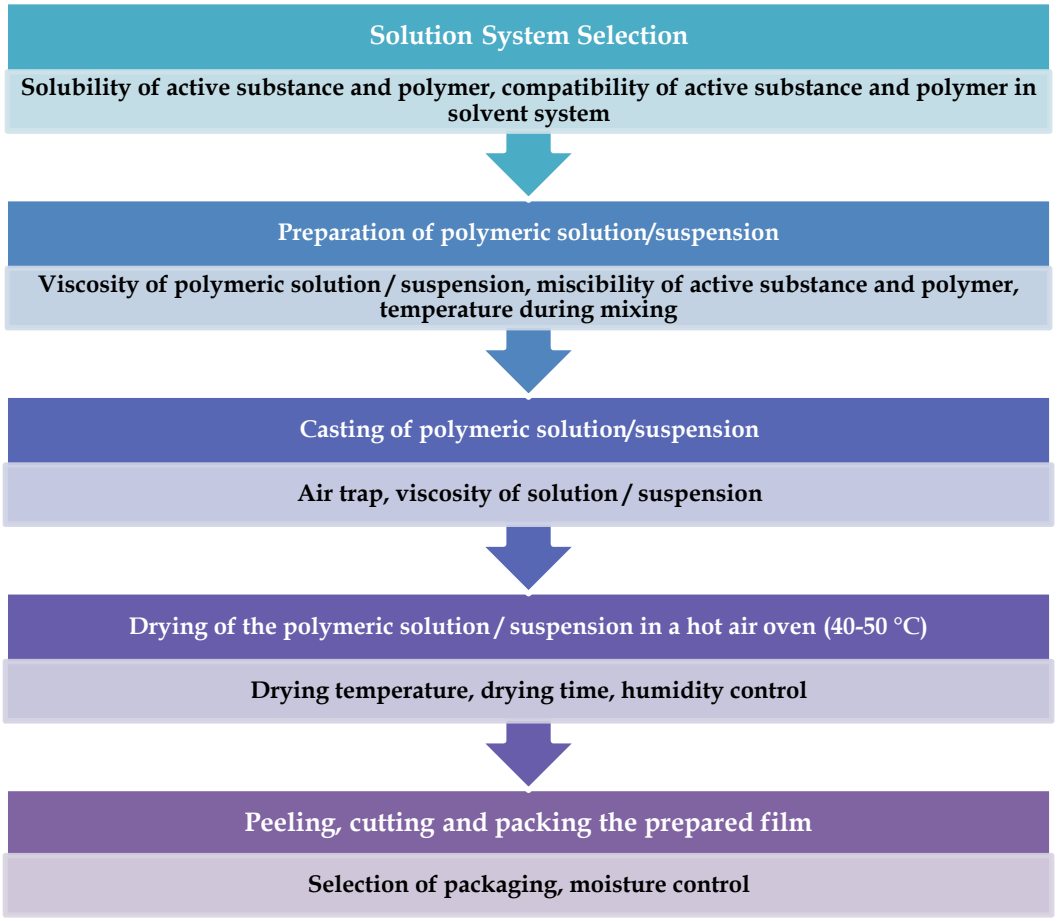

Figure 1. Production steps and related control tests conducted to produce ODFs by solvent casting method

Production of a new formulation requires extensive studies, as mentioned in previous sections. In this context, the production process presented in Figure 1 constitutes the pre-formulation stage in the workflow chart for developing a new oral film formulation that will be discussed in this study. The general workflow chart for developing a new drug formulation is given in Figure 2.

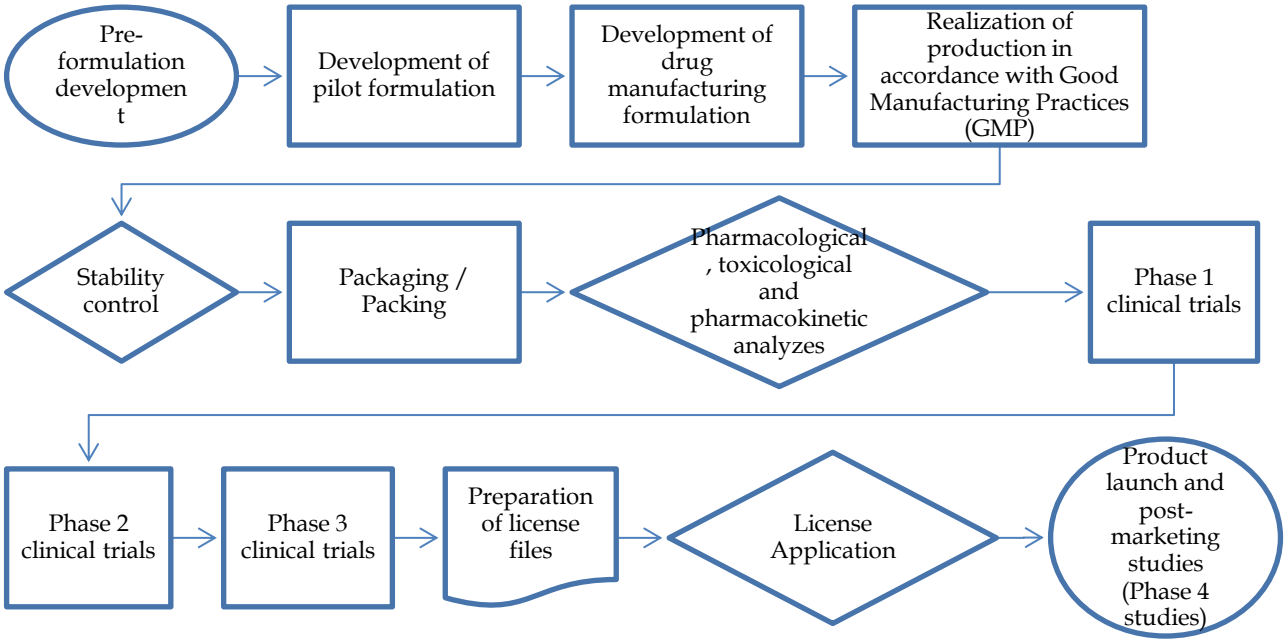

Figure 2. The general workflow of formulation development [35]

3. RESULTS

3.1. Defining the problem in Super Decisions Version 3.2 software

The problem is defined hierarchically in Super Decisions Version 3.2 software, in line with the flow chart shown in Figure 6. The hierarchical nature of the problem is shown in Figure 3.

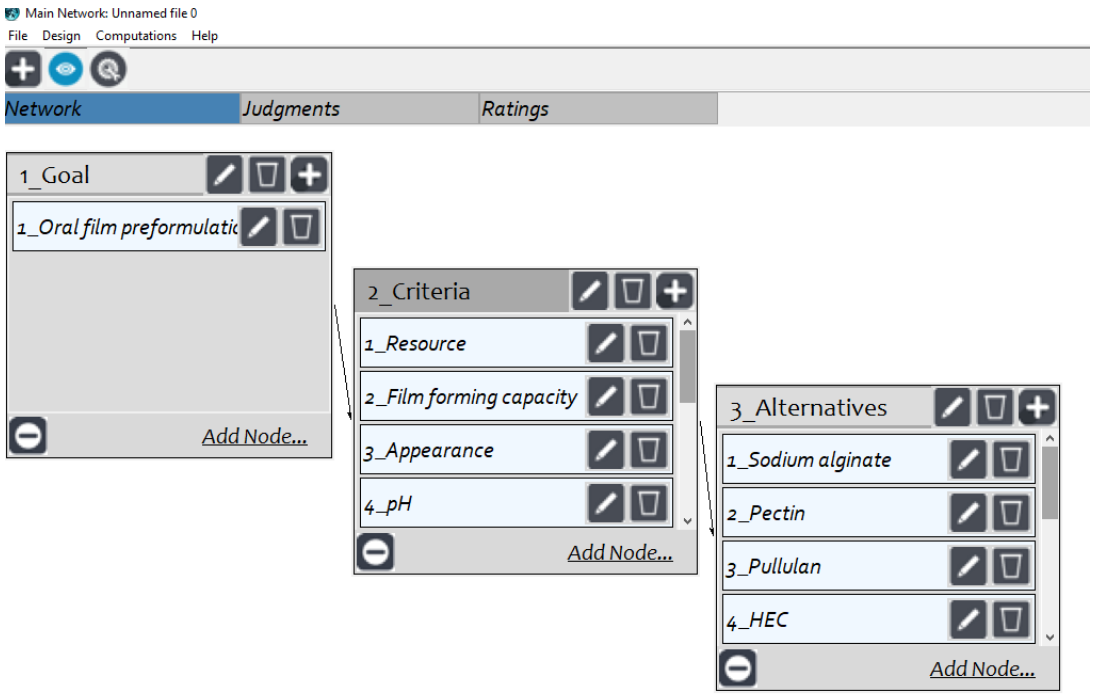

Figure 3. Super Decisions Version 3.2 AHP Network model

3.2. Creating a paired comparison matrix for the criteria

At this stage of the study, decision-makers were asked to compare the criteria in pairs. The answers given by the decision-makers and their geometric averages are presented in Table 3. In Table 3, the comparisons made by decision-makers are presented as a matrix. There are wi/wj terms in each cell of this matrix. These values express how much more important criterion i is than criterion j in order to achieve the determined goal. For example, if this value is 5, it is understood that criterion i is strongly important compared to criterion j. In this case, similarly, criterion j becomes important at the 1/5 level compared to criterion i.

Table 3. Paired comparison chart for criteria

Criterion (i)	Decision maker 1	Decision maker 2	Decision maker 3	Geometric mean	Criterion (j)
Resource	1/5	1/5	1/7	0.18	Film forming capacity
Resource	1/3	1/3	1/3	0.33	Appearance
Resource	1/3	1/5	1/3	0.28	pH
Resource	1/5	1/5	1/7	0.18	Viscosity
Resource	1/3	1/3	1/3	0.33	Solubility
Resource	1/3	1/3	1/3	0.33	Molecular weight
Resource	1	1	1	1	Ionisation
Resource	1/5	1/5	1/7	0.18	Disintegration time
Resource	1/5	1/7	1/5	0.18	Humidity ratio
Film forming capacity	3	5	3	3.56	Appearance
Film forming capacity	5	3	5	4.22	pH
Film forming capacity	1	1	1	1	Viscosity
Film forming capacity	3	3	3	3	Solubility
Film forming capacity	3	3	3	3	Molecular weight
Film forming capacity	5	5	5	5	Ionisation
Film forming capacity	1	1	1	1	Disintegration time
Film forming capacity	1	3	1	0.69	Humidity ratio
Appearance	1/3	1/3	1/3	0.33	pH
Appearance	1/5	1/5	1/5	0.20	Viscosity
Appearance	1/3	1/5	1/5	0.24	Solubility
Appearance	1/3	1/3	1/3	0.33	Molecular weight
Appearance	1	1	1	1	Ionisation
Appearance	1/9	1/7	1/7	0.13	Disintegration time
Appearance	1/5	1/5	1/5	0.20	Humidity ratio
pH	1/3	1/3	1/3	0.33	Viscosity
pH	1	1	1	1	Solubility
pH	1/3	1/3	1/3	0.33	Molecular weight
pH	5	5	5	5	Ionisation
pH	1/5	1/5	1/5	0.20	Disintegration time
pH	1	1	1	1	Humidity ratio
Viscosity	1	1	1	1	Solubility
Viscosity	3	3	3	3	Molecular weight
Viscosity	7	7	7	7	Ionisation
Viscosity	1/3	1	1/3	0.48	Disintegration time
Viscosity	3	3	1	2.10	Humidity ratio
Solubility	3	3	1	2.10	Molecular weight
Solubility	7	7	7	7	Ionisation
Solubility	1	1	1	1	Disintegration time
Solubility	1	1	1	1	Humidity ratio
Molecular Weight	5	5	5	5	Ionisation
Molecular Weight	3	1	3	2.10	Disintegration time
Molecular Weight	3	1	3	2.10	Humidity ratio
Ionisation	1/7	1/7	1/9	0.13	Disintegration time
Ionisation	1/5	1/5	1/5	0.20	Humidity ratio
Humidity ratio	1/3	1/3	1/3	0.33	Disintegration time

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The geometric mean values calculated in Table 3 were rounded to the nearest integer and transferred to the Super Decisions Version 3.2 software. This software offers 4 different methods for binary comparisons: Graphic, Verbal, Matrix, and Questionnaire. Questionnaire representation was used in this study, and the program output related to the problem is given in Figure 4.

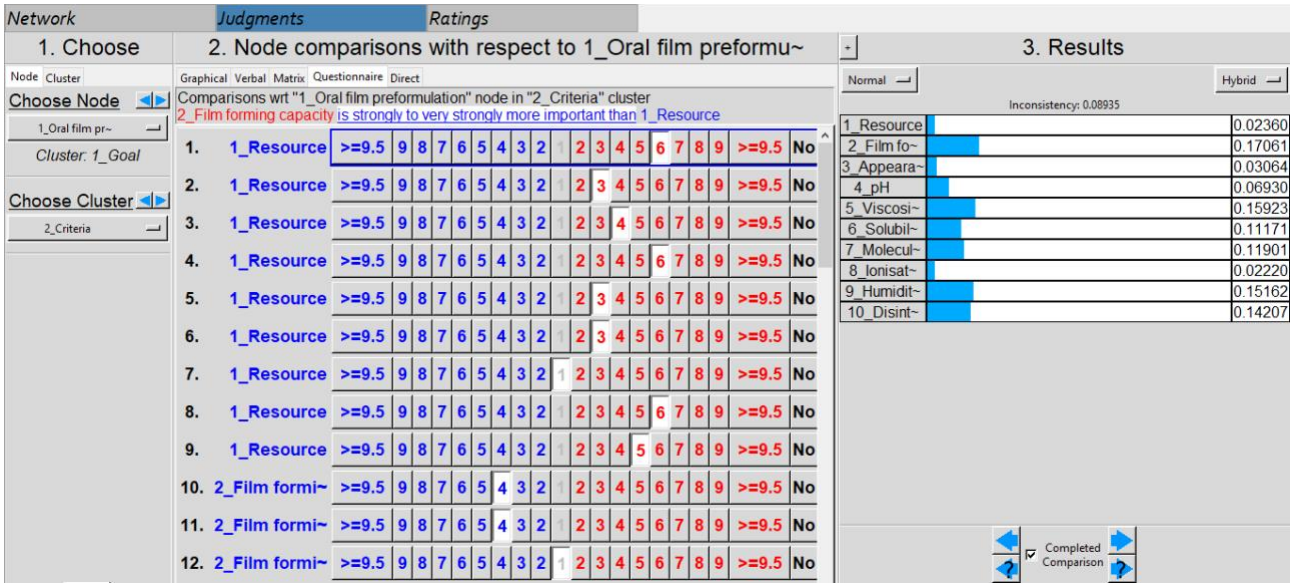

Figure 4. Program output for binary comparison of criteria

The inconsistency coefficient for this evaluation was calculated as 0.089, and a value below 0.1 indicates that it is acceptable.

In line with the ratios presented in Figure 4, it is seen that the most important criterion affecting the choice of polymer to be included in oral film pre-formulation is film-forming capacity with a rate of 17.1%, followed by viscosity at 15.9% and humidity ratio at 15.2%.

3.3. Creating a paired comparison matrix for alternatives based on criteria

The decision-makers compared the alternatives in terms of each criterion to select the best alternative. For this aim, firstly, they evaluated alternatives in terms of the first criterion, "sources." The responses' geometric means were rounded to the nearest integer and transferred to the program. These operations were performed for each criterion respectively.

By the pairwise comparison of the alternatives regarding the "source" criterion, the best alternatives were sodium alginate, pectin, and pullulan, with the same percentage (18.75%). When the alternatives were compared in terms of the "film forming capacity" criterion, the best alternative was pullulan, with 21.83%, followed by CMC, with 16.77%, and HPMC, with 15.97%. The best alternative in terms of the "appearance" criterion was found to be HPMC with a rate of 16.69%, the best alternative in terms of the "pH" criterion was PVA with a rate of 18.44%, and the best alternative in terms of the "viscosity" criterion was HPMC with a rate of 36.10%. As a result of the pairwise comparison of the alternatives in terms of the "solubility" criterion, PVP, with 26.71%, and HEC, with 26.42%, were determined as the best alternatives. According to an evaluation in terms of the "molecular weight" criterion, it was seen that pectin, PVA, and PEO were the best alternatives, with the same percentages (approximately 16%). As a result of the pairwise comparison of the alternatives in terms of the "ionization" criterion revealed that the alternatives had similar values to each other, and HPC was the best alternative with a rate of 14.19%. The best alternative regarding the "disintegration time" criterion was PVP, with a rate of 22.21%, and the best alternative in terms of the "humidity ratio" criterion was HPC, with a rate of 22.73%.

When the priority values for the alternatives are combined in line with the pairwise comparisons presented above, the priority order of the polymers that should be included in the formulation at the pre-formulation stage is shown in Table 4.

In light of the data presented in Table 4, it was determined that HPMC (14.9%) was the best alternative among the polymers, followed by HEC (12.0%) and CMC (11.58%). Furthermore, it was revealed that the least preferred polymers were sodium alginate (5.6%) and pectin (6.8%), which are natural polymers. The inconsistency coefficient for this evaluation was calculated as 0.083.

Table 4. Priorities of alternatives

Name of the alternative	Normalized by cluster	Percentages (%)
Sodium alginate	0.056	5.6
Pectin	0.068	6.8
Pullulan	0.083	8.3
HEC	0.120	12.0
HPC	0.096	9.6
HPMC	0.149	14.9
CMC	0.116	11.6
PVA	0.105	10.5
PEO	0.097	9.7
PVP	0.109	10.9

4. DISCUSSION & CONCLUSION

The manufacturing of pharmaceuticals is a very special and intricate process. Operating a highly valued product with strict regulations is more challenging. The pharmaceutical industry is collectively called the procedures, businesses, and activities involved in creating, planning, and producing practical pharmacological medications. Due to special procurement, manufacturing, and preservation requirements, the pharmaceutical supply chain is more complex than other industries [36, 37]. Generally, supply chain problems are discussed and evaluated in basic topics such as cost, quality, liability, service, regulations, etc., whereas R&D-based problems focus on formulation, market access, manufacturing, patient needs, etc. Even supply chains, especially procurement operations and R&D departments and their operations, need to be designed and integrated. For instance, during a formulation design, R&D formulators only focus on manufacturing, patent rights, currently available raw materials, current literature, and patient needs. Still, they must be aware of cost, price, quality (Pharma grade availability), service, etc. These procurement operations directly affect the producibility and saleability of the formulated drug [38, 39].

Within this study, one of the multi-criteria decision tools, AHP, which has a wide application in supply chain operations, tried to be applied in the R&D operations [22, 40]. However, due to the design and underlying mathematical method of the AHP approach, many limitations were observed in application in the R&D frame. In contrast, cost quality and regulation also needed to be added as primary criteria. Still, as a comparison between the pH of the formulation and the cost is not feasible, those types of criteria cannot be integrated into the AHP approach field [41]. Hence, we could only analyze the problem of choosing the most suitable excipient when preparing oral dispersible films using the AHP technique. This research utilized a hierarchy model with ten primary criteria and ten alternatives. The overall priority weight of each alternative was calculated using the Super Decisions Version 3.2 software. The study's finding showed that the most crucial factor affecting the choice of polymers to be used in the pre-formulation of ODFs is film-forming capacity, followed by viscosity and humidity ratio, respectively. According to the criteria, the best alternative polymer to be preferred was HPMC, followed by HEC and CMC.

Kaur and Garg (2018) state that polymer selection in oral film formulations is one of the most critical points of the formulation stage [42]. Therefore, a holistic multi-criteria decision tool should be designed that can simultaneously evaluate R&D and supply chain needs and provide more durable formulations and products that have a chance to reach patients. Also, it should be considered that manufacturing principles have entirely changed in the twenty-first century [43]. Accordingly, a shorter product life cycle with higher risk and uncertainty, highly variable demand, and susceptible supply situations currently define today's market needs. More integrated research approaches should be established for sustainable businesses in the pharmaceutical industry.

5. MATERIALS AND METHODS

Within the scope of the study, it will be tried to contribute to the solution of the problem encountered by the XYZ pharmaceutical company, which is working on an analgesic (analgesic) effective oral drug formulation during the pre-formulation stage. The company deemed the oral dispersible film formulation suitable for the target product among the orally dispersible drug formulations. At this point, it is expected that a study will be conducted to guide the selection of polymers, which are one of the main components in the formation of orally dispersible film formulations, at the pre-formulation stage before starting the formulation by the company. Thus, the main aim of this study is to identify the ideal polymer types that can be used to produce ODFs during the pre-formulation stage and to provide novel solutions.
In this context, first of all, general information about the films dispersed in the mouth, the active substances and excipients used in the formulations, and the production stages will be given briefly. Afterward, the factors affecting the choice of the polymer at the pre-formulation stage as criteria and the polymers that can be included in the formulation as alternatives were determined by reviewing the literature and taking the opinions of the company's production manager and experts in the relevant field. At the application stage, the AHP approach was used to prioritize the criteria and select the most suitable alternative. Therefore, pairwise comparison matrices were created for the AHP, the resulting matrices were transferred to the Super Decision Version 3.2 software, and a solution was made.

5.1. Analytical Hierarchy Process

The structure of the decision-making process is complicated and involves both quantifiable and external influences, such as natural phenomena [44]. Like in many other sectors, the pharmaceutical sector places a high value on decision-making, which involves weighting all available options to achieve a goal while maximizing benefits at the lowest possible cost [23, 45]. AHP, developed by Thomas L. Saaty in the 1970s, is one of the multiple criteria decision-making (MCDM) techniques based on paired comparisons [46]. When complex issues need consideration of multiple elements, the MCDM discipline helps decision-makers make decisions [44]. AHP, among these techniques, was mainly used for "sequencing and selection problems." AHP enables the decision-maker to concentrate on comparing just two criteria or options at once and allows the problem under evaluation to be organized in a hierarchy [40].

The implementation stages of AHP can be summarised in Figure 5 [20, 21, 45, 47, 48]. Briefly, the first step of the AHP is determining the main purpose of the decision problem and establishing a decision hierarchy. The number of levels of the decision hierarchy depends on the complexity and depth of the decision problem and generally consists of three levels [23, 24, 49]. The top level of the hierarchy is the main goal. It covers second-level criteria (may also include sub-criteria), and the last level consists of alternatives.

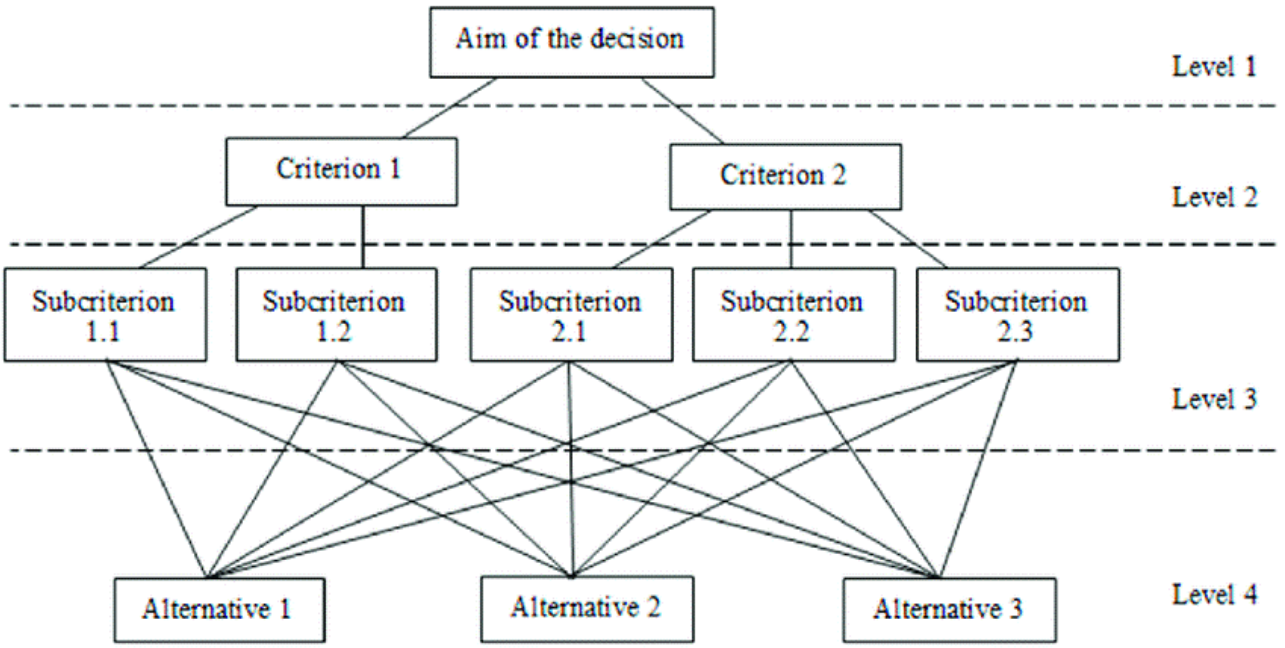

Figure 5. The general hierarchical structure of AHP [47, 48]

The second step of the AHP is the determination of relative priorities for criteria and alternatives in terms of their importance in achieving the goal. The priority (importance) scale developed by Thomas Saaty and given in Table 5 is used when making binary comparisons.

Table 5. Saaty's pairwise comparison [21]

Numerical Value	Description
1	Equal importance
3	Slight importance of one over another
5	Moderate importance of one over another
7	Very strong importance
9	Extreme importance of one over another
2,4,6,8	Intermediate values between two adjacent values

Paired comparison matrices are created for both criteria and alternatives. In these matrices, there should be an "$a_{ij}=1/a_{ji}$" relationship between matrix elements, where $a_{ij}>0$, $i \neq j$; and $i, j = 1,2,...,n$.. The pairwise comparison matrix is square, and its size is the number of criteria if criteria are compared; if the options are compared, it is the number of choices. Thus, as the number of criteria/alternatives increases, the number of pairwise comparisons increases [40, 45].

5.2. Application of AHP

The flow diagram shown in Figure 6 has been used to solve the problem addressed in this study.

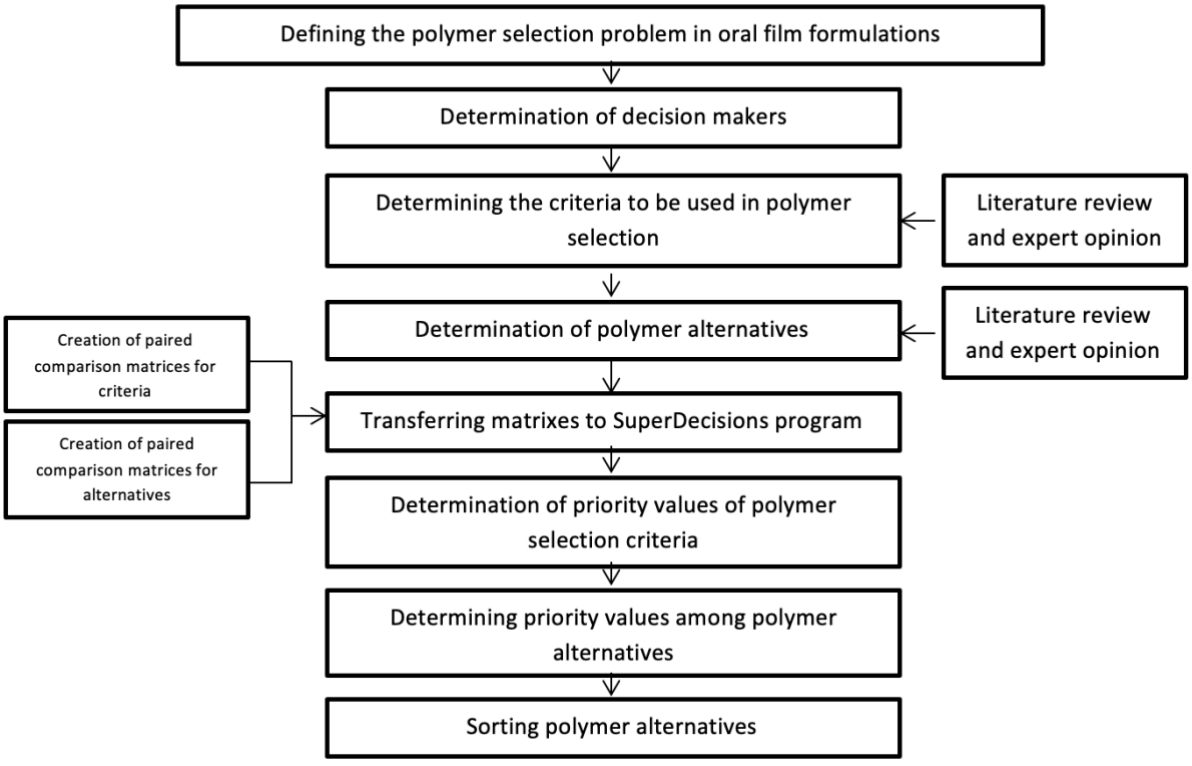

Figure 6. Flow diagram followed during the application [38]*
*Created by the Authors

The decision problem of this study is "the choice of polymers to be used in the production of ODFs in the pre-formulation stage". The company's production manager responsible for the relevant production process and two academicians who are experts in the field of pharmaceutical technology were determined as decision-makers as related to the problem dealt with. Then, in the pre-formulation stage, 10 criteria and 10

polymer alternatives were determined in line with the relevant literature and expert opinions regarding polymer selection in oral film production.

Criteria: (i) Source, (ii) Film-forming capacity, (iii) Appearance, (iv) pH, (v) Viscosity, (vi) Solubility, (vii) Molecular weight (Mw), (viii) Ionization, (ix) Disintegration time; and (x) Humidity ratio.

Alternatives are those that are not incompatible with the active ingredient selected for pre-formulation: (i) Sodium alginate, (ii) Pectin, (iii) Pullulan, (iv) HEC, (v) HPC, (vi) HPMC, (vii) CMC, (viii) PVA, (ix) PEO, and (x) PVP is preferred.

Table 6 presents the parameters that need to be taken into consideration when solving the alternative polymer problem. Additionally, before starting pairwise comparisons, relevant experts had a chance to investigate Table 6.

Table 6. Properties of polymers [30, 50, 51]

Polymer	Source	Film forming capacity	Appearance	pH	Viscosity	Solution	Mw	Ionisation	Speed	External Humidity Level (%)
Sodium alginate	Natural	%0.3-0.9	White powder	6-8	20-200 Cps	It is water soluble. Insoluble in ethanol and ether	20000-240000	Anionic	20-206 min Slow	5
Pectin	Natural	%3	White/ yellowish powder	6-7.2	2.5-4.9 dl/g	Soluble in water	30000-100000	Non-ionic	60 min Easy	10
Pullulan	Natural	%5-25	White/ yellowish powder	5	100–180 mm^2/s	Soluble in hot and cold water	8000-2000000	Non-ionic	Easy	6
HEC	Synthetic	%2-20	White/ yellowish-white/ greyish-white, hygroscopic powder or granule	5.5-8	<4000Cps	It dissolves in hot and cold water giving colloidal solutions. Acetone, anhydrous alcohol, ether, toluene, etc.	50000-1250000	Non-ionic	20-206 min Easy	<5
HPC	Synthetic	%5	White/ yellowish powder	5-8	75-6500 mPas	Ethanol, methanol, isopropyl alcohol, propylene glycol etc.	50000-1250000	Non-ionic	20-206 min Easy	1.6
HPMC	Synthetic	%2-20	Fibrous/ granular powder	5.5-8	3-100 ,000 mPas	It dissolves in cold water giving a colloidal solution; insoluble in ethanol (95%), chloroform and ether	10000-1500000	Non-ionic	20-206 min Easy	1.6
CMC	Synthetic	%2-20	A white granular powder	4-12	5-13 ,000 mPas	Soluble in water	90000-700000	Non-ionic	20-206 min Easy	<10
PVA	Synthetic	%3-5	White or cream-coloured granules or powder	5-8	<95 Cps	Soluble in water	20000-200000	Non-ionic	<37 min Fast	5
PEO	Synthetic	%3-5	White hydrophilic powder	8-10	Non-stable	Soluble in water	<100000	Non-ionic	<37 min Fast	<1
PVP	Synthetic	%3-5	A fine, white or creamy white powder with hygroscopic properties	3-7	<95 Cps	Easily soluble in acids, chloroform, ethanol, ketones, methanol and water; insoluble in ether, hydrocarbons and liquid paraffin	2500-3000000	Non-ionic	Easy, Fast	<1

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